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

June 17-19, 2003

Final Meeting-29 Highlights

U.S. Department of Labor
200 Constitution Avenue, N.W., Rm 3437-B,C,D
Washington, DC 20210

INTRODUCTION

George Rusch, NAC/AEGL Chair, and Ernie Falke, EPA Representative, began the meeting with a tribute to Roger Garrett. Among many other projects with which Roger was associated, his involvement in the successful AEGL program may be his most lasting legacy. George Rusch handed out mini-posters, copies of posters of final AEGLs presented by ORNL staff at the 42nd Annual Meeting of the Society of Toxicology in Salt Lake City. Paul Tobin, EPA Designated Project Officer, updated the Committee on the status of the EPA internet site. It was also mentioned that files of draft documents of AEGL chemicals are available for review by committee members on the non-public ORNL web site prior to NAC meetings. Federal Register Notice 7 is now at the EPA Assistant Administrator's Office, and should be signed shortly. In response to the USEPA concern on human studies, Ernie Falke had previously noted that the Standing Operation Procedures (SOPs) already has a statement addressing the use of human data. George Rusch mentioned the availability of electronic Organization of Economic Development (OECD) data on high production chemicals. Warren W. Jederberg is Navy's nomination to replace Kenneth Still (who has taken a new position as Director, Fleet Safety and Occupational Health for the U.S. Pacific Fleet).

The draft NAC/AEGL-28 meeting highlights were reviewed. One change - a clarification of the basis for the AEGL-1 for formaldehyde - was suggested by George Alexeeff. Bob Benson volunteered to clarify the basis/effect for the AEGL-1. A motion was made by Loren Koller and seconded by Bob Benson to accept the meeting highlights as presented with the aforementioned revision. The motion passed unanimously by voice vote. The final version of the NAC/AEGL-28 meeting highlights is attached (Appendix A) and was distributed to the NAC/AEGL by e-mail. At this time Paul Tobin passed out information sheets to be filled out by the chemical managers (assuming they are not making the presentation) and to be used for writing up the meeting minutes (Attachment 1). Ernie Falke promised to send a WAV file covering the discussion of the chemical of interest to each chemical manager.

Ernie Falke discussed the status of chemicals that will be considered at the NAC-30 and -31 meetings (Attachment 2). A possible change in the process by which Proposed AEGLs are announced in the Federal Register was discussed. Proposed AEGL chemicals could be listed in the Federal Register with a notice to go to the EPA web site to view the actual values as well as the technical support documents. A discussion among Ernie and several NAC members addressed the listing of several chemicals with low production data but that appear on lists of potential terrorist chemicals.

The highlights of the NAC/AEGL-29 meeting are summarized below along with the Meeting Agenda (Attachment 3) and the Attendee List (Attachment 4). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-29 Agenda.

TECHNICAL ISSUE DISCUSSIONS

Revisit of Fundamental Principles of Industrial Hygiene
John Morawetz

John Morawetz discussed the five points to be considered in evaluation of occupational studies (Attachment 5). These points are under consideration for addition to the SOPs. John stressed the need for personal sampling data in using human studies to set AEGL values and the need to always associate an exposure level with a sampling time. He reiterated the problems associated with other types of monitoring data including the different types of occupational samples, variability in sampling time, variability in exposures in the work environment, and the different types of collection devices. Although there was general agreement with all five statements suggested by John, there was further discussion on rearranging and/or combining points. These included moving point 2 to point 1, combining points 1 and 4, and omitting point 5. There should also be inclusion of the statement that other routes of exposure (other than inhalation) are recognized. Richard Niemeier reported that the Health Hazard Evaluation program has a monitoring data base, but it is not easily searchable. George Rusch recommended that the committee vote on this issue electronically before the next meeting.

Industrial Hygiene/Emergency Planning Considerations in AEGL Development
Edward Bishop (NRC/COT AEGL Subcommittee)

Ed Bishop, an industrial hygienist, environmental engineer, member of the National Academy of Sciences Subcommittee on AEGLs, and lead COT reviewer for the nerve agent AEGLs, presented his address to the Chemical Stockpile Emergency Preparedness Program (CSEPP) National Preparedness Workshop entitled, “AEGLs and CSEPP.” The Workshop was held in Mobile, AL, on June 24-26, 2003. The CSEPP, jointly managed and supported by FEMA and the Department of the Army, provides technical and training support for chemical warfare agent emergency preparedness in the states where agent stockpiles are located. During a short introductory discussion of industrial hygiene considerations, Ed stressed the necessity for

rigorous evaluation of occupational monitoring data. He noted that exposure assessments from exposure reconstructions are generally poor. For emergency planning, planners first consider hazard vs toxicity. For example, for high-production volume chemicals, the first question should be, "is there a hazard?" Extremely hazardous chemicals are considered first. Transport and storage of chemicals also need to be considered. For emergency planners, the AEGL-1 is considered a notification level, not an evacuation level (evacuations have their own risk). For the AEGL-2, which is an evacuation or shelter-in-place level, mitigations should be considered ahead of time. These include storage of insufficient quantities to reach an AEGL-2 level, implementation of a public risk communication program, and issuance of evacuation or shelter-in-place procedures. As an example of risk communication, Ed discussed his role as a National Academy of Sciences member in communicating the safety of the AEGL-1 for nerve agents that are stored at the Anniston, AL, depot. Ed pointed out that the final adjustment factors for VX AEGLs were those recommended by the COT and were reductions of those originally recommended by the NAC. The talk was followed by a discussion among Ed, John Morawetz, and other NAC members concerning evaluation of industrial hygiene studies. There appeared to be a general consensus among participants concerning the definition of an adequate monitoring study.

Derivation of an Uncertainty Factor for NOAEL to LOAEL Extrapolation
George Alexeeff

George Alexeeff discussed his findings on extrapolation from LOAELs to NOAELs for mild health effects (Attachment 6). This work is published in *Regulatory Toxicology and Pharmacology* 36:96-195 (2002). The results are based on 40 hazardous air pollutants (88 data sets). George listed the signs and symptoms identified with mild health effects. Ratios of LOAELS to NOAELs ranged from 1.1 to 13.8 (median 2.0). The 95th percentile was 6.3. Results were not affected by species, group size, exposure duration, or endpoint. Paul Tobin pointed out that thresholds for AEGLs are neither NOAELs or LOAELs but somewhere in between; using either NOAELs or LOAELS reduced by certain factors may be conservative. With approval of the NAC/AEGL a description of George's findings along with how the NAC/AEGL will use this information will be placed in the SOPs.

Categorizing the Signs and Symptoms at the AEGL and Sub-AEGL
George Alexeeff

George Alexeeff passed out summary sheets of effects used as endpoints at the sub-AEGL-1, AEGL-1, and AEGL-2 levels (Attachment 7). These descriptors will be added to the USEPA web site.

AEGL Application in Emergency Planning
Robert Snyder

Robert Snyder demonstrated an Emergency Response Center program that integrates AEGL levels with chemical release modeling data over time. This program identifies the time and distance at which AEGL concentrations are reached downwind following a release. The model

can be specific for geographic areas/cities in that vulnerable sites (schools, hospitals) and sites of emergency responders can be mapped. A chlorine release was used as an example of both emergency planning and an educational tool. A question arose concerning the use of averaging AEGL concentrations across time intervals vs using the specific time intervals set by the NAC.

Relevance of Developmental Endpoints
Marcel van Raaij

Marcel van Raaij stressed that developmental toxicity is a relevant endpoint for setting AEGL values. He evaluated data for single day vs multiple exposures (i.e. regular guideline based developmental studies) in order to determine which effects observed in regular guideline based studies were relevant or useful for setting acute health limits. Comparisons were made for a specific species-substance-route-effect combination. Endpoints of interest were: maternal toxicity, resorptions, fetal body weight, and malformations. For most endpoints, higher doses were required for single exposure studies to get the same effect as from a repeat dose.

It was indicated that general maternal toxicity in regular guideline studies is not a good indicator for acute effects. Resorptions can be induced in single dose studies with similar doses (or slightly higher) than those used in repeated dose studies. Fetal body weight analysis showed variable data. For some substance-species-route combination there was no difference in the NOAEL/LOAEL values between single and repeated doses while for others a substantial difference was observed (NOAEL/LOAEL about 4-5 fold higher in single dose studies). This requires a case-by-case evaluation taking into account also other developmental effects. For malformations, a similar pictures was found (no difference for some, substantial difference for others). By default, it was proposed to consider malformations as relevant endpoints for acute limit setting, unless information was available to indicate the contrary. The full report of this investigation can be downloaded from the RIVM-website (www.rivm.nl).

Review of Criteria Document of Simple Asphyxiants
Marcel van Raaij (Author)
Jonathan Borak (Chemical Manager)
George Rusch and George Rodgers (Chemical Managers)

Marcel presented highlights from his paper on simple asphyxiants (Attachment 8). The purpose is to develop criteria for handling hypoxia within the scope of AEGLs. So, the document is intended to serve as a guideline for handling the effect of asphyxia rather than handling asphyxiants per se. Discussion covered starting points, physiological response to hypoxia, susceptible populations including individuals with obstructive pulmonary and cardiovascular diseases and individuals with reduced oxygen transport capacity. Comments on susceptible populations were made (e.g. sickle cell anemia). Endpoints for hypoxia could be correlated with the arterial saturation level. Data for effects at different levels of arterial oxygen saturation were taken from high altitude physiology, air travel, and experimental observations on patients with coronary or pulmonary diseases. Levels of 80% (190,000 ppm) and 65% arterial oxygen saturation (330,000 ppm) were suggested for the AEGL-2 and -3, respectively. No AEGL-1 was proposed. It was agreed that comments could be sent to the author before August 2003. The

description of the clinical part of the document should be edited and additional attention should be paid to the 10-minute interval.

REVIEW of PRIORITY CHEMICALS

Revisit of Nickel Carbonyl AEGL-2
(CAS No. 13463-39-3)

Chemical Manager: Ernie Falke, EPA
Staff Scientist: Bob Young, ORNL

In response to concerns expressed by the COT AEGL Subcommittee, the AEGL-2 for nickel carbonyl was revisited for the second time (Attachment 9). Following earlier derivations, the COT stated that death or unknown health status of dams at the concentrations chosen as the points of departure for the AEGL-2 (1998: 8.4 ppm for the hamster, Sunderman et al. 1980; and 2002: 11 ppm for the rat Sunderman et al. 1979) precluded the contention that nickel carbonyl is a developmental toxicant (developmental toxicity was originally chosen as the AEGL-2 endpoint). Because dams died or their health status was unknown at concentrations that caused malformations, the COT stated that the data do not support the contention that nickel is a selective developmental toxin. A discussion of malformations as a toxicant endpoint as well as the relative sensitivity of the rat, mouse, and hamster for the endpoint of developmental toxicity ensued. The NAC tended to accept malformations as an AEGL endpoint. A suggestion for reducing the AEGL-3 value by 3 in order to derive an AEGL-2 value was also entertained. However, the NAC chose to use the available data rather than dividing the AEGL-3 by 3. It was moved by Bob Benson and seconded by Tom Hornshaw to use 2.17 ppm, a 30-minute non-lethal value for the mouse, the most sensitive species in lethality studies, as the point of departure for the AEGL-2. This value was divided by inter- and intraspecies uncertainty factors of 3 each for a total of 10 and a modifying factor of 3. In the absence of time-scaling data, the default n values of 3 and 1 had previously been established. The resulting values for the 10-minute through 8-hour exposure durations are 0.10, 0.72, 0.036, 0.0090, and 0.0045 ppm, respectively. The motion passed (YES: 13: NO: 3; ABSTAIN: 0) (Appendix B). The AEGL-3 values will be retained. Justification for not using the hamster data needs to be added to the TSD.

Benzene
CAS Reg. No.71-43-2

Chemical Manager: Robert Snyder,
Staff Scientist: Marcel van Raaij, RIVM, The Netherlands

The chemical revisit/review on benzene was presented by Marcel van Raaij (Attachment 10). The AEGL-1 values of benzene had been accepted at the NAC-27 meeting in December 2002. The endpoint for the AEGL-1 was absence of CNS effects in humans exposed to 110 ppm for 2 h;

there were several support studies. AEGL-1 values were 127, 73, 52, 18, and 9 ppm for 10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours respectively.

Marcel discussed studies relevant to derivation of AEGL-2 and AEGL-3 values, noting the lack of clinical studies compared with toluene. Therefore, an animal neurobehavioral study with the rat (Molnar et al. 1986) was suggested for the AEGL-2, and the same study with the endpoint of no deaths (Molnar et al. 1986) was suggested for the AEGL-3. The various indications from (old) occupational and some case studies, with exposures over 1000 ppm, was suggested to serve as a back-ground framework, although caveats are present with most of these studies. At this point there was a lengthy discussion of the quality of the monitoring studies, and how the information from these studies might be used or interpreted. In particular the usefulness of area sampling values (from historic literature) for human exposure was discussed. John Morawetz moved to remove the study of Greenberg et al. (1926, 1939) from the derivation section because the exposure duration was only 20 minutes and involved an area sample. The motion was seconded by George Alexeeff. The motion failed (YES: 7; NO: 9; ABSTAIN: 0) (Appendix C). In addition, Morawetz made comments on the description of studies by Midzenski et al. (1992) and Wong (2002), especially with respect to the derivation sections. John Hinz and George Alexeeff proposed to shorten the description of the monitoring studies in derivation sections and to refer back to the primary study summaries. After considerable discussion it was decided that reference to the human studies (which are not inconsistent with the AEGL values) in the derivation sections for AEGL-2 and AEGL-3 will be reduced as possible, and if referenced, their limitations would be clearly described in order to provide the same message in the derivation sections as in the primary study summaries.

At this point, John Hinz moved and Bill Bress seconded AEGL-2 values of 2000, 1100, 800, 400, and 200 ppm based on a 4-hour no-effect level for adverse locomotor depression (CNS-related effect) of 4000 ppm with the rat. Inter- and intraspecies uncertainty factors of 3 each for a total of 10 were applied. These uncertainty factors are adequate as higher values do not comply with the (limited) human experience (occupational exposures above 1000 ppm), and CNS depression does not vary by more than a factor of 2-3 in the human population. In addition, higher uncertainty factors would provide AEGL-values that do not match the values of toluene and xylene. Time scaling was based on n values of 2 for shorter exposure durations and 1 for longer exposure durations. The data of von Oettingen had shown that a value of 3 for the shorter exposure durations was too conservative. The motion passed (YES: 14; NO: 2; ABSTAIN: 1) (Appendix D).

A motion was made by John Hinz and seconded by Mark McClanahan to accept AEGL-3 values of 9700, 5600, 4000, 2000, and 990 ppm based on no deaths in rats exposed to 5900 ppm for 4 hours (Molnar et al. 1986). Inter- and intraspecies uncertainty factors of 1 (based on allometric arguments as evidenced by the data on toluene), and 3 (see above), respectively, were applied. Time scaling utilized n values of 2 and 1 as for the AEGL-2 above. The AEGL-values are supported by Svirbely et al. (1943). In addition, the (high) values for the 10 and 30 minutes are supported by a range of animal data. The motion passed (YES: 15; NO: 1; ABSTAIN: 1) (Appendix D).

Summary of AEGL Values for Benzene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	127 ppm	73 ppm	52 ppm	18 ppm	9 ppm	Derived earlier
AEGL–2	2000 ppm	1100 ppm	800 ppm	400 ppm	200 ppm	NOAEL, CNS effects - rat (Molnar et al. 1986)
AEGL–3	9700 ppm	5600 ppm	4000 ppm	2000 ppm	990 ppm	NOAEL for mortality in rats (Molnar et al. 1986)

Chlorine Pentafluoride
CAS No. 13637-63-3

Staff Scientist: Sylvia Talmage, ORNL
Chemical manager: Bill Bress, ASTHO

Sylvia Talmage reviewed the data base on chlorine pentafluoride, a strong oxidizing chemical once proposed for use as a rocket fuel (Attachment 11). Only animal data were available. The AEGL-3 was based on the highest 1-hour non-lethal value of 80 ppm for the rat (Darmer et al. 1972). The calculated $BMCL_{05}$ was the same value (81 ppm). The rat data were used because they provided the best dose-response relationship and because group sizes were larger for the rat than for the monkey or dog. The 80 ppm was adjusted by interspecies and intraspecies uncertainty factors of 3 each for a total of 10. Time scaling was based on the same rat lethality data which covered exposure durations from 15 minutes to 1 hour. The time-scaled exponent (n) was 2. It was moved by John Hinz and seconded by Steve Barbee to accept AEGL-3 values of 20, 11, 8, 4, and 2.8 ppm for the 10-minute through 8-hour exposure durations. The motion passed unanimously (YES: 17; NO: 0; Abstain: 0) (Appendix E).

The proposed AEGL-2 was based on a series of studies with monkeys, dogs, rats, and mice (MacEwen and Vernot 1972, 1973). Exposures were to 5 or 10 ppm for 60 minutes, 20 ppm for 30 minutes, and 30 ppm for 10 minutes. Following discussion of which series of studies to use, it was decided to use the higher value of 10 ppm at the 60-minute exposure and the respective values at the 10 and 30-minute exposures. Each of these concentrations was adjusted by interspecies and intraspecies uncertainty factors of 3 each for a total of 10. The 4- and 8-hour values were extrapolated from the 1-hour value. It was moved by John Hinz and seconded by Bob Snyder to accept AEGL-2 values of 3, 2, 1, 0.5, and 0.36 ppm for the 10-minute through 8-hour exposure durations. The motion passed (YES: 14; NO: 1; ABSTAIN: 1) (Appendix E).

The proposed AEGL-1 value was based on a NOAEL for signs of irritation in the rat (MacEwen and Vernot 1973). The TSD author suggested dividing this value by interspecies and intraspecies uncertainty factors of 10 and 3, respectively, in order to obtain a value consistent with the breakdown product, HF (AEGL-1 = 1 ppm) and the related chemical, ClF_3 (AEGL-1 = 0.12 ppm). The NAC agreed with the 3 ppm concentration, but adjusted by intraspecies and interspecies uncertainty factors of 3 each for a total of 10. The resulting 0.3 ppm was used across all exposure

durations because there is adaptation to the slight irritation that defines the AEGL-1. The motion passed (YES: 13; NO: 4; ABSTAIN: 0) (Appendix E). It was noted that the 8-hour AEGL-1 of 0.3 ppm is essentially the same value as the 8-hour AEGL-2 of 0.36 ppm.

Summary of AEGL Values for Chlorine Pentafluoride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.30 ppm	0.30 ppm	0.30 ppm	0.30 ppm	0.30 ppm	No signs of sensory irritation - rat (MacEwen and Vernot 1973)
AEGL–2	3.0 ppm	2.0 ppm	1.0 ppm	0.50 ppm	0.36 ppm	Lacrimation, salivation - monkey, rat, mouse (MacEwen and Vernot 1972)
AEGL–3	20 ppm	11 ppm	8.0 ppm	4.0 ppm	2.8 ppm	Highest non-lethal value, $BMCL_{05}$ - rat (Darmer et al. 1972)

Bromine pentafluoride
CAS No. 7789-30-2

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Bill Bress, ASTHO

Sylvia Talmage described the data base for bromine pentafluoride (Attachment 12). The data base consisted of a single lethality study with the rat, conducted at two concentrations (Dost et al. 1968, 1970). The AEGL-3 was based on the highest non-lethal value in this study, 500 ppm for 40 minutes. This concentration was divided by inter- and intraspecies uncertainty factors of 3 each for a total of 10 and time scaled using the default values for n of 3 for shorter time intervals and 1 for longer time intervals. In the absence of conflicting data, a total uncertainty factor of 10 for irritants has been acceptable to the NAC and the COT. It was moved by Bob Benson and seconded by John Hinz to accept the resulting values of 79, 55, 33, 8.3 and 4.2 ppm for the 10-minute through 8-hour exposure durations, respectively. The motion passed unanimously (YES: 16; NO: 0; ABSTAIN 0) (Appendix F).

In the absence of data for the AEGL-2, the values for chlorine pentafluoride were used. These values are acceptable as bromine pentafluoride has been shown to be less reactive and slightly less toxic than chlorine pentafluoride. Tom Hornshaw moved and Bill Bress seconded the motion that AEGL-2 values of 3.0, 2.0, 1.0, 0.50, and 0.36 ppm be accepted. The motion passed unanimously (YES: 16; NO: 0; ABSTAIN: 0) (Appendix F).

It was decided that, in the absence of data, the AEGL-1 values for bromine pentafluoride would not be set equal to the AEGL-1 values for chlorine pentafluoride. It was moved by George

Alexeeff and seconded by Nancy Kim to use NR (not recommended) for the AEGL-1 due to the absence of data. The motion passed (YES: 12; NO: 3; ABSTAIN: 2) (Appendix F). It was then moved and seconded by Richard Niemeier and Loren Koller, respectively, to add a notation below the summary table that emergency responders may refer to chlorine pentafluoride or chlorine trifluoride for AEGL-1 values. The motion did not pass (YES: 6; NO: 7; ABSTAIN: 4) (Appendix F). The NAC noted that if this chemical becomes important to some agency, it would be beneficial to have additional testing done to improve the precision of the data.

Summary of AEGL Values for Bromine Pentafluoride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR[a]	NR	NR	NR	NR	
AEGL–2	3.0 ppm	2.0 ppm	1.0 ppm	0.50 ppm	0.36 ppm	Based on analogy with chlorine pentafluoride
AEGL–3	79 ppm	55 ppm	33 ppm	8.3 ppm	4.2 ppm	Highest non-lethal value - rat (Dost et al. 1970)

NR: AEGL-1 values are not recommended due to the lack of data.

Nitric acid
CAS No. 7697-37-2

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

Carol Wood reviewed the history of and data for nitric acid (Attachment 13). Values had been adopted in 1997, but the key studies for the AEGL-2 and AEGL-3 were questionable. At the present meeting, an additional study (DuPont 1987) was made available. This study was a nose-only exposure of rats to >70% respirable particles of nitric acid; nitrogen dioxide was monitored and not detected. The AEGL-3 was based on the 1-hour LC_{01}, calculated from the LC_{50} study by log-probit analysis. The resulting 1-hour LC_{01} of 919 ppm was used to derive AEGL-3 values. Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 10- and 30-minute time points and n = 1 for the 4- and 8-hour time points. An total uncertainty factor of 10 was used including a 3 for interspecies extrapolation and 3 for intraspecies extrapolation. It was moved by Loren Koller and seconded by Richard Niemeier to accept values of 170, 120, 92, 23, and 11 ppm for the 10-minute through 8-hour exposure durations, respectively. The motion passed (YES: 12; NO: 3; ABSTAIN: 1) (Appendix G). Ernie Falke stated that the above scenario is not realistic and that nitric acid will convert to nitrogen dioxide. Therefore, the values should defer to nitrogen dioxide.

The same study (DuPont 1987) served as the basis for the AEGL-2. Discussion centered around options for the point of departure: one-third of the AEGL-3, the non-lethal value of 470 ppm, or a lower, no-effect value of 260 ppm. A concern over the presence of ulcers on the noses of confined rats was answered by a telephone call to Dave Kelly, author of the DuPont study (the ulcers were

an artifact of the exposure method). The accepted point of departure was a 1-hour exposure of rats to 470 ppm which resulted in transient body weight loss 1-2 days post-exposure. In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 10- and 30-minute time points and n = 1 for the 4- and 8-hour time points. A total uncertainty factor of 10 was used including a 3 for interspecies extrapolation and 3 for intraspecies extrapolation. In addition, a modifying factor of 2 was applied because clinical observations were not well described, a concentration-response could not be determined for nonlethal effects, and clear evidence of AEGL-2 effects was not available in the study. As supporting evidence, no effects or cancer were observed in rats exposed to 19 ppm 6 hr/day every other day for a total of 6 exposures followed by observation for 22 months. It was moved by Steve Barbee and seconded by Bob Snyder (with the provision that the NAC sees the final document) to accept values of 43, 30, 24, 6, and 3 ppm for the 10-minute through 8-hour exposure durations, respectively. The motion passed (YES: 12: NO: 2; ABSTAIN: 0) (Appendix G).

For the AEGL-1, a 30-minute through 8-hour value of 0.53 ppm had been adopted previously. The highest NOAEL in humans of 1.6 ppm for 10 minutes was used to derive AEGL-1 values. An uncertainty factor of 3 was applied to account for sensitive populations since both human and animal data suggest that asthmatics may be especially sensitive to acidic atmospheres. Extrapolations were not performed because this was based on a no-effect level and because irritation is generally concentration dependent but not time dependent. It was moved by Bob Benson and seconded by McClanahan to adopt the same value for the 10-minute exposure duration. The motion passed unanimously by a show of hands.

Summary of AEGL Values for Nitric Acid						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.5 ppm	0.5 ppm	0.5 ppm	0.5 ppm	0.5 ppm	NOAEL for irritation - humans
AEGL–2	43 ppm	30 ppm	24 ppm	6 ppm	3 ppm	Transient weight loss - rat (DuPont 1987)
AEGL–3	170 ppm	120 ppm	92 ppm	23 ppm	11 ppm	LC_{01} - rat (DuPont 1987)

Hydrogen Selenide
CAS No. 7783-07-5

Staff Scientist: Carol Wood, ORNL
Chemical manager: Robert Snyder, Rutgers University/EOHSI

Carol Wood presented the data on hydrogen selenide (Attachment 14). The AEGL-3 was based on an estimated LC_{01} of 66 ppm obtained by a log-probit analysis of data from a 1-hour LC_{50} study in Wistar rats (Zwart and Arts 1989). Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). A value of n = 2 was calculated by Zwart and Arts (1989) from a probit analysis of lethality data in the rat. A total uncertainty factor of 30 was

applied which includes 3 to account for sensitive individuals and 10 for interspecies extrapolation. The intraspecies uncertainty factor of 3 is considered sufficient due to the relatively steep concentration-response relationship with regard to lethality in rats, suggesting little individual variability. An interspecies UF of 10 is needed because data were available in only two species and the limited data available indicate that the rat is not the most sensitive. Bob Benson moved and Steve Barbee seconded the motion to accept the AEGL-3 values for the 10-minute through 8-hour exposure durations of 5.4, 3.1, 2.2, 1.1, and 0.78 ppm, respectively. The motion passed (YES: 14; NO: 1; ABSTAIN: 0) (Appendix H).

Because no data with appropriate endpoints were found, the AEGL-2 was derived by dividing the AEGL-3 by 3. The motion was made by Ernie Falke and seconded by Richard Niemeier to accept values of 1.8, 1.0, 0.73, 0.37, and 0.26 ppm. The motion passed (YES: 12; NO: 3; ABSTAIN: 1) (Appendix H).

An AEGL-1 was not recommended because no data with the appropriate endpoints were found. The motion was made by Mark McClanahan and seconded by Steve Barbee to not recommend an AEGL-1. The motion passed with a show of hands.

Summary of AEGL Values for Hydrogen Selenide						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR[a]	NR	NR	NR	NR	
AEGL–2	1.8	1.0	0.73	0.37	0.26	One-third of the AEGL-3
AEGL–3	5.4	3.1	2.2	1.1	0.78	1-hour LC_{01} - mouse (Zwart and Arts 1989)

NR: AEGL-1 values are not recommended due to the lack of data.

Methyl thiocyanate
CAS No.

Staff Scientist: Carol Wood, ORNL
Chemical Manager:

Carol Wood noted the lack of data for methyl thiocyanate, other than an intraperitoneal injection study with mice (Attachment 15). Two options were presented: (1) values should not be recommended (NR), or (2) adopt HCN values, based on the breakdown of methyl thiocyanate to HCN. However, there was no data on relative potency. It was moved by Ernie Falke and seconded by Loren Koller to not adopt values. The motion passed (YES: 12; NO: 1; ABSTAIN: 1) (Appendix I). The chemical will not be forwarded to the National Academy of Sciences.

Bromine trifluoride
CAS No. 7787-71-5)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Bill Bress, ASTHO

In the absence of any data, Sylvia Talmage proposed using the AEGL values for the chemical analogue, chlorine trifluoride (Attachment 16). Information on chemical reactivity and toxicity shows that bromine fluorides are less reactive and less toxic than chlorine fluorides. Therefore, using the chlorine trifluoride values, which are based on empirical data, would be conservative. The chlorine trifluoride values were based on studies with rats and dogs in which slight irritation (Horn and Weir 1956), severe irritation (Horn and Weir 1955), and the LC_{01} for the mouse (MacEwen and Vernot 1970), were endpoints for the AEGL-1, -2, and -3, respectively. It was moved by Ernie Falke and seconded by Mark McClanahan to adopt the chlorine trifluoride values for bromine trifluoride. The motion passed (YES: 14; NO: 1; ABSTAIN: 0) (Appendix J). The values appear in the table below. The NAC suggested adding a caveat to the TSD to the effect that, if the chemical becomes important, additional testing be done.

Summary of AEGL Values for Bromine Trifluoride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.12 ppm	0.12 ppm	0.12 ppm	0.12 ppm	0.12 ppm	Analogy with chlorine trifluoride
AEGL–2	6.20 ppm	6.2 ppm	3.1 ppm	0.77 ppm	0.39 ppm	Analogy with chlorine trifluoride
AEGL–3	81 ppm	27 ppm	14 ppm	3.4 ppm	1.7 ppm	Analogy with chlorine trifluoride

Revisit of Formaldehyde AEGL-1 and Time-Scaling of AEGL-3
CAS No. 50-00-0

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

The AEGL-1 value of 0.41 ppm, passed at the NAC-28 meeting, was reconsidered because the study on which the value was based was flawed (Attachment 17). Sylvia Talmage pointed out that not only did the study authors find irritation at levels not irritating in approximately 20 other well-conducted clinical studies, but the authors did not take analytical measurements. Following review of the clinical studies, there was a debate as to the perception of mild vs moderate irritation. Sylvia Talmage suggested using 3 ppm for the AEGL-1, based on an average irritation score of mild in over 100 subjects. It was moved by Bob Benson and seconded by Steve Barbee to use the NOAEL for slight irritation of 0.9 ppm for the AEGL-1. This was the highest exposure of subjects whose eyes were sensitive to formaldehyde at which the subjects' "responses were not significantly different from clean air" (Bender et al. 1983). At 1 ppm there was slight to moderate

eye irritation. Exposures were eye-only for 6 minutes. The 0.9 ppm was used across all exposure durations. The motion passed (YES: 11; NO: 3; ABSTAIN: 0) (Appendix K).

At the NAC-28 meeting, time scaling for the AEGL-3 was based on two LC_{50} values for the rat. The value of n was 3.9. In the meantime, another LC_{50} study was located. Sylvia Talmage presented graphs of the n values using the rat and mouse data separately and combined. The value of n ranged from 1.4 (mouse data) to 2.4 (rat data). However, based on the age of the studies and flaws in most of the studies, the default n values of 3 and 1 appeared appropriate. The point of departure remained the same, a 4-hour non-lethal value of 350 ppm for the rat (Nagorny et al. 1979). The adjusted 10-minute to 8-hour values were 100, 70, 56, 35, and 35 ppm, respectively (the 8-hour value was set equal to the 4-hour value because formaldehyde is well scrubbed in the nasal passages). It was moved by Mark McClanahan and seconded by Ernie Falke to accept the adjusted values. The motion passed (YES: 11; NO: 1; ABSTAIN: 2) (Appendix K).

Administrative Matters

The site and time of the next meeting, NAC/AEGL-30, will be September 16-18, 2003 in Washington. D.C. The date for NAC/AEGL-31 has been set tentatively as December 10-12, 2003 in San Antonio, Texas. John Hinz will provide more details on the December meeting.

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by 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. Chemical Manager sheet
Attachment 2. Status update of chemicals to be considered at the NAC-30 and -31
Attachment 3. NAC/AEGL-29 Meeting Agenda
Attachment 4. NAC/AEGL-29 Attendee List
Attachment 5. Revised Proposal for Evaluation of Occupational Monitoring Studies for inclusion in TSDs
Attachment 6. Evaluation of Data for LOAEL to NOAEL Extrapolation
Attachment 7. Categorizing the Signs and Symptoms at the AEGL sub-1, 1, and 2 Levels
Attachment 8. Criteria for Simple Asphyxiants
Attachment 9. Data Analysis of Nickel Carbonyl
Attachment 10. Data Analysis of Benzene
Attachment 11. Data Analysis of Chlorine Pentafluoride
Attachment 12. Data Analysis of Bromine Pentafluoride
Attachment 13. Data Analysis of Nitric Acid
Attachment 14. Data Analysis of Hydrogen Selenide
Attachment 15. Data Analysis of Methyl Thiocyanate
Attachment 16. Data Analysis of Bromine Trifluoride
Attachment 17. Data Analysis of Formaldehyde

LIST OF APPENDICES

Appendix A. Revised meeting highlights of NAC/AEGL-28
Appendix B. Ballot for nickel carbonyl
Appendix C. Ballot for omitting human studies in benzene derivation
Appendix D. Ballot for benzene
Appendix E. Ballot for chlorine pentafluoride
Appendix F. Ballot for bromine pentafluoride
Appendix G. Ballot for nitric acid
Appendix H. Ballot for hydrogen selenide
Appendix I. Ballot for methyl thiocyanate
Appendix J. Ballot for bromine trifluoride
Appendix K. Ballot for formaldehyde

The following are suggestions of information to be recorded by chemical managers at the NAC AEGL meetings. At the conclusion of deliberations for each chemical, notes will be retrieved and copied. The original will be returned to the chemical manager and the copy will be given to one of the ORNL scientists. Please keep all copies, including values that are not approved. These notes are important for meeting summaries and any revisions needed in the Technical Support Documents.)

CHEMICAL:_____ AEGL TIER: 1 2 3

CHEMICAL MANAGER:_____ STAFF SCIENTIST:_____

Major issues and highlights from discussion and action items.(use additional pages as needed):

Attachment 1

Key Reference	
Critical effect	
Rationale for Critical Effect	
Point of Departure	Duration = Exposure concentration =
Rationale for point of departure	
Interspecies UF	Interspecies UF = Rationale =
Intraspecies UF	Intraspecies UF = Rationale =
Modifying Factor (MF)	Moidfying factor MF = Rationale =
Total UF	Total UF including MF = Rationale for total UF if other than multiplying UFs & MF
Value(s) of the exponent 'n' used for time scaling and how it was derived	n = How was n derived =

NAC-30 September 03

CAS-NO	ChemicalName	PlanningByActivity	Status	Author	Chemical Manager
71-55-6	1,1,1-trichloroethane	NAC-30 Sep03 Recycle PBPK ??? NAS-13	Interim-NAS ??? Status	Talmage	McClanahan
75-86-5	Acetone cyanohydrin	FR-07 & NAC-30 & NAS-13 New	Proposed	Griem	Gephart
75-05-08	Acetonitrile	NAC-30 Sep03 New	Draft in preparation	Bast	Rodgers
7664-41-7	Ammonia	FR-07 & NAC-30 & NAS-13 New	Proposed	Davidson	Gephart
7726-95-6	Bromine	FR-07 & NAC-30 & NAS-13 New	Proposed	Talmage	Post
106-97-8	Butane	NAC-30 Sep03 New	Planning	The Netherla	Gephart
107-14-2	Chloroacetonitrile	NAC-30 Sep03 New	Planning	ORNL	Rodgers
77-78-1	Dimethylsulfate	NAC-30 Sep03 New	Planning	Germany	Snyder
10025-67-9	Disulfur dichloride	NAC-30 Sep03 New	Planning	Davidson	McClanahan
7782-41-4	Fluorine	FR-07 & NAC-30 & NAS-13 Return	Interim-NAS-Comment	Talmage	Falke
78-82-0	Isobutyronitrile	NAC-30 Sep03 Revisit ???	Interim-NAS ??? Status	Bast	Rodgers
8008-20-6	Jet Fuel 8	FR-07 & NAC-30 & NAS-13 New	Proposed	Talmage	Hinz
70892-10-3	Jet Fuels (JP-5 & JP-8)	FR-07 & NAC-30 & NAS-13 New	Proposed	Talmage	Hinz
109-77-3	Malonoitrile	NAC-30 Sep03 New	Planning	ORNL	Rodgers
78-93-3	Methyl ethyl ketone	FR-07 & NAC-30 & NAS-13 New	Proposed	Talmage	McClanahan
75-09-2	Methylene chloride	NAC-30 Sep03 Wait on NAS CO comments & Valida	Draft	Bos	Benson
79-11-8	Monochloroacetic acid	FR-07 & NAC-30 & NAS-13 New	Proposed	Griem	Falke
10025-87-3	Phosphorus oxychloride	FR-07 & NAC-30 & NAS-13 New	Proposed	Young	Hornshaw
7719-12-2	Phosphorus trichloride	FR-07 & NAC-30 & NAS-13 New	Proposed	Young	Hornshaw
74-98-6	Propane	NAC-30 Sep03 New	Planning	The Netherla	Gephart
107-12-0	Proprionitrile	NAC-30 Sep03 New	Interim-NAS ??? Status	Bast	Rodgers
100-42-5	Styrene	NAC-30 Sep03 New	Planning	Germany	Barbee
10545-99-0	Sulfur dichloride	NAC-30 Sep03 New	Planning	Davidson	McClanahan
127-18-4	Tetrachloroethylene	NAC-30 Sep03 Recycle PBPK ??? NAS-13	Interim-NAS-Comment	Troxel	Bress
1330-20-7	Xylenes	FR-07 & NAC-30 & NAS-13 New	Proposed	Troxel	Koller

Attachment 2

NAC-31 December 03

CAS-NO	ChemicalName	PlanningByActivity	Status	Author	Chemical Manager
75-36-5	Acetyl chloride	NAC-31 Dec03 New	Planning	Milanez	McClanahan
107-13-1	Acrylonitrile	NAC-31 Dec03 New	Draft in preparation	Bast	Rodgers
100-47-0	Benzonitrile	NAC-31 Dec03 New	Planning	Bast	Rodgers
106-99-0	Butadiene	NAC-31 Dec03 New	Planning	The Netherla	Gephart
79-04-9	Chloroacetyl chloride	NAC-31 Dec03 New	Planning	Milanez	McClanahan
110-54-3	Hexane	NAC-31 Dec03 New	Planning	The Netherla	Gephart
126-98-7	Methacrylonitrile	NAC-31 Dec03 Revisit ???	Interim-NAS ??? Status	Bast	Rodgers
74-83-9	Methyl bromide	NAC-31 Dec03 New	Planning	Talmage	Rodgers
74-87-3	Methyl chloride	NAC-31 Dec03 New	Planning	Talmage	Rodgers
8014-95-7	Oleum	NAC-31 Dec03 New	Remaining-Priority list 1	The Netherla	Koller
7446-11-9	Sulfur trioxide	NAC-31 Dec03 New	Remaining-Priority list 1	The Netherla	Koller
7664-93-9	Sulfuric acid	NAC-31 Dec03 New	Remaining-Priority list 1	The Netherla	Koller
76-02-8	Trichloroacetyl chloride	NAC-31 Dec03 New	Planning	Milanez	McClanahan
108-05-4	Vinyl acetate monomer	NAC-31 Dec03 New	Draft in preparation	Troxel	Thomas

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-29
June 17-19, 2003

US Department of Labor
200 Constitution Ave., N.W., Rm. N.3437-B,C,D.
Washington DC 20210

Metro Subway Judiciary Square (Red Line)

AGENDA

Tuesday, June 17, 2003

10:00 a..m.	Introductory remarks and approval of NAC/AEGL-28 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
10:15	Revisit Industrial Hygiene Principles: points 3, 4, and 5 (John Morawetz)
10:45	Industrial hygiene/emergency planning considerations in AEGL development (Edward Bishop)
11:30	Deriving an uncertainty factor for LOAEL to NOAEL extrapolation (George Alexeeff)
12:00 noon	Lunch
1:00	Categorizing the signs and symptoms at the AEGL: sub-1,1,and 2 levels (George Alexeeff)
1:30	Report on LOA data quality and presentation in the TSD (Mark McClanahan/Marc Ruijten)
2:30	Revisit of Nickel carbonyl AEGL-2 (Ernie Falke/Bob Young)
3:00	Break
3:15	Revisit of Benzene (Bob Snyder/Marcel T.M. van Raaij)
5:30	Adjourn for the day

Wednesday, June 18, 2003

8:00 a.m.	Review of Nitric acid (Loren Koller/Carol Wood)
9:45	Break
10:00	Overview and demonstration of EPA/NOAA-CAMEO system (Armando Santiago)
11:00	AEGL application in emergency planning (Bob Snyder)
11:45	Limitations on application of AEGL values (George Rusch)
12:00 noon	Lunch
1:00	Review of Chlorine pentafluoride (Bill Bress/Sylvia Talmage)
2:15	Review of Bromine pentafluoride (Bill Bress/Sylvia Talmage)
3:00	Break
3:15	Review of Hydrogen selenide (Bob Snyder/Carol Wood)
4:30	Review of Bromine trifluoride (Bill Bress/Sylvia Talmage)
5:00	Adjourn for the day

Thursday, June 19, 2003

8:00 a.m.	Review of Methyl thiocyanate (Loren Koller/Carol Wood)
8:30	Revisit of Formaldehyde AEGL-1 (Mark McClanahan/Sylvia Talmage)
9:30	Review of Criteria Document of Simple Asphyxiants (Jonathan Borak/Marcel T.M. van Raaij)
10:15	Break
10:30	Review of Criteria Document of Simple Asphyxiants (continued)
11:00	Review of Hydrogen iodide (Mark McClanahan/Sylvia Talmage)
11:45	Administrative matters
12:00 noon	Adjourn meeting

NAC/AEGL Meeting 29: June 16-18, 2003

List of Attendees

	NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL2	AEGL3	LOA
(1)	George Alexeeff	N	(P)	Y	(10)	Nancy Kim	Y	Y	Y	
(2)	Steven Barbee	Y	Y	Y	(11)	Loren Koller	Y	Y	Y	
(3)	Lynn Beasley	Y	Y	Y	(12)	Glenn Leach	Y	Y	Y	
	David Belluck	A	A	A	(13)	Mark McClanahan	N	N	Y	
(4)	Robert Benson	Y	Y	Y	(14)	John Morawetz	N	Y	Y	
	Jonnthan Borak	A	A	A	(15)	Richard Niemeier	Y	N	Y	
(5)	William Bress	Y	Y	Y		Marinelle Payton	A	A	A	
	George Cushmac	A	A	A		Zarena Post	A	A	A	
	Al Dietz	A	A	A		George Rodgers	A	A	A	
(6)	Ernest Falke	Y	Y	Y	(16)	George Rusch, Chair	Y	Y	Y	
	Larry Gephart	A	A	A	(17)	Robert Snyder	Y	Y	Y	
(7)	John Hinz	Y	Y	Y		Thomas Sobotka	A	A	A	
(8)	Jim Holler	Y	Y	Y		Kenneth Still	A	A	A	
(9)	Thomas Hornshaw	N	Y	Y		Richard Thomas	A	A	A	
						TALLY	13/17	14/16	17/17	

DFO: Paul S. Tobin Date: 6/18/03

Revised version after AEGL–28 meeting, March, 2003

To incorporate these points in the SOP, the following language should be added to the SOP's Evaluation section.

In using occupational studies,

1) Breathing zone samples are the preferred estimate of workers' exposures since it most accurately reflects the air that workers breath in.

2) All occupational monitoring results should clearly describe their measurement type (such as breathing zone, area/general workplace, bulk sample or theoretical calculation from bulk sample) and sampling duration (instantaneous, short term, full shift).

3) General workplace, bulk samples and theoretical calculations from bulk samples by their collection methods are designed to collect measurements that are fundamentally different from breathing zone samples. They should only be utilized in the AEGL derivation sections if there is substantial documentation on workers tasks, their relationship to these samples and the reliability of the methodology.

4) Breathing zone short term samples should clearly state the sampling duration and be used primarily for the sampled time period.

5) Exposure assessments from a single workplace in a multiple workplace study should clearly state the number of worksites that found any specific exposure levels. This should include the number, duration, types of measurements and relationship of workers tasks to these samples.

Deriving an Uncertainty Factor for LOAEL to NOAEL Extrapolation

NAC/AEGL-29

June 17, 2003

George V. Alexeeff, Ph.D., D.A.B.T.
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Purpose of Analysis

- Improve our understanding of the uncertainty in acute inhalation risk assessment
- Evaluate what type of uncertainty factor (UF) should be used to extrapolate from a LOAEL to a NOAEL for mild health effects
- Published in Regulatory Toxicology and Pharmacology 36:96-105 (2002)

Study Design

- Focused on mild acute inhalation effects
- Considered all available articles and studies on 40 Hazardous Air Pollutants (HAPs)
- Identified LOAELs and NOAELs in the studies and calculated their ratios.

Substances Considered

- Acetaldehyde
- Acrolein
- acrylic acid
- Aniline
- Benzene
- benzyl chloride
- carbon tetrachloride
- Chlorine
- Chloroform
- chloromethyl methyl ether
- dimethylhydrazine(1,1-)
- dioxane(1,4-)
- Epichlorohydrin
- epoxybutane(1,2-)
- ethylene oxide
- Formaldehyde
- hydrazine *
- hydrogen chloride
- hydrogen fluoride
- Methanol
- methyl bromide
- methyl chloroform
- methyl ethyl ketone *
- methyl hydrazine
- methyl isocyanate
- methylene chloride
- nickel chloride
- perchloroethylene
- phenol
- phosgene
- phosphine
- propylene oxide *
- propylenelmine *
- styrene
- toluene
- toluene diisocyanate(2,4-)
- trichloroethylene
- triethylamine
- vinyl chloride
- xylenes (m,o,p-isomers)

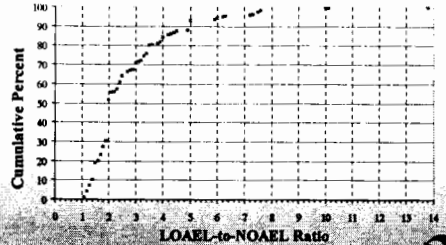
Some Signs and Symptoms Identified

- Conjunctival irritation, eye irritation, lacrimation.
- G6PD decrease, methemoglobinemia, hemoglobin level and hematocrit decreases.
- Bacterial infectivity increase, cell proliferation.
- Behavioral change, headache, slightly heady.
- Cough urge, respiratory irritation, upper airway symptoms, airway resistance changes.

Data Analysis Results

- **Identified 215 data sets for 36 substances**
- **Ratios ranged from 1.1 to 13.8**
- **The median was 2.0**
- **The 95th percentile was 6.3 (5.0-7.5)**
- **Results not affected by species, group size, exposure duration or endpoint.**

Cumulative Comparison



Summary of Results by Species

Species	Mean	50th %ile	95th %ile	99th %ile	Range
Human (62)	2.8	2.0	5.0	13.8	1.2-13.8
Mouse (43)	2.7	2.0	7.6	10.1	1.1-10.1
Rat (82)	2.9	2.0	7.3	10.0	1.2-10.0
Other (28)	2.8	2.5	5.0	6.2	1.1-6.2
TOTAL (215)	2.8	2.0	6.3	10.0	1.1-13.8

Summary of Results by Endpoint

Endpoint Category	Mean	50th %ile	95th %ile	99th %ile	Range
Alimentary (31)	3.1	2.1	7.6	10.0	1.3-10.0
Eyes (36)	3.3	2.5	6.3	13.8	1.3-13.8
Nervous (56)	2.1	1.7	5.0	7.3	1.1-7.3
Respiratory (88)	2.9	2.2	7.2	13.8	1.1-13.8
Other (22)	3.5	2.3	10.0	10.1	1.4-10.1
TOTAL (233)					1.1-13.8

Conclusions/Observations

- Treating a LOAEL as a NOAEL, likely overestimates the no effect level 2 to 6 fold.
- Using 2 to estimate a NOAEL from a LOAEL, is likely correct 50% of the time
- Using 6 to estimate a NOAEL from a LOAEL, is likely correct 95% of the time.
- Eye and respiratory irritation require UFs similar to the nervous system, etc.

Categorizing the signs and symptoms at the AEGL: sub-1, 1, and 2 levels

NAC/AEGL-29

June 17, 2003

George V. Alexeeff, Ph.D., D.A.B.T.
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Office of Environmental Health Hazard Assessment

Purpose of Analysis

- To clarify the signs and symptoms used to establish various AEGL levels
- To help identify inconsistencies in our evaluations.
- To improve communication and understanding of the basis for establishing AEGL levels.
- To help distinguish the basis for AEGLs in contrast to non-emergency guidelines.

Office of Environmental Health Hazard Assessment

Study Design

- Reviewed 83 AEGL documents.
- Evaluated the basis for the AEGL Levels as described in the Summary, Rationale and Derivation sections.
- Determined whether the description indicated the described effect occurred that level, a lower level or a higher level.

Office of Environmental Health Hazard Assessment

Study Design (continued)

- Only included effects if they could be attributed to a specific AEGL level.
- Prepared a speadsheet including level, chemical, level, effect associated with that level.
- Communicated with Oak Ridge staff for clarification.

Office of Environmental Health Hazard Assessment

Study Design (continued)

- Provided table for review by subcommittee.
- Condensed table by AEGL level
- Provided Table for review by subcommittee.

Office of Environmental Health Hazard Assessment

Example of Initial Spreadsheet

Chemical	Health Effects Associated with the AEGL Level 1*
1,2-Dichloroethylene (cis, trans)	eye irritation in humans
Acetone Cyanohydrin	irritative effects observed in rats; red nasal discharge in rats

Office of Environmental Health Hazard Assessment

Sub-AEGL-1 Health Effects in Humans

- Odor detection; odor perception; no to low sensory irritation; eye irritation; slight eye irritation; mild eye irritation; slight burning of the eyes; rhinitis; fine injection across exposed bulbar conjunctiva; lacrimation in one of six exposed; slight headache; chest tightness; chest tightness or labored breathing in exercising asthmatics; throat and nose irritation; slight nose and throat irritation;

Sub-AEGL-1 Health Effects in Humans (cont.)

- severe eye and throat irritation in one of six exposed; cough, dyspnea; increased airway resistance in asthmatics; slight nausea; nervousness; slight dizziness; feeling of intoxication; reeling; swimming head; confusion; changes in visual perception and manual dexterity, tendency to prolonged reaction time; CNS depression in one of eight subjects; sleepiness; decrease in pulse rate; weakness; moderate fatigue;

Sub-AEGL-1 Health Effects in Humans (cont.)

- fullness in the head; mild or slight headache; headache; increased subjective symptoms; 50% increase in blood acetaldehyde level; increase in the percentage of CD3 cells and myeloperoxidase in bronchial portion of bronchiolar alveolar lavage.

Sub-AEGL-1 Health Effects in Animals

- Lacrimation in rats; nasal discharge in dogs; pulmonary hyperplasia, broncheotracheal squamous metaplasia in rats.

AEGL-1 Health Effects in Humans

- Eye irritation; miosis; decline in perceptual acuity; photophobia[2]; mucous membrane irritation; rhinorrhea; skin irritation; mild irritation; respiratory tract irritation, urge to cough; changes in pulmonary function; tightness in chest; dyspnea[2]; increased pulse and respiratory rates[2]; burning sensation in the nose and chest[2], mild bronchoconstriction in exercising asthmatics;

AEGL-1 Health Effects in Humans (cont.)

- moderate to severe, but reversible, respiratory response (increased airway resistance of 102% ~ 580%) in exercising asthmatics[2]; serious asthmatic-like symptoms and pulmonary function changes[2]; sputum production in humans[2]; nausea; vomiting[2]; headache; subjective complaints; nausea; slight dizziness; change in neurobehavioural function; severe headaches and dizziness[2]; increase in simple reaction time in humans[2];

AEGL-1 Health Effects in Humans (cont.)

- CNS depression[2]; decrease in time to onset of angina pectoris during physical exercise at 4 % COHb[2]; 60% RBC-CHE inhibition in humans[2].

AEGL-1 Health Effects in Animals

- Irritation in rats; reversible irritation effects in dogs[2]; red nasal discharge in rats; Slight lacrimation/ lacrimation in rats, dogs; rhinorrhea in dogs; eye blinking in dogs; slight salivation/salivation in rats, dogs; slight red ocular discharge in rats; partially closed eyes of rats; skin flushing and swollen eyes in monkeys; histopathological changes of the nasal epithelium of rats; labored breathing in rats;

AEGL-1 Health Effects in Animals (cont.)

- minor perivascular edema and increased protein and LDH in lavage fluid in rats; focal subacute interstitial pneumonia in rats; increase in lung weights in rats; inflammatory epithelial degeneration in the bronchioles in rats; bronchiolar edema in rats[2]; lesions of the nasal transitional epithelium in rats (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, and mild apoptosis)[2]; perivascular edema, and cellular infiltration[2];

AEGL-1 Health Effects in Animals (cont.)

- chemical pneumonia in rats[2]; reversible kidney tubular pathology in dogs; light cloudy kidney swelling in rats[2]; increased but reversible hepatocyte hypertrophy in rats; 2-3 fold increase in serum activities of liver enzymes in rats; poor coordination (reversible equilibrium disturbances) in rats[2]; slight central nervous system depression in monkeys evident by a change in brain wave activity[2]; slightly lethargy in rats, interpreted as an effect on the central nervous system[2];

AEGL-1 Health Effects in Animals (cont.)

- cardiovascular lesions in rats including scattered myofibril fragments with loss of striation; cardiac arrhythmia in dogs; fetal growth retardation in rats manifested by a statistically significant decrease in fetal weight and non-statistically significant increase in the incidence of delayed ossification[2]

AEGL-2 Health Effects in Humans

- Severe irritation; unbearable irritation; soreness, widespread conjunctivitis, photophobia, and chemosis, necessitating medical treatment; dyspnea; lung congestion; intolerance to exposure; significant increase in the frequency of exercise-induced arrhythmias; dizziness; light-headedness lethargy, and reduced neurobehavioural performance in humans; escape impairment.

AEGL-2 Health Effects in Animals

- Significant irritation in mice; impaired pulmonary function (manifest as a 20-40% reduction in carbon monoxide and ether uptake rates compared to pre-exposure value) in rats; bronchiole lesions in rats; increased secretory response in rats; respiratory distress in rats; dyspnea in rats; severe respiratory effects in rats; gray areas on lungs; histopathology including severe necrotizing rhinitis, turbinate necrosis,

AEGL-2 Health Effects in Animals (cont.)

- thrombosis of nasal submucosa vessels (nose breathers) and severe ulcerative tracheitis accompanied by necrosis and luminal ulceration (mouth breathers) in rats; lung effects include small increases in myeloperoxidase and polymorphonuclear leukocytes in the BAL of rats; histologic changes in the trachea of rats; respiratory difficulty impairing escape in guinea pigs; pallor in rats; hair coat stains, pulmonary edema, increased mucous secretions,

AEGL-2 Health Effects in Animals (cont.)

- alveolitis, or interstitial fibroplasia in rats; reversible lacrimation, corneal opacity, rales, gasping, and nasal discharge in rats; corneal opacity; ocular opacity; irreversible ocular lesions in rats; dark red material in anterior chamber/inner cornea of the eye in rats; cardiac sensitization in dogs; cardiac arrhythmias in rats; alopecia in rats; hunched posture in rats; CNS depression as evidenced by reduced activity in rats thought to impair escape; impaired escape in dogs;

AEGL-2 Health Effects in Animals (cont.)

- attention deficits in monkeys; incapacitation in monkeys; ataxia in rats; narcosis in rats; signs of stress, discomfort, limb rigidity, tremors, agitation in beagles after adrenalin challenge; weakness in rats; shallow breathing and hypoactivity in mice; clear lethargy effects in rats; gait disturbances in rats; hyperexcitability or somnolence in rats[2]; muscle spasms and a slight loss of coordination within 4 hours and tremors and prostration in rats;

AEGL-2 Health Effects in Animals (cont.)

- necrotic and swollen paws in rats; significant increase in cervical ribs, exencephaly, or cleft palate in mice; increased resorptions or a decrease in live fetus per litter in rats; maternal or fetal toxicity in rats; decreased fetal body weight in rats; increased number of dead rat pup fetuses at birth; significant increased malformations, increased proportions of litters with malformed fetuses, and serious cavity hemorrhage in hamster offspring; 5 % lethality in orally cannulated rats.

Observations

- Describing an effect level as a "threshold" is not very helpful when trying to determine if an effect is occurring.
- In many cases our deliberations and documents have not always been very clear on what the effect is or if the effect is occurring at, below or above a specific level.

Draft

Health Effects Associated with Specific Acute Emergency Guidance Levels[1]

Sub-AEGL-1 Health Effects	In humans: Odor detection; odor perception; no to low sensory irritation; eye irritation; slight eye irritation; mild eye irritation; slight burning of the eyes; rhinitis; fine injection across exposed bulbar conjunctiva; lacrimation in one of six exposed; slight headache; chest tightness; chest tightness or labored breathing in exercising asthmatics; throat and nose irritation; slight nose and throat irritation; severe eye and throat irritation in one of six exposed; cough, dyspnea; increased airway resistance in asthmatics; slight nausea; nervousness; slight dizziness; feeling of intoxication; reeling; swimming head; confusion; changes in visual perception and manual dexterity, tendency to prolonged reaction time; CNS depression in one of eight subjects; sleepiness; decrease in pulse rate; weakness; moderate fatigue; fullness in the head; mild or slight headache; headache; increased subjective symptoms; 50% increase in blood acetaldehyde level; increase in the percentage of CD3 cells and myeloperoxidase in bronchial portion of bronchiolar alveolar lavage. In animals: Lacrimation in rats; nasal discharge in dogs; pulmonary hyperplasia, broncheotracheal squamous metaplasia in rats.

AEGL-1 Health Effects	In humans: Eye irritation; miosis; decline in perceptual acuity; photophobia[2]; mucous membrane irritation; rhinorrhea; skin irritation; mild irritation; respiratory tract irritation, urge to cough; changes in pulmonary function; tightness in chest; dyspnea[2]; increased pulse and respiratory rates[2]; burning sensation in the nose and chest[2], mild bronchoconstriction in exercising asthmatics; moderate to severe, but reversible, respiratory response (increased airway resistance of 102% ~ 580%) in exercising asthmatics[2]; serious asthmatic-like symptoms and pulmonary function changes[2]; sputum production in humans[2]; nausea; vomiting[2]; headache; subjective complaints; nausea; slight dizziness; change in neurobehavioural function; severe headaches and dizziness[2]; increase in simple reaction time in humans[2]; CNS depression[2]; decrease in time to onset of angina pectoris during physical exercise at 4 % COHb[2]; 60% RBC-CHE inhibition in humans[2]. In animals: Irritation in rats; reversible irritation effects in dogs[2]; red nasal discharge in rats; Slight lacrimation/ lacrimation in rats, dogs; rhinorrhea in dogs; eye blinking in dogs; slight salivation/salivation in rats, dogs; slight red ocular discharge in rats; partially closed eyes of rats; skin flushing and swollen eyes in monkeys; histopathological changes of the nasal epithelium of rats; labored breathing in rats; minor perivascular edema and increased protein and LDH in lavage fluid in rats; focal subacute interstitial pneumonia in rats; increase in lung weights in rats; inflammatory epithelial degeneration in the bronchioles in rats; bronchiolar edema in rats[2]; lesions of the nasal transitional epithelium in rats (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, and mild apoptosis) [2]; perivascular edema, and cellular infiltration[2]; chemical pneumonia in rats[2]; reversible kidney tubular pathology in dogs; light cloudy kidney swelling in rats[2]; increased but reversible hepatocyte hypertrophy in rats; 2-3 fold increase in serum activities of liver enzymes in rats; poor coordination (reversible equilibrium disturbances) in rats[2]; slight central nervous system depression in monkeys evident by a change in brain wave activity[2]; slightly lethargy in rats, interpreted as an effect on the central nervous system[2]; cardiovascular lesions in rats including scattered myofibril fragments with loss of striation; cardiac arrhythmia in dogs; fetal growth retardation in rats manifested by a statistically significant decrease in fetal weight and non-statistically significant increase in the incidence of delayed ossification[2].

AEGL-2 Health Effects	In humans: Severe irritation; unbearable irritation; soreness, widespread conjunctivitis, photophobia, and chemosis, necessitating medical treatment; dyspnea; lung congestion; intolerance to exposure; significant increase in the frequency of exercise-induced arrhythmias; dizziness; light-headedness lethargy, and reduced neurobehavioural performance in humans; escape impairment. In animals: Significant irritation in mice; impaired pulmonary function (manifest as a 20-40% reduction in carbon monoxide and ether uptake rates compared to pre-exposure value) in rats; bronchiole lesions in rats; increased secretory response in rats; respiratory distress in rats; dyspnea in rats; severe respiratory effects in rats; gray areas on lungs; histopathology including severe necrotizing rhinitis, turbinate necrosis, thrombosis of nasal submucosa vessels (nose breathers) and severe ulcerative tracheitis accompanied by necrosis and luminal ulceration (mouth breathers) in rats; lung effects include small increases in myeloperoxidase and polymorphonuclear leukocytes in the BAL of rats; histologic changes in the trachea of rats; respiratory difficulty impairing escape in guinea pigs; pallor in rats; hair coat stains, pulmonary edema, increased mucous secretions, alveolitis, or interstitial fibroplasia in rats; reversible lacrimation, corneal opacity, rales, gasping, and nasal discharge in rats; corneal opacity; ocular opacity; irreversible ocular lesions in rats; dark red material in anterior chamber/inner cornea of the eye in rats; cardiac sensitization in dogs; cardiac arrhythmias in rats; alopecia in rats; hunched posture in rats; CNS depression as evidenced by reduced activity in rats thought to impair escape; impaired escape in dogs; attention deficits in monkeys; incapacitation in monkeys; ataxia in rats; narcosis in rats; signs of stress, discomfort, limb rigidity, tremors, agitation in beagles after adrenalin challenge; weakness in rats; shallow breathing and hypoactivity in mice; clear lethargy effects in rats; gait disturbances in rats; hyperexcitability or somnolence in rats[2]; muscle spasms and a slight loss of coordination within 4 hours and tremors and prostration in rats; necrotic and swollen paws in rats; significant increase in cervical ribs, exencephaly, or cleft palate in mice; increased resorptions or a decrease in live fetus per litter in rats; maternal or fetal toxicity in rats; decreased fetal body weight in rats; increased number of dead rat pup fetuses at birth; significant increased malformations, increased proportions of litters with malformed fetuses, and serious cavity hemorrhage in hamster offspring; 5 % lethality in orally cannulated rats.

[1] Most effects identified were not achieved with the starting point selected for AEGL-1 calculation. In those cases where the effect was achieved, the starting point reflected incorporation of a modifying factor to estimate the NOEL for the effect of concern.
[2]The effects were identified when establishing an AEGL-2. The effects were considered to be the NOEL for AEGL-2 effects. Consequently, they reflect AEGL-1 effects that are below AEGL-2 effects.

Attachment 8

Criteria for simple asphyxiants. A discussion paper.

Author: Marcel van Raaij
CM: Jonathan Borak
CR: George Rusch, George Rodgers

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Starting points

- Simple asphyxiant:
  - A substance that has as (one of its) major health hazards, the displacement of oxygen in air causing environmental hypoxia.
- Examples: Methane, Propane, Butane, N_2, He, Ar.
- When asphyxia is a relevant endpoint, health effects are induced primarily by the environmental hypoxia encountered.
- In order to handle this issue consistently, criteria should be developed how to handle hypoxia wihtin the scope of the AEGL's

Starting points - 2

- NL agreed to develop criteria document for asphyxia
- It should be short but focussed document clarifying the issue of environmental hypoxia and how to handle it for AEGL's
- It should be a basis for discussion within NAC/AEGL (and COT ?)
- The hypoxia levels coupled to the AEGL-tiers provide consistent benchmarks for any substance.

Physiological response to hypoxia

- Respiration in primarily regulated by PaCO2.
- When oxygen pressure falls further, also PaO2 has a role
- Oxygen transported by Hemoglobin (dissociation curve)
- Upon hypoxia:
  - Increased ventilation
  - Increased cardiac output
  - Redistribution of blood flow (to vital organs, eg. Brain)
- Most sensitive tissues: Brain and heart.

Susceptible populations

- People with pulmonary disease
  - obstructive lung diseases
  - reduced diffusion capacity (emphysema, edema, fibrosis)
- People with cardiovascular diesease
  - Isschemic/coronary heart disease
- People with reduced oxygen transport capacity
  - anemia
  - sickle cell disease

- Probably people with reduced diffusion capacity most susceptible.
- Most important consequence is reduced scope for activity.

How to handle the problem

1. Basic problem is tissue (brain) oxygenation
2. Oxygen delivery is taken as starting point
3. A suitable parameter for oxygen delivery is the arterial oxygen saturation level (SaO2)
4. Define SaO2 levels that induce health effects compatible with AEGL-tiers.
5. Calculate what extent of environmental oxygen level is needed to reach a specified SaO2 level in a susceptible individual.
6. Susceptible individual has reduced oxygen diffusion capacity and performs light level of exercise.

Correlation between health effects and oxygen levels.

Stages with O_2 saturation in arterial blood	Health effects
1. Indifferent stage 90% O2 saturation	Night vision decreased
2. Compensatory stage 82-90% O2 saturation	Compensatory increase in respiratory and pulse rate. Night vision decreased further. Somewhat reduced performance ability, symptoms may begin in those with significant pre-existing cardiac, pulmonary, or hematofogical diseases.
3. Disturbance stage 64-82% O2 saturation	Compensatory mechanisms become inadequate. Air hunger, fatigue, tunnel vision, dizziness, headache, belligerence, euphoria, visual acuity reduced, tingling of extremities, hyperventilation, poor judgement, memory loss, cyanosis, decreased ability to escape.
4. Critical stage 60-70% O2 saturation or less.	Deforiation in judgement and coordination may occur in 3-5 minutes or less. Total incapacitation and unconsciousness follow rapidly.

Other regulatory input

- NIOSH guide to safety in confined spaces (1987)
  - Do not enter atmosphers with less than 19.5% oxygen.
    Not coupled to health effects
- TLV committee
  - Uses 18% oxygen in air for setting TLV values for simple asphyxiants.
    Not coupled to health effects.
    Should be considered as a 'good practice standard'.

Other useful information

- High Altitude physiology
  - Very similar to hypoxia due to simple asphyxiants
  - Difference is pressure (hypobaric vs normobaric)
- Air travelling
  - Commercial air travel is assocaited with moderate (hypobaric) hypoxia
  - Large number of people (including susceptible subgroups) travel by plane.
  - Provides evidence for influence of hypoxia on susceptible populations.
- Experimental observations

High Altitude Physiology

- Guyton Medical Physiology:
- Important acute effects of hypoxia (drowsiness, lassitude, mental and muscle fatigue, headache, nausea, euphoria) start at 3600 m (about 82% SaO2)
- Progression of effects to convulsions above 4870 m (about 70% SaO2)
- Coma in unacclimatized persons above 7000 m (SaO2 is lower than 50%).

Air Travel

- Air plane cabins have hypobaric atmosphere similar to an altitude of 1700-2400 m). Oxygen levels are about 16-19% compared to 20.9% at sea level.
- Many people "exposed" including susceptible groups
- Medical incidents: 0.003% of passengers
- 12/260 COPD patients (4.6%) had exacerbations during flight.
- Normal commercial air travel not considered as an emergency ?

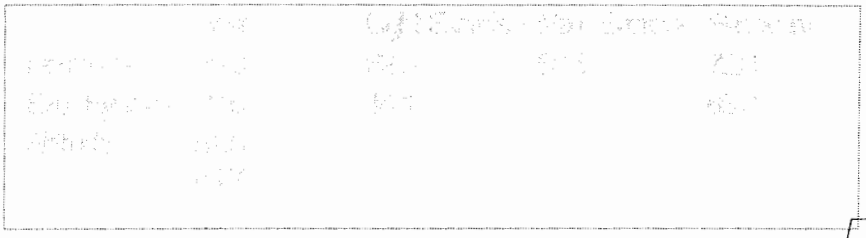
Experimental observations - 1

- **Erdmann et al. 1998**
- Coronary artery disease patiens and controls (both n=23)
- Bicycle stress test at 1000 m and 2500 m
- maximal exercise levels were 20% lower in patients compared to controls
- Max heart rate and blood pressure did not differ between 1000 and 2500 m
- Controls SaO2: 97% at 1000 m; 94% at 2500 m
- Patients SaO2: 95% at 1000 m; 94% at 2500 m
- Exercise reduced these values 1 or 2 percent.

Experimental observations - 2

- **Schwartz et al. 1984**
- 13 severe COPD patients: PaO2 levels measured
- Normoxia: rest, light exercise, maximum exercise
- Exp. hypoxia: rest, light exercise, recovery & Simulated altitude: 1650 and 2250 m

Mean PaO2 levels (mm Hg) in table, No signs or symptoms reported



PaO2 levels of about 45 mm Hg correspond to SaO2 of 75-80%

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naam presentatie | naam auteur 13

AEGL-1 values

- No AEGL-1 values are proposed
- Asphyxiants are generally oderless, colorless, tasteless. They do not provide warning signs.
- Discussion: can physiological effects like increased ventilation and minor signs such as decreased night vision be regarded as "notable discomfort " ????

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naam presentatie | naam auteur 14

AEGL-2 values

- Studies with healthy volunteers: SaO2 of 75-90% produced mild effects
- Poisindex: SaO2 of 82-90% symptoms may begin in susceptible individuals.
- Severe COPD patients: SaO2 of about 75-80% had reduced level of maximal exercise. 1/18 patients had ectopic beats.
- Take 80% SaO2 as threshold for AEGL-2 effects.
- Using SatCur: this corresponds to 17% O2 in air for a susceptible individual
- ~~This corresponds to 190,000 ppm of an asphyxiant~~

AEGL-3 values

- Death due to asphyxia is in most instances instantaneously.
- Small scope between loss of consiousness and death
- No quantitative information about range of variation between normal and susceptible individuals. So, value should be safe for all individuals.
- Proposed to use 65% of SaO2.
- Using SatCur: this corresponds to 14% oxygen in air for susceptible individual.
- ~~This correspons to 330,000 ppm of an asphyxiant~~

Discussion

- For this criteria document: take reviews and textbooks or only primary data ?
- What is the most suceptible subpopulation ?
- Is it OK to use SaO2 ?
- Choice of levels for AEGL-2 and 3 ?
- Extrapolation to environmental air using SatCur ?
- Set AEGL values on asphyxia compared to explosive or flammability aspects ?

NICKEL CARBONYL
CAS Reg. No. 13463-39-3

DERIVATION OF AEGL-2 VALUES

Chemical Manager: Ernest V. Falke, US EPA
ORNL Staff Scientist: Robert A. Young, ORNL

1998

AEGL-2 values - originally proposed based upon the Sunderman et al. (1980) study in hamsters.

Summary of Interim AEGL Values For Nickel Carbonyl [ppm]						
Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	not recommended
AEGL-2 (Disabling)	0.096	0.042	0.021	0.0063	NR	developmental toxicity in hamsters; 8.4 ppm for 15 minutes (Sunderman et al., 1980)
AEGL-3 (Lethal)	0.46	0.32	0.16	0.040	0.020	estimated lethality threshold (LC_{01} of 3.17 ppm); mouse lethality data (Kincaid et al., 1953)

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

Sunderman et al. (1980) data

Exposure duration = 15 minutes

FETUS	DAM	EXPOSURE CONC.
Neonate mortality Serious cavity hemorrhage Malformed fetus	5/14 died	8.4 ppm

POD = 8.4 ppm for 15 minutes with a total UF = 100

NAS COMMENTS:
Concerns expressed by COT Subcommittee (Seventh Interim Report, 2002): death in dams precludes contention that nickel carbonyl is selective developmental toxicant; not consistent with AEGL-2 definition. Total UF=100

2002

AEGL-2 values - revised values based upon the Sunderman et al. (1979) study in rats.

AEGL-2 values - revised because of NAS comments - based upon the Sunderman et al. (1979) study in rats

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

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

2002

AEGL-2 values - revised values based upon the Sunderman et al. (1979) study in rats.

Sunderman et al. (1979) data

Exposure duration = 15 minutes

FETUS	DAM	EXPOSURE CONC.
No significant eye malformation or litter body weight effect	None stated	11.2 ppm
Eye malformations Decreased fetal body weights	0/14 died 2/15 died 0/13 died	22.4 ppm
Eye malformations Decreased fetal body weights	9/19 dams died	42 ppm

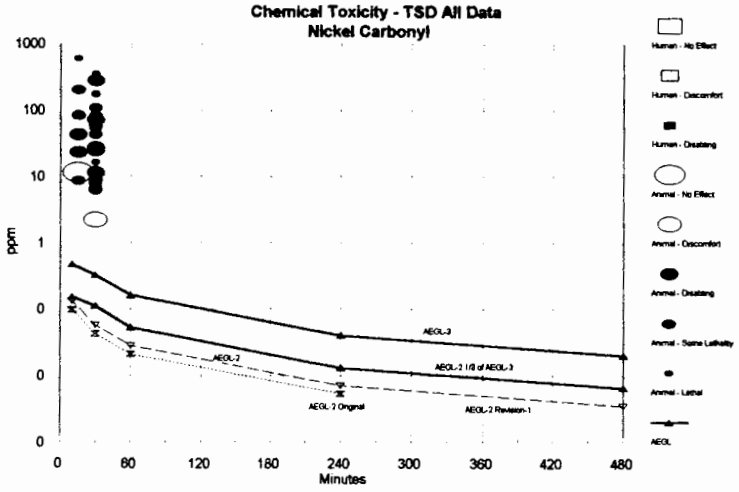
POD = 11.2 ppm for 15 minutes with a total UF = 100

NAS COMMENTS:
The NAC selected the Sunderman et al. (1979) 15-minute rat inhalation protocol for AEGL-2 derivation. Sunderman reported 52% and 64% maternal mortality after exposure at 22 and 42 ppm, respectively, but no maternal mortality after exposure at 11 ppm. No description of signs of maternal poisoning other than death was included. It appears that the 11 ppm NOAEL for developmental toxicity is identical to the maternal NOAEL for death. Thus, it appears that nickel carbonyl teratogenicity cannot be separated from the overt maternal toxicity, and the extrapolation can be carried out based on the response of the dams. As written, it appears that the NAC judged nickel carbonyl to be a selective developmental toxin though the data do not support that supposition.

RELATIVE SPECIES SENSITIVITIES

Acute Lethality of Nickel Carbonyl in Animal Species		
Species	**Acute lethality value 30-min LC_{50}:**	**Reference**
Mouse	9.38 ppm	Kincaid et al., 1953
Rat	56 ppm	Kincaid et al., 1953 (Barnes and Denz, 1951)[a]
Rat	33.6 ppm	Kincaid et al., 1953
Rat	80 ppm	Sunderman and Donnelly,1965
Rabbit	42-168 ppm	Kincaid et al., 1953 (Barnes and Denz, 1951)[a]
Cat	266 ppm[b]	Kincaid et al., 1953

[a] 50% mortality value determined by Kincaid et al. (1953) using probit analysis and multiple exposure time data of Barnes and Denz (1951).
[b] value estimated by authors based upon 100% (3/3) mortality at 280 ppm for 30 minutes but no mortality (0/2) at 271.6 ppm for 30 minutes.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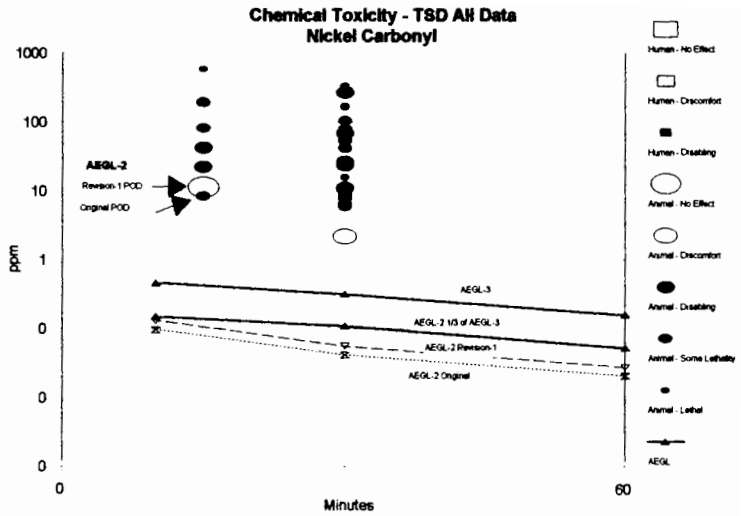
Nickel Carbonyl
1000
100
10
1
0
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2 1/3 of AEGL-3
AEGL-2
AEGL-2 Original
AEGL-2 Revision-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL


Chemical Toxicity - TSD All Data
Nickel Carbonyl
1000
100
10
1
0
0
ppm
0
60
Minutes
AEGL-2
Revision-1 POD
Original POD
AEGL-3
AEGL-2 1/3 of AEGL-3
AEGL-2 Revision-1
AEGL-2 Original
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

SYNOPSIS

- Original value POD - 1998
  - was above the AEGL-2 threshold
    - lethal to dams
    - neonate mortality
    - malformed fetus
    - no evidence for developmental toxicity at doses below those causing maternal toxicity
  - most sensitive species not used
- Revised POD - 2002
  - POD is NOEL for developmental toxicity and is ½ the dose which is lethal to dams
  - most sensitive species not used
  - POD is above the level which is lethal to hamsters
  - no evidence for developmental toxicity at doses below those causing maternal toxicity
- Where do we go
  - Data set is limited to 15 and 30 minute data
  - Only data point below a level lethal in animals is in mice (Kincaid et al., 1953)
    - 2.17 ppm exposure for 30 minutes did not kill mice
    - LC_{01} used as POD for the AEGL-3 is 3.17 ppm
  - At a minimum the AEGL-2 POD should be below a lethal level
  - Either develop no AEGL-2 for nickel carbonyl or follow the iron pentacarbonyl example and divide the AEGL-3 by 3 to develop AEGL-2 levels
    - The ratio between the calculated LC_{01} of 3.17 ppm in the Kincaid et al. (1953) experiment and the level which killed 10/10 animals (12.6 ppm) is approximately 4. Given the steep dose-response curve of nickel carbonyl, dividing the AEGL-3 values to develop AEGL-2 values is a reasonable approach.

AEGL-2 values based upon dividing AEGL-3 values by 3

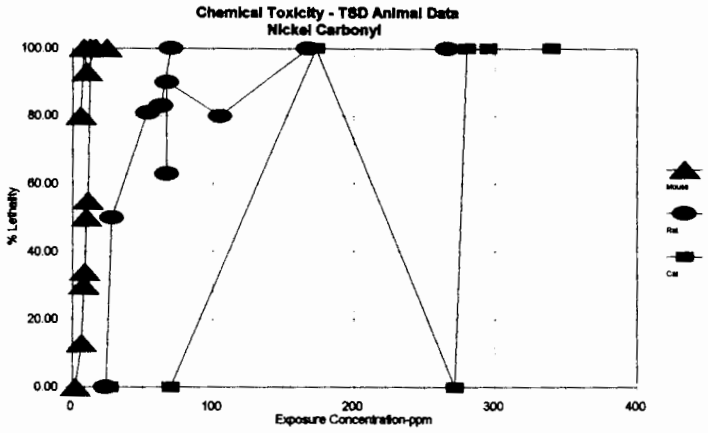
Summary of Proposed AEGL Values For Nickel Carbonyl [ppm (mg/m³)]						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	not recommended
AEGL-2 (Disabling)	**0.15 (1.1)**	**0.11 (0.73)**	**0.053 (0.36)**	**0.013 (0.091)**	**0.0066 (0.046)**	**three-fold reduction of AEGL-3 values**
AEGL-3 (Lethal)	0.46 (3.2)	0.32 (2.2)	0.16 (1.1)	0.040 (0.27)	0.02 (0.14)	estimated lethality threshold (LC_{01} of 3.17 ppm); mouse lethality data (Kincaid et al., 1953)

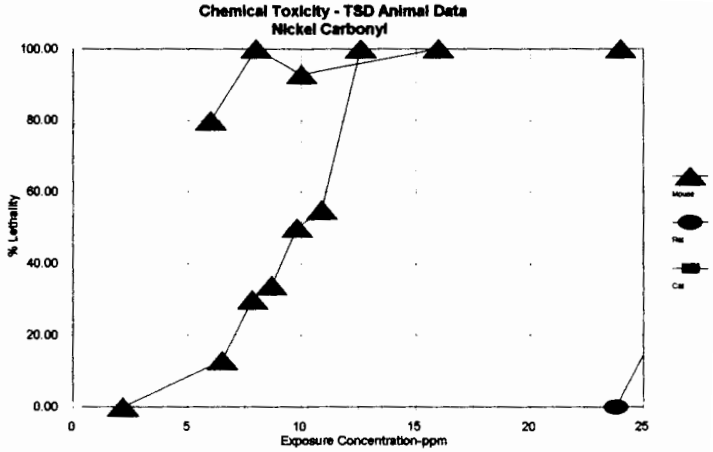
NR: Not recommended. Numeric values for AEGL-1 are not recommended because (1) the lack of available data, and (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

Bolded text indicates revisions; revised AEGL-2 values are approximately 2-fold higher than previous AEGL-2 values

APPENDIX-HISTORICAL TIME-LINE OF THE DEVELOPMENT OF AEGL-2 VALUES

- Draft TSD (1998): data insufficient to develop AEGL-2 values
- June 1998 (NAC/AEGL-10): In the initial review of draft TSD, NAC/AEGL selected developmental effects in hamsters (8.4 ppm for 15 min., Sunderman et al., 1980) as point of departure for AEGL-2
  - concerns expressed by COT Subcommittee (Seventh Interim Report, 2002): death in dams precludes contention that nickel carbonyl is selective developmental toxicant; not consistent with AEGL-2 definition. Total UF=100
- June, 2002 (NAC/AEGL-25): NAC presented with three options for revising AEGL-2 in response to COT Subcommittee concerns
  - 1) no AEGL-2 values be developed due to limited data
  - 2) 3-fold reduction of AEGL-3; use developmental toxicity as supporting data
  - 3) use rat developmental data (Sunderman et al., 1979); 11.2 ppm, 15 min. gestational exposure; health status of dams not reported. Total UF=100
  - NAC/AEGL selected and approved third option
- COT/AEGL Subcommittee (Eight Interim Report, 12/2002): AEGL-2 point of departure (11.2 ppm, rat developmental study) and rationale unacceptable
  - no description of maternal toxicity; therefore difficult to justify nickel carbonyl as a selective developmental toxicant
- One-third reduction of AEGL-3 appears to be justifiable
  - developmental toxicity approach flawed
  - values from 1/3 AEGL-3 are similar to previous AEGL-2 values
  - category plots justify approach
  - 1/3 AEGL-3 previously approved by NAS (NRC, 2000; NRC, 2001)


Chemical Toxicity - TSD Animal Data
Nickel Carbonyl
% Lethality
100.00
80.00
60.00
40.00
20.00
0.00
0
100
200
300
400
Exposure Concentration-ppm
Mouse
Rat
Cat


Chemical Toxicity - TSD Animal Data
Nickel Carbonyl
% Lethality
100.00
80.00
60.00
40.00
20.00
0.00
0
5
10
15
20
25
Exposure Concentration-ppm
Mouse
Rat
Cat

Benzene - AEGL values
NAC-AEGL 29 (june 2003)

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

rivm

Research for men and environment

Benzene characteristics

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

Benzene TSD development

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

Human data - 1 (lethality)

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

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 ?

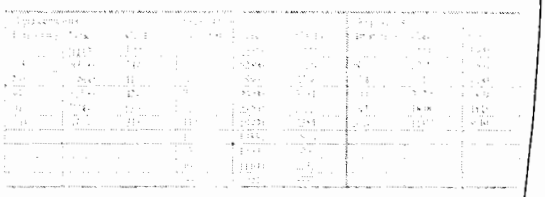
Acute toxicity Benzene - "Table by Gerarde"

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

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)

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 (Molnar et al., 1986).
- In mice effects are seen at somewhat lower levels. Considered less relevant because mice have higher body load or experiments used static conditions.

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AEGL-2 derivation

- With regard to CNS depression benzene is less or about equipotent to toluene (for which much more human data are available) and xylene.
- 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.

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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)

1960 1190 500 400 200

toluene -

xylene -

rivm

AEGL-3 derivation

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

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AEGL-3 derivation

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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

NICKEL CARBONYL
CAS Reg. No. 13463-39-3

DERIVATION OF AEGL-2 VALUES

Chemical Manager: Ernest V. Falke, US EPA
ORNL Staff Scientist: Robert A. Young, ORNL

1998

AEGL-2 values - originally proposed based upon the Sunderman et al. (1980) study in hamsters.

Summary of Interim AEGL Values For Nickel Carbonyl [ppm]						
Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	not recommended
AEGL-2 (Disabling)	0.096	0.042	0.021	0.0063	NR	developmental toxicity in hamsters; 8.4 ppm for 15 minutes (Sunderman et al., 1980)
AEGL-3 (Lethal)	0.46	0.32	0.16	0.040	0.020	estimated lethality threshold (LC_{01} of 3.17 ppm); mouse lethality data (Kincaid et al., 1953)

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

Sunderman et al. (1980) data

Exposure duration = 15 minutes

FETUS	DAM	EXPOSURE CONC.
Neonate mortality Serious cavity hemorrhage Malformed fetus	5/14 died	8.4 ppm

POD = 8.4 ppm for 15 minutes with a total UF = 100

NAS COMMENTS:
Concerns expressed by COT Subcommittee (Seventh Interim Report, 2002): death in dams precludes contention that nickel carbonyl is selective developmental toxicant; not consistent with AEGL-2 definition. Total UF=100

2002

AEGL-2 values - revised values based upon the Sunderman et al. (1979) study in rats.

AEGL-2 values - revised because of NAS comments - based upon the Sunderman et al. (1979) study in rats

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

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

2002

AEGL-2 values - revised values based upon the Sunderman et al. (1979) study in rats.

Sunderman et al. (1979) data

Exposure duration = 15 minutes

FETUS	DAM	EXPOSURE CONC.
No significant eye malformation or litter body weight effect	None stated	11.2 ppm
Eye malformations Decreased fetal body weights	0/14 died 2/15 died 0/13 died	22.4 ppm
Eye malformations Decreased fetal body weights	9/19 dams died	42 ppm

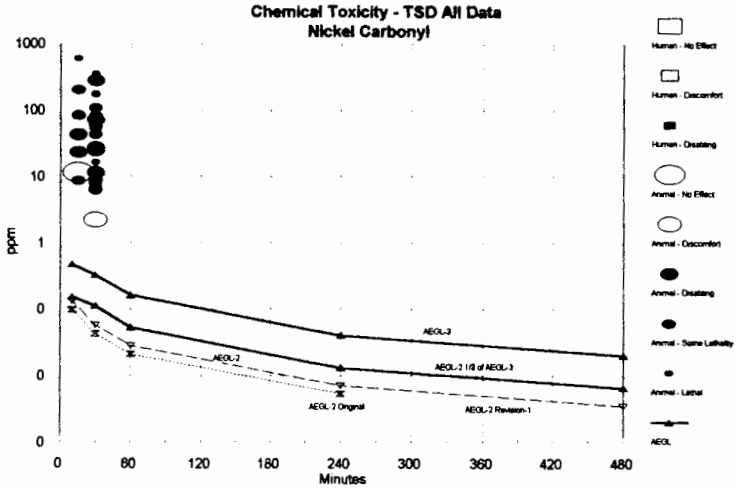
POD = 11.2 ppm for 15 minutes with a total UF = 100

NAS COMMENTS:
The NAC selected the Sunderman et al. (1979) 15-minute rat inhalation protocol for AEGL-2 derivation. Sunderman reported 52% and 64% maternal mortality after exposure at 22 and 42 ppm, respectively, but no maternal mortality after exposure at 11 ppm. No description of signs of maternal poisoning other than death was included. It appears that the 11 ppm NOAEL for developmental toxicity is identical to the maternal NOAEL for death. Thus, it appears that nickel carbonyl teratogenicity cannot be separated from the overt maternal toxicity, and the extrapolation can be carried out based on the response of the dams. As written, it appears that the NAC judged nickel carbonyl to be a selective developmental toxin though the data do not support that supposition.

RELATIVE SPECIES SENSITIVITIES

Acute Lethality of Nickel Carbonyl in Animal Species		
Species	**Acute lethality value 30-min LC_{50}:**	**Reference**
Mouse	9.38 ppm	Kincaid et al., 1953
Rat	56 ppm	Kincaid et al., 1953 (Barnes and Denz, 1951)[a]
Rat	33.6 ppm	Kincaid et al., 1953
Rat	80 ppm	Sunderman and Donnelly,1965
Rabbit	42-168 ppm	Kincaid et al., 1953 (Barnes and Denz, 1951)[a]
Cat	266 ppm[b]	Kincaid et al., 1953

[a] 50% mortality value determined by Kincaid et al. (1953) using probit analysis and multiple exposure time data of Barnes and Denz (1951).
[b] value estimated by authors based upon 100% (3/3) mortality at 280 ppm for 30 minutes but no mortality (0/2) at 271.6 ppm for 30 minutes.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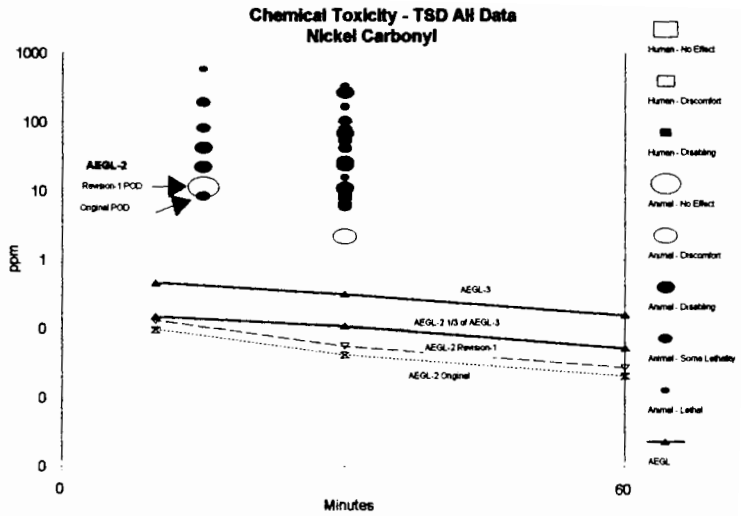
Nickel Carbonyl
1000
100
10
1
0
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2 1/3 of AEGL-3
AEGL-2
AEGL-2 Original
AEGL-2 Revision-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL


Chemical Toxicity - TSD All Data
Nickel Carbonyl
1000
100
10
1
0
0
ppm
0
60
Minutes
AEGL-2
Revision-1 POD
Original POD
AEGL-3
AEGL-2 1/3 of AEGL-3
AEGL-2 Revision-1
AEGL-2 Original
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

SYNOPSIS

- Original value POD - 1998
  - was above the AEGL-2 threshold
    - lethal to dams
    - neonate mortality
    - malformed fetus
    - no evidence for developmental toxicity at doses below those causing maternal toxicity
  - most sensitive species not used
- Revised POD - 2002
  - POD is NOEL for developmental toxicity and is ½ the dose which is lethal to dams
  - most sensitive species not used
  - POD is above the level which is lethal to hamsters
  - no evidence for developmental toxicity at doses below those causing maternal toxicity
- Where do we go
  - Data set is limited to 15 and 30 minute data
  - Only data point below a level lethal in animals is in mice (Kincaid et al., 1953)
    - 2.17 ppm exposure for 30 minutes did not kill mice
    - LC_{01} used as POD for the AEGL-3 is 3.17 ppm
  - At a minimum the AEGL-2 POD should be below a lethal level
  - Either develop no AEGL-2 for nickel carbonyl or follow the iron pentacarbonyl example and divide the AEGL-3 by 3 to develop AEGL-2 levels
    - The ratio between the calculated LC_{01} of 3.17 ppm in the Kincaid et al. (1953) experiment and the level which killed 10/10 animals (12.6 ppm) is approximately 4. Given the steep dose-response curve of nickel carbonyl, dividing the AEGL-3 values to develop AEGL-2 values is a reasonable approach.

AEGL-2 values based upon dividing AEGL-3 values by 3

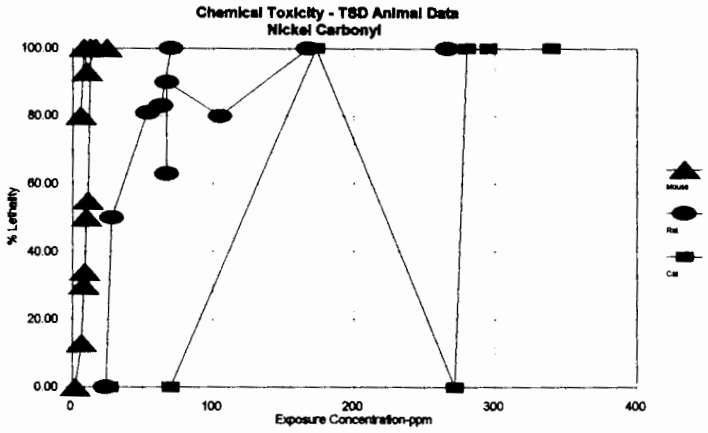
Summary of Proposed AEGL Values For Nickel Carbonyl [ppm (mg/m³)]						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	not recommended
AEGL-2 (Disabling)	**0.15 (1.1)**	**0.11 (0.73)**	**0.053 (0.36)**	**0.013 (0.091)**	**0.0066 (0.046)**	**three-fold reduction of AEGL-3 values**
AEGL-3 (Lethal)	0.46 (3.2)	0.32 (2.2)	0.16 (1.1)	0.040 (0.27)	0.02 (0.14)	estimated lethality threshold (LC_{01} of 3.17 ppm); mouse lethality data (Kincaid et al., 1953)

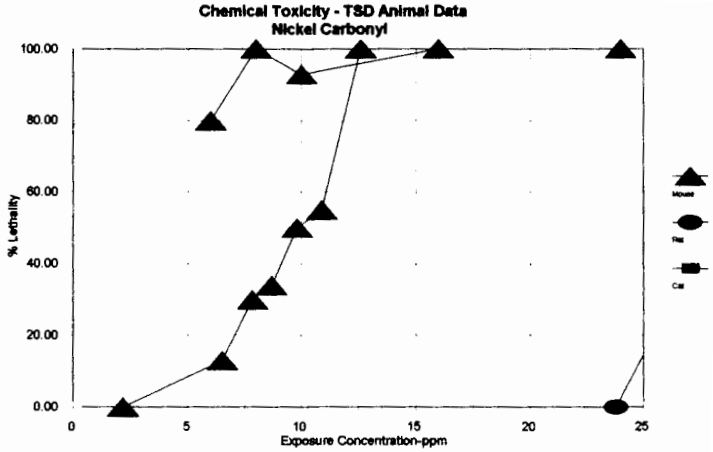
NR: Not recommended. Numeric values for AEGL-1 are not recommended because (1) the lack of available data, and (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

Bolded text indicates revisions; revised AEGL-2 values are approximately 2-fold higher than previous AEGL-2 values

APPENDIX-HISTORICAL TIME-LINE OF THE DEVELOPMENT OF AEGL-2 VALUES

- Draft TSD (1998): data insufficient to develop AEGL-2 values
- June 1998 (NAC/AEGL-10): In the initial review of draft TSD, NAC/AEGL selected developmental effects in hamsters (8.4 ppm for 15 min., Sunderman et al., 1980) as point of departure for AEGL-2
  - concerns expressed by COT Subcommittee (Seventh Interim Report, 2002): death in dams precludes contention that nickel carbonyl is selective developmental toxicant; not consistent with AEGL-2 definition. Total UF=100
- June, 2002 (NAC/AEGL-25): NAC presented with three options for revising AEGL-2 in response to COT Subcommittee concerns
  - 1) no AEGL-2 values be developed due to limited data
  - 2) 3-fold reduction of AEGL-3; use developmental toxicity as supporting data
  - 3) use rat developmental data (Sunderman et al., 1979); 11.2 ppm, 15 min. gestational exposure; health status of dams not reported. Total UF=100
  - NAC/AEGL selected and approved third option
- COT/AEGL Subcommittee (Eight Interim Report, 12/2002): AEGL-2 point of departure (11.2 ppm, rat developmental study) and rationale unacceptable
  - no description of maternal toxicity; therefore difficult to justify nickel carbonyl as a selective developmental toxicant
- One-third reduction of AEGL-3 appears to be justifiable
  - developmental toxicity approach flawed
  - values from 1/3 AEGL-3 are similar to previous AEGL-2 values
  - category plots justify approach
  - 1/3 AEGL-3 previously approved by NAS (NRC, 2000; NRC, 2001)


Chemical Toxicity - TSD Animal Data
Nickel Carbonyl
% Lethality
100.00
80.00
60.00
40.00
20.00
0.00
0
100
200
300
400
Exposure Concentration-ppm
Mouse
Rat
Cat


Chemical Toxicity - TSD Animal Data
Nickel Carbonyl
% Lethality
100.00
80.00
60.00
40.00
20.00
0.00
0
5
10
15
20
25
Exposure Concentration-ppm
Mouse
Rat
Cat

Benzene - AEGL values
NAC-AEGL 29 (june 2003)

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

rivm

Research for men and environment

Benzene characteristics

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

Benzene TSD development

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

Human data - 1 (lethality)

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

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 ?

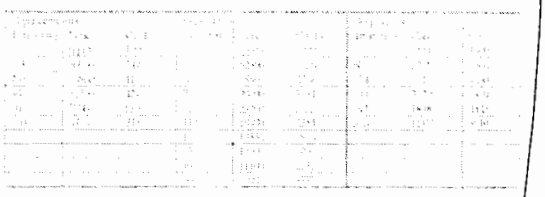
Acute toxicity Benzene - "Table by Gerarde"

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

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)

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 (Molnar et al., 1986).
- In mice effects are seen at somewhat lower levels. Considered less relevant because mice have higher body load or experiments used static conditions.

rivm

AEGL-2 derivation

- With regard to CNS depression benzene is less or about equipotent to toluene (for which much more human data are available) and xylene.
- 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.

rivm

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)

1960 1190 500 400 200

toluene -

xylene -

rivm

AEGL-3 derivation

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

rivm

AEGL-3 derivation

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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

Attachment 13

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR

NITRIC ACID

(CAS Reg. No. 7697-37-2)

DRAFT

ORNL Staff Scientist:
Name: Carol S. Wood
phone: (865) 574-0596 fax: (865) 574-9888 e-mail: forsythcs@ornl.gov

Chemical Manager:
Name: Loren Koller
phone: 541-745-5131 fax: e-mail: kollerl@pacifier.com

Chemical Reviewer:
Name:
phone: fax: e-mail:

Chemical Reviewer:
Name:
phone: fax: e-mail:

Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Dept. of Energy under contract DE-AC05-00OR22725

NITRIC ACID OVERVIEW

AEGL values adopted previously
(except 10-min)

Key study for AEGL-2 questioned

Key study for AEGL-3 questioned

Use of n = 3.5 from NO_2

Exposure: content/composition varies

1

NITRIC ACID CONTENT

Commercial grade: 52-68%

Fuming: >86%

WFNA: 0.5% dissolved NO_2 max.

RFNA: up to 17% dissolved NO_2

2

EXPOSURE

- HNO_3 as aerosol
- NO_2 (amount not known)
  - dissolved
  - by product of oxidation reaction
- Need estimate of acid purity and NO_2 content

3

NITRIC ACID TOXICITY

- Burns due to acid
- Contamination with NO_2

4

NITRIC ACID CONVERSION TO NO_2

$$2HNO_3 \xrightarrow{\text{light}} H_2O + 2NO_2 + \tfrac{1}{2}O_2$$

- Does not readily convert in large amounts;
- Not complete;
- Depends on temperature, humidity, other reactants;
- Oxidation-Reduction reaction not an acid reaction;
- Valence state of N differs (5+ to 4+)

LC_{50} VALUES for the RAT (30 min)

Chemical	LC_{50}	Reference
WFNA	244 ppm (as NO_2)	Gray et al. 1954
RFNA	138 ppm (as NO_2)	Gray et al. 1954
NO_2	174 ppm	Gray et al. 1954
Nitric Acid (?)	2716 ppm (1 hr)	BASF 1992
HCl	4700 ppm	Darmer et al. (1974)

SUMMARY OF HUMAN DATA

Conc.	Duration	Subjects	Effect	Ref.
0.05 ppm	40 min	asthmatic adolescents with exercise	NOAEL	Koenig et al., 1989
1.6 ppm	10 min	healthy adults	NOAEL	Sackner and Ford, 1981
12 ppm	1 hour	2 healthy adults	marked irritation	Diem, 1907
85 ppm	2-3 min	1 healthy adult	intolerable	Diem, 1907
62 ppm*	1 hour	healthy adult	slight irritation	Lehmann and Hasegawa, 1913
88 ppm*	1 hour	healthy adult	irritation with cough	Lehmann and Hasegawa, 1913
158 ppm*	10 min	healthy adult	intolerable	Lehmann and Hasegawa, 1913

*reported as mg nitric acid; ppm from NIOSH 1976

SUMMARY OF ANIMAL DATA

Conc.	Duration	Species	Effect	Ref.
287 ppm	1 hr 50 min	cat	None	Lehmann and Hasagawa, 1913
341 ppm	3 hr 8 min	cat	death	Lehmann and Hasagawa, 1913
244 ppm WFNA (as NO_2)	30 min	rat	LC_{50}	Gray et al., 1954
≤194 ppm	150 min	cat	severe irritation; signs persist for 8 d	Diem, 1907
263 ppm	120 min	cat	death	Diem, 1907

CURRENT CONCERNS

Nitric Acid AEGL-3

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

Response: -as stated in TSD
-WFNA contains ~0.5% NO_2

W. ten Berge comments on Gray et al. paper:

- analytical method specific for NO_2
- no reason to doubt accuracy of analysis
- wrong to convert NO_2 to HNO_3 on a molecular weight basis

Therefore if WFNA is ~0.5% NO_2:

244 ppm as NO_2 should be 48,8000 ppm HNO_3

Reasonable???

ALTERNATIVES

1) Develop AEGL values based on existing data for nitric acid;

2) NR for exposure to nitric acid aerosol with footnote that dissolved NO_2 is released;

3) Adopt NO_2 values with caveat that content will need to be estimated;

4) Combine 2) and 3).

Attachment 14

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

HYDROGEN SELENIDE

(CAS Reg. No. 7783-07-5)

DRAFT 1

ORNL Staff Scientist:
Name: Carol S. Wood
phone: (865) 574-0596 fax: (865) 574-9888 e-mail: forsythcs@ornl.gov

Chemical Manager:
Name: Robert Snyder
phone: (732) 445-0205 fax: (732) 445-0131 e-mail: rsnyder@eohsi.rutgers.edu

Chemical Reviewer:
Name: Tom Hornshaw
phone: (217) 785-0832 fax: (217) 782-1431 e-mail: thomas.hornshaw@epa.state.il.us

Chemical Reviewer:
Name: Zarena Post
phone: (512) 239-1332 fax: (512) 239-1794 e-mail: zpost@tnrcc.state.tx.us

Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Dept. of Energy under contract DE-AC05-00OR22725

H_2Se - HUMAN DATA

1) Case reports with no exposure information.

2) Dudley and Miller (1941)

>1.5 ppm: nose and throat irritation severe enough to leave work

0.3 ppm: no effects for several minutes

Problems:
- mentioned in discussion
- no methods
- no exposure description
- no primary reference

H_2Se - ANIMAL DATA

Dudley and Miller 1937, 1941

Guinea pig:

>6.8 ppm: signs of severe irritation; difficulty breathing

<6.8 ppm: mild irritation; difficulty breathing after 24 hours

Problems:
- control deaths
- full body exposure
- dated analytical methods

Lethality data in guinea pigs	
Exposure Duration	Calculated LC_{50}
10 minutes	105.91 ppm
30 minutes	4.49 ppm
60 minutes	3.18 ppm
120 minutes	3.93 ppm
240 minutes	2.78 ppm
480 minutes	0.54 ppm

Calculated from Dudley and Miller 1937, 1941.

H_2Se - ANIMAL DATA

Zwart and Arts 1989; Zwart et al. 1992

Rats:

≥81 ppm for ≥30 min: lethal

40 ppm: 60 min, no death
120 min, partial lethality
recurring "breathing problems"

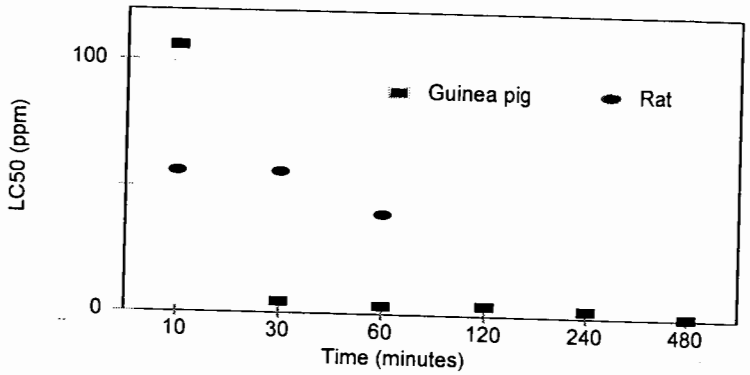
Conc-related clinical signs of respiratory irritation.

Estimated LC_{50} values:

30 min 56 ppm
60 min 56 ppm
120 min 40 ppm

Lethality of rats exposed to H_2Se (no. dead/no. exposed)				
Conc.	4-20 minutes	30 minutes	60 minutes	120 minutes
Study 1				
40 ppm	n/a	0/2	0/2	1/2
81 ppm	n/r	2/2	2/2	2/2
121 ppm	1/6	2/2	2/2	n/r
437 ppm	10/10	n/r	n/r	n/r
898 ppm	8/8	2/2	n/r	n/r
Study 2				
48 ppm	n/r	n/r	0/10	n/r
73 ppm	n/r	n/r	2/10	n/r
76 ppm	n/r	n/r	6/10	n/r

Data from Zwart and Arts 1989 and Zwart et al. 1992.
n/r: data not recorded for these concentration-time values.



Scatter plot of LC_{50} values for the rat and guinea pig.

MECHANISM OF TOXICITY

1) Pulmonary:
   - acute edema due to irritation: death in 2 days
   - bronchial pneumonia: death in 5+ days

2) Liver:
   - lesions due to glutathione depletion: death in 8-10 days

DERIVATION OF AEGL-3

10-minute	30-minute	1-hour	4-hour	8-hour
2.9 ppm	2.0 ppm	1.6 ppm	0.4 ppm	0.2 ppm

Key Study: Zwart and Arts 1989; Zwart et al. 1992

Endpoint: 48 ppm for 60 min, highest nonlethal exposure

Time scaling: $C^n \times t = k$
n = 3 for extrapolating to the 10- and 30-minute timepoints
n = 1 for extrapolating to the 4- and 8-hour timepoints

Uncertainty factors: 3 for intraspecies variability and 10 for interspecies variability

DERIVATION OF AEGL-2

10-minute	30-minute	1-hour	4-hour	8-hour
1.0 ppm	0.7 ppm	0.5 ppm	0.1 ppm	0.07 ppm

Key Study: Zwart and Arts 1989; Zwart et al. 1992

Endpoint: one-third of the AEGL-3 values

Time scaling: $C^n \times t = k$
n = 3 for extrapolating to the 10- and 30-minute timepoints
n = 1 for extrapolating to the 4- and 8-hour timepoints

Uncertainty factors: 3 for intraspecies variability and 10 for interspecies variability

DERIVATION OF AEGL-1

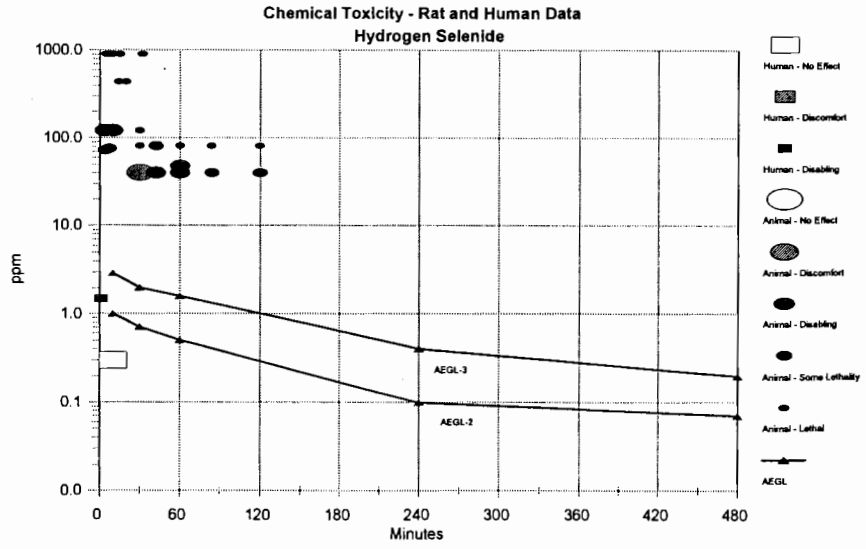
10-minute	30-minute	1-hour	4-hour	8-hour
NR	NR	NR	NR	NR

Key Study: none

Endpoint: no data; insufficient to calculate LOA

Summary of AEGL Values					
Class.	Exposure Duration				
	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.0 ppm	0.7 ppm	0.5 ppm	0.1 ppm	0.07 ppm
AEGL-3	2.9 ppm	2.0 ppm	1.6 ppm	0.4 ppm	0.2 ppm

NR = not recommended



ALTERNATIVE CALCULATIONS

1) 10 min: 121 ppm for 15 min as threshold for lethality;

2) 30 min: 40 ppm for 30 min as highest nonlethal;

3) additional UF = 2 for sparse data base

ALTERNATIVE DERIVATION OF AEGL-3
10-MINUTE VALUE

10-minute	30-minute	1-hour	4-hour	8-hour
4.6 ppm	2.0 ppm	1.6 ppm	0.4 ppm	0.2 ppm

Key Study: Zwart and Arts 1989; Zwart et al. 1992

Endpoint: 121 ppm for 15 min, lethality threshold
48 ppm for 60 min, highest nonlethal exposure

Time scaling: $C^n \times t = k$
n = 3 for extrapolating to the 10- and 30-minute timepoints
n = 1 for extrapolating to the 4- and 8-hour timepoints

Uncertainty factors: 3 for intraspecies variability and 10 for interspecies variability

ALTERNATIVE DERIVATION OF AEGL-3
30-MINUTE VALUE

10-minute	**30-minute**	1-hour	4-hour	8-hour
2.9 ppm	**1.3 ppm**	1.6 ppm	0.4 ppm	0.2 ppm

Key Study: Zwart and Arts 1989; Zwart et al. 1992

Endpoint: 40 ppm for 30 min, highest nonlethal
48 ppm for 60 min, highest nonlethal exposure

Time scaling: $C^n \times t = k$
n = 3 for extrapolating to the 10- and 30-minute timepoints
n = 1 for extrapolating to the 4- and 8-hour timepoints

Uncertainty factors: 3 for intraspecies variability and 10 for interspecies variability

ALTERNATIVE DERIVATION OF AEGLs
ADDITIONAL UF = 2 FOR DATA BASE

	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-2	**0.5 ppm**	**0.33 ppm**	**0.27 ppm**	**0.07 ppm**	**0.03 ppm**
AEGL-3	**1.5 ppm**	**1.0 ppm**	**0.8 ppm**	**0.2 ppm**	**0.1 ppm**

Key Study: Zwart and Arts 1989; Zwart et al. 1992
Endpoint: 48 ppm for 60 min, highest nonlethal exposure

Time scaling: $C^n \times t = k$
n = 3 for extrapolating to the 10- and 30-minute timepoints
n = 1 for extrapolating to the 4- and 8-hour timepoints

Uncertainty factors: 3 for intraspecies variability;
10 for interspecies variability;
2 for data base

Attachment 15

Summary of AEGL Values for Methyl Thiocyanate						
Class.	10-min	30-min	1-hr	4-hr	8-hr	Endpoint
AEGL-1	NR	NR	NR	NR	NR	
AEGL-2	NR	NR	NR	NR	NR	
AEGL-3	NR	NR	NR	NR	NR	

NR = not recommended

OPTIONS

- not recommend values
- adopt HCN values
(no basis for relative potency)

METABOLISM OF CH_3SCN

$CH_3SCN \rightarrow CH_2SSG + HCN$

GSH S-transferase
GSH

↗ cyanocytochrome oxidase
HCN → cyanomethemoglobin
↘ SCN^-

METABOLISM PRODUCTS of CH_3SCN

Mice: 160 nmoles/g; i.p.; sac after 15 min

HCN	SCN^-
Liver	
23 nmoles/g tissue	98 nmoles/g tissue
Brain	
8 nmoles/g tissue	17 nmoles/g tissue

Ohkawa et al. 1972

LC_{50} in mice, i.p.

MeSCN 23 mg/kg (Ohkawa et al. 1972)
HCN 3 mg/kg (HSDB 2003)

Summary Table of AEGL Values for Hydrogen Cyanide (ppm)						
Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	Endpoint (Reference)
AEGL-1	2.5	2.5	2.0	1.3	1.0	No adverse health effects - humans (Leeser et al. 1990); mild central nervous system effects - humans (El Ghawabi et al. 1975)
AEGL-2	17	10	7.1	3.5	2.5	Slight central nervous system depression - monkey (Purser 1984)
AEGL-3	27	21	15	8.6	6.6	Lethality (LC_{01}) - rat (E.I. du Pont de Nemours 1981)

NRC 2002 (vol. 2)

Attachment 16

ACUTE EXPOSURE GUIDELINE LEVELS
for
BROMINE TRIFLUORIDE

National Advisory Committee for AEGLs Meeting 29
June 17-19, 2003

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Bill Bress

Chemical Reviewers:
Nancy Kim
Mark McClanahan

BROMINE TRIFLUORIDE

Human Toxicity Data

No data

Animal Toxicity Data

No data

Structure-Activity Relationships

The chemical reactivity of the halogenated fluorine compounds in order of decreasing reactivity are ClF_5, ClF_3, BrF_5, and BrF_3 (Patty's Industrial Hygiene and Toxicology 1994).

The toxicity of the halogenated fluorine compounds follows the same order.

BROMINE TRIFLUORIDE

Comparative 60-minute LC_{50} Values for Halogenated Fluoride Compounds (ppm)				
Species	**ClF_5**	**ClF_3**	**BrF_5**	**HF**
Monkey	173	230		1774
Dog	122	—		—
Rat	122	299	375 (estimated)	1276
Mouse	57	178		501

BROMINE TRIFLUORIDE

Base the AEGL values on analogy with ClF_3 because of predicted similar toxicity and adequate data.

ClF_3 AEGL-1:
Based on slight irritation (NOAEL) in dogs exposed to exposed 1.17 ppm for 3 hours
Inter- and intraspecies uncertainty factors of 3 each (=10)
Use same value (0.12 ppm) across all exposure durations because there is adaptation to the slight irritation that defines the AEGL-1

ClF_3 AEGL-2:
Based on obvious signs of irritation - salivation, lacrimation, rhinorrhea, and blinking of eyes - in dogs exposed to 5.15 ppm for 6 hours.
Inter- and intraspecies uncertainty factors of 3 each (=10)
Time scaling utilized empirical data from lethality studies (n = 1)

ClF_3 AEGL-3:
Based on 1-hour LC_{01} of 135 ppm for the mouse, the most sensitive species
Inter- and intraspecies uncertainty factors of 3 each (=10)
Time scaling utilized empirical data from lethality studies (n = 1)

BROMINE TRIFLUORIDE

Proposed Bromine Trifluoride AEGLs

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	0.12 ppm	0.12 ppm	0.12 ppm	0.12 ppm	0.12 ppm
AEGL-2	6.2 ppm	6.2 ppm	3.1 ppm	0.77 ppm	0.39 ppm
AEGL-3	81 ppm	27 ppm	14 ppm	3.4 ppm	1.7 ppm

Attachment 17

ACUTE EXPOSURE GUIDELINE LEVELS
for
FORMALDEHYDE:
Reconsideration of AEGL-1 and Time Scaling for AEGL-3

National Advisory Committee for AEGLs Meeting 29
June 17-19, 2003

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Mark McClanahan

Chemical Reviewers:
George Rusch
George Rodgers

Table 1: Critique of Clinical Studies

Irritant Effects of Formaldehyde in Controlled Human Studies		
Exposure (Reference)	**Subjects/Effect (number of subjects)**	**Comments**
0, 0.35, 0.56, 0.7, 0.9, 1.0 ppm for 6 minutes (Bender et al. 1983)	Healthy subjects (groups of 7-28): Eye irritation evaluated: irritation considered less than slight at 0.35 to 0.9 ppm; slight but less than moderate at 1.0 ppm. Responses to concentrations below 1 ppm were not significantly different from the response to clean air. Slight adaptation at 1.0 ppm, even though exposure was short.	Only subjects sensitive to formaldehyde at 1.3 and 2.2 ppm were tested. This is the only study that used carefully chosen panels of subjects that were responsive to formaldehyde. Used standard analytical measurement method. Raw data, scoring system presented.
0, 0.10, 0.69 ppm for 90 minutes (Harving et al. 1986; 1990)	Asthmatic subjects (15): No differences in asthmatic symptoms (undefined) among exposure days., i.e., for sensory irritation, appears subjects were unable to distinguish between 0 and 0.69 ppm.	Well-conducted, double blind Danish study. The authors considered these concentrations typical of indoor air. Interesting that these asthmatic subjects had no response to 0.69 ppm, whereas, the healthy and asthmatic subjects in Pazdrak et al. (1983) responded at 0.41 ppm.
0, 0.41 ppm for 2 hours (Pazdrak et al. 1993) Krakowiak et al. 1998)	Healthy (11) and patients with skin hypersensitivity to formaldehyde (9) (Pazdrak et al. 1993); Healthy (10) and asthmatic subjects (10) (Krakowiak et al. 1998) No differences in response between groups; increase in nasal symptoms of sneezing, rhinorrhea, or eye irritation; nasal washes: increases in eosinophils, albumin, total protein, but not neutrophil, basophil or mononuclear cells	Single-blind study. Analytical measurements were not taken on the day of exposure for either study (chamber was calibrated 7 times/year). There was an irritation scoring system but it was not explained and no raw data were presented. The authors did not explain how they controlled for the irritation that might have been experienced by the subjects due to nasal washes prior to the formaldehyde exposure. Krakowiak et al. (1998) mentions placebo washes but provides no data. The same symptoms as in the Pazdrak study are listed without explanation.
0, 0.12, 0.33, 1.0 ppm for 5.5 hours (Bach et al. 1987; 1990)	Formaldehyde exposed workers (32); controls (29): subjective symptoms of irritation did not correlate with exposure in a dose-response relationship; (for control subjects there was no clear effect of concentration on memory whereas for formaldehyde-exposed workers there were some differences)	Study design difficult to understand. Irritation effects from an earlier paper (in Danish) were summarized. The authors concluded that there were some differences in performance tests related to exposure, but their data failed to make a convincing case. For example, performance was often poorest at the intermediate concentration. They also stated that the perceived effect may have been due to chronic exposure.

1.0 ppm for 90 minutes (Day et al. 1984)	Healthy (9) and formaldehyde-sensitive (9) subjects: No effects on pulmonary function parameters. Complaints of eye irritation, nasal congestion, tearing, and throat irritation at 1.0 ppm but no symptom scoring system.... adaptation noted.	No control exposures.....
0, 0.2, 0.4, 0.8, 1.6 ppm for 4 hours (Andersen and Molhave (1983)	Healthy subjects (16): No differences in nasal airway resistance or pulmonary function parameters; decrease in nasal mucus flow at all concentrations; no discomfort at 0.2 or 0.4 ppm for 2 hours; average discomfort scored as slight during exposure to 1.6 ppm	Although fairly old, the study appears to be well conducted and is quoted in many reviews.
0, 2.0 ppm at rest 0, 2.0 ppm with exercise, both for 40 minutes Witek et al. 1986; 1987; Schachter et al. 1985; 1986)	Healthy (15) and asthmatic subjects (15): No significant decrement in pulmonary function parameters or bronchial reactivity both at rest and with exercise. Asthmatic subjects: highest score for subjective symptom was odor at 2 ppm at rest (= moderate); median scores for nose, throat and eye irritation were ≤moderate; no increase in symptomology with exercise; similar scores for healthy subjects	Double-blind studies conducted at Yale University School of Medicine. Healthy and asthmatic subjects studied at different times. Analytical measurements by several methods including NIOSH-approved method. Interesting that some subjects reported mild irritation in the clean air room (7% reported eye irritation, 20% nasal irritation, 27% throat irritation, and 33% odor perception)...and some subjects reported greater irritation at rest than during exercise....
0, 0.1, 1.0, 3.0 ppm for 20 minutes via facemask (Frigas et al. 1984)	Asthmatic patients (13): No significant differences in pulmonary functions. Symptoms of eye, nose, and throat irritation reported as frequently with the placebo exposures as with all formaldehyde challenges.	Double and/or single blind study depending on patient being tested. conducted at Mayo Clinic, MN. Patients selected for probability of formaldehyde-induced asthma. Analytical measurement not discussed (calibrated automated delivery system).
0, 1, 3 ppm for 10 minutes (Sheppard et al. 1984)	Asthmatic subjects (7) No increase in asthmatic symptoms (cough, wheezing0 during moderate exercise or for 24 hours postexposure	Double-blind study; exposures were with a mouthpiece

0, 0.5, 1.0, 2.0, 3.0 ppm for 3 hours at rest; 2.0 ppm with exercise (Kulle et al. 1987; Kulle 1993)	Healthy subjects (19): No significant decrements in pulmonary function parameters or increases in bronchial reactivity at any concentration.; nasal flow resistance ↑ at 3.0 ppm. Significant dose-response relationship for odor sensation and eye irritation. At 1 and 2 ppm all symptoms mean scores between none and mild; at 3 ppm all symptoms ≤mild except for eye irritation which was between mild and moderate. Threshold* for eye irritation considered between 0.5 and 1.0 ppm.	Well conducted study. First in a series conducted at the University of Maryland, Department of Medicine (see also Green et al. 1987; 1989; Sauder et al. 1986; 1987). Analytical measurements made by several methods including NIOSH-approved chromotropic method. 0.5 ppm: no eye, nose, or throat irritation 1, 2 ppm: mean irritation scores below mild 3 ppm: eye irritation between mild and moderate Some subjects reported mild eye and nose/throat irritation during the control exposures.
0, 3.0 ppm with heavy exercise for 1 hour (healthy subjects) moderate exercise (asthmatic subjects) (Green et al. 1987) 0, 3.0 ppm for 2 hours (healthy subjects) (Green et al. 1989)	Healthy (22) and asthmatic subjects (16) (Green et al. 1987) Healthy subjects (24) (Green et al. 1989) No difference in symptoms between groups in first study; mean odor, eye, and nose/throat irritation all scored less than moderate in both studies; no changes in pulmonary function parameters for asthmatics.	First study: data presented as mean values. Responses highest following exercise periods. Some responses of mild irritation during control exposures. Second study: data presented graphically. Well conducted study with good analytical measurements.
0, 3.0 ppm for 3 hours (Sauder et al. 1986) (Sauder et al. 1987)	Healthy subjects (9); asthmatic subjects (9) non-biologically significant change in some pulmonary function parameters for healthy subjects: odor and nose/throat and eye irritation all scored less than moderate. Second study: 1 of 9 asthmatic subjects scored eye irritation as severe.	Same group of investigators as Green et al. above: study expanded to 3 hours. (mild irritation was considered non-annoying; moderate irritation was considered annoying) Well conducted study with NIOSH-approved sampling method.

0.03, 1.2, 2.1, 2.8, 3.2 ppm, increasing over a 35-minute period; 0.03, 1.2, 2.1, 2.8, 4.0 ppm for 1.5 minutes each (Weber-Tschopp et al. 1977)	Healthy subjects (two exposures, groups of 33 and 48, respectively): Poorer air quality and greater nose irritation reported during the short exposures than during the 35-minute exposure, whereas the opposite was true for eye irritation; with increasing concentrations during the 35 minute exposures, both eye and nose irritation increased from none to "a little:" eye blinking was not affected at 0.5 and 1.2 ppm, but was statistically significantly increased to same degree at 1.7, 2.1, 2.5, 2.8, and 3.2 ppm. Thresholds* for eye, nose, throat, and eye blinking response were 1.2, 1.2, 2.1, and 1.7 ppm, respectively.	Article in German with English summary and extensive review in Andersen and Molhave (1983); sections also translated by S. Talmage. The authors compared the exposure symptoms to those from sidestream cigarette smoke. All exposures were much less irritating than sidestream cigarette smoke. Minor irritation reported during control exposures.... Continuous analytical measurements with a gas chromatograph. Again, this study is quoted in many reviews.
0, 1, 2, 4, 5 ppm for 5-12 minutes; exposure via goggles (Stephens et al. 1961)	Healthy students (groups of 7 to 75): Addressed eye irritation only: 1 ppm considered threshold* for detection; 5 ppm produced "severe" eye irritation. Responses depended to some degree as to air flow, static vs dynamic. A few individuals (6/75) gave a "positive" response, i.e., irritation, at 1 ppm under static conditions	Older study. Although values agree with other studies, delivering the chemical via goggles may produce a drying/irritant effect on the eyes.
6, 8, 12, 18, 24, 30 ppm for 15 seconds via goggles (Douglas 1974)	Healthy/atopic subjects (1-6): 6 ppm: no irritation, single subject 8 ppm: eye irritation, 1 of 5 subjects; 12 ppm: eye irritation, 5 of 6 subjects 18 ppm: no eye irritation, 2 subjects 24, 30 ppm: eye irritation within 10 sec., single subject	This Ph.D. dissertation rambles; responses of subjects varied considerably, showing great interindividual differences. But, even though the airstream was delivered via goggles (which may increase the irritant response), little irritation was reported at the lowest concentrations tested, 6 and 8 ppm. No good scoring system for irritation.
13.8 ppm for 30 minutes (Sim and Pattle (1957)	Healthy male subjects (12): Nasal and eye irritation with mild lacrimation upon chamber entry; adaptation to eye irritation in 10 min.	Older study; analytical measurement via acid titration method.
20 ppm for several minutes (Barnes and Speicher 1942)	Healthy subjects (2): Lacrimation; eye, nose, and throat irritation considered "distinctly uncomfortable" and objectionable but could be tolerated for "some length of time."	Old study (the authors note that 20 ppm was once the exposure limit for several states). Not a controlled human study; subjects entered chamber for up to several minutes. Analytical measurements by two methods... these methods no longer used.

*Threshold is not defined in these studies (someone asked). It is assumed that threshold is where irritation is first noticed, and, at that point, irritation would be very slight. This is common sense, as, at increasingly higher concentrations, the descriptors mild, moderate, and severe are used in most studies.

Total subjects exposed to 1-3 ppm in well-documented studies: 418
Total subjects exposed to 3 ppm in well-documented studies: 193

Example, Clinical Studies:
Kulle et al. 1987
Healthy subjects (19); no exercise; exposures were for 3 hours
Green et al. 1987
Healthy (22) and asthmatic subjects (16) with exercise

Table 2

Concentration (ppm)	No Exercise (Kulle) Irritation Response		Exercise (Green) Irritation Response	
	Eye	Nose/throat	Eye	Nose/throat
0.0	0.0	0.0	0.0	0.1
0.5	0.0	0.0		
1.0	0.4	0.1		
2.0	0.9	0.3		
3.0	1.4	0.2	1.3, 1.5	1.7, 1.8

Irritation Scores:

Kulle et al. (1987)	Green et al. (1987)
0 = none	0 = none
1 = mild	1 = mild
2 = moderate	2 = mild-moderate
3 = severe	3 = moderate
	4 = moderate-severe
	5 = severe

Derivation of AEGL-1: Four Clinical Studies

Based on the well-conducted studies of Kulle et al. 1987 (19 healthy subjects), Green et al. 1987 (22 healthy and 16 asthmatic subjects, Green et al. 1989 (24 healthy subjects), and Sauder et al. 1986; 1987 (9 healthy subjects and 9 asthmatic subjects) (see Table 1) in which eye and nose/throat irritation were all scored "less than mild" or "mild to moderate" at 3 ppm for exposure durations of 1 to 3 hours, the AEGL-1 should be set at 3 ppm. The rankings of "less than mild" to "less than moderate" sensory irritation at 3 ppm falls below the definition of notable discomfort or irritation defined by the AEGL-1 and therefore is a NOAEL for the AEGL-1. The definition of the AEGL-1 reads, "AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure. Airborne concentrations *below* the AEGL-1 represent exposure levels that could produce *mild and progressively increasing* but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects."

Because 99 subjects were tested including asthmatics (a potentially sensitive population), there is no need for an uncertainty factor. The 3 ppm concentration is supported by the less than moderate eye, nose, and throat irritation at 2 ppm in the well conducted study of Witek, et al. 1986; 1987; and Schachter et al. 1985; 1986 with 15 healthy and 15 asthmatic subjects and by the studies of Frigas et al. 1984 (symptoms similar between control exposures and exposures to 3 ppm) and Weber-Tschopp et al. 1977 (eye and nose irritation reported as "a little" during short exposures to 4 ppm).

Support for AEGL-1 of 3 ppm: well-conducted histopathological animal studies

Rats

1 ppm for 6 hours/day, for 3 days: **no** nasal lesions (Cassee et al. 1996)
1 ppm for 22 hours/day, 7 days/week for 26 weeks: **no** nasal lesions (Rusch et al. 1983)
2 ppm for 1, 4, or 9 days or 6 weeks: **no** nasal lesions (Monticello et al. 1991)
3 ppm for 6 hours for 1 day: **no** nasal lesions (Cassee et al. 1996)
nasal lesions observed when exposure was extended to 3 days (Cassee et al. 1996)
3 ppm for 22 hours/day, 7 days/week for 26 weeks: squamous metaplasia/hyperplasia of the nasal turbinates (Rusch et al. 1996)

Mice

2 ppm 6 hours/day, 5 days/week for 13 weeks: **no** nasal lesions (Maronpot et al. 1986)
3 ppm for 6 hours/day, for 5 days: minimal respiratory epithelial hypertrophy (Buckley et al. 1984)
4 ppm for 6 hours/day 5 days/week for 13 weeks: nasal lesion in 1/20 mice ((Maronpot et al. 1986)
5 ppm for 6 hours/day for 4 days: **no** nasal lesions (Zissu 1995)
nasal lesions observed at 15.8 ppm under same conditions (Zissu 1995)

Time Scaling of AEGL-3

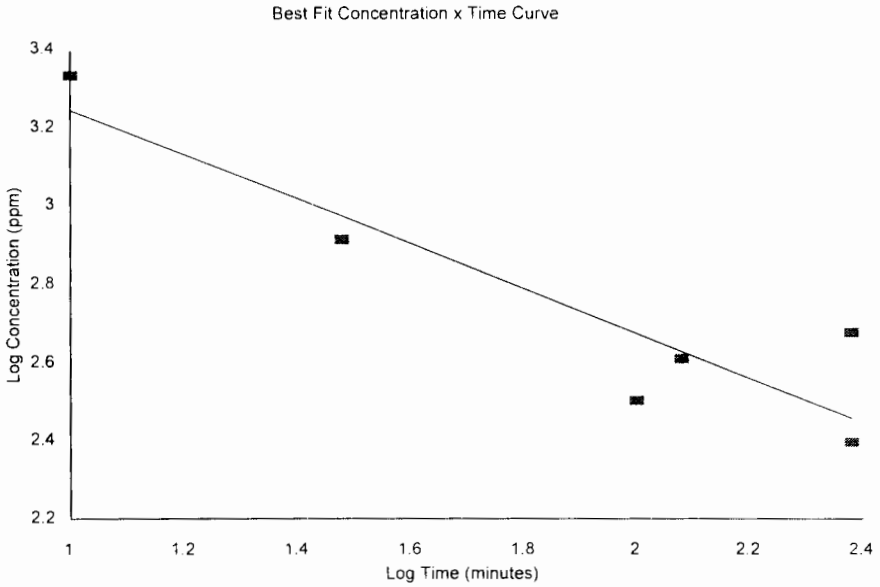
At the NAC-28, the n value for time scaling of the AEGL-3 was set at 3.9. This value was based on two of five LC_{50} values: the 30-minute LC of 820 ppm (Skog 1950) and the 4-hour LC_{50} of 478 ppm (Nagorny et al. 1979). Both of these were rat studies. This n value is extremely high for an irritant (dose-response curves for irritants are generally steep, resulting in low n values). Since the NAC-28 meeting, an additional 10-minute LC_{50} of 2162 ppm for the mouse (Alarie 1981) was located. All of the LC_{50} studies suffer from shortcomings. However, when graphed together, whatever the defects, the n value is 1.76 (see graph). I suggest that either we use all of the empirical data, rat and mouse, or, because most of the data are somewhat flawed, we use the default time-scaling values of 3 and 1. In either case, we would need to set the 8-hour value equal to the 4-hour value of 35 ppm because formaldehyde is well scrubbed by the nasal tissues. A lower value at 8 hours would be inconsistent with the animal data. For example, mice, the most sensitive species, survived three weeks of exposure to 40 ppm (6 hours/day, 5 days/week); one of 20 mice died during the third week (Maronpot et al. 1986). There are additional studies at similar concentrations.

Proposed Formaldehyde AEGLs

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	3 ppm	3 ppm	3 ppm	3 ppm	1 ppm
AEGL-2	14 ppm	14 ppm	14 ppm	14 ppm	14 ppm
AEGL-3					
n = 3.9 (NAC-28)	79 ppm	60 ppm	50 ppm	35 ppm	29 ppm
n = 3,1	100 ppm	70 ppm	56 ppm	35 ppm	35 ppm
n = 2	170 ppm	99 ppm	70 ppm	35 ppm	35 ppm
n = 1.76	210 ppm	114 ppm	77 ppm	35 ppm	35 ppm

AEGL-3 PoD: 4-hour non-lethal exposure of rats to 350 ppm (Nagorny et al. 1979).

Regression curve of formaldehyde LC_{50} values



Reference	Species	Time	Concentration	Log Time	Log Conc.
Alarie (1981)	mouse	10	2160	1.0000	3.3345
Skog (1950)	rat	30	820	1.4771	2.9138
B&A (1978)	mouse	100	320	2.0000	2.5051
Nagorny	mouse	120	410	2.0792	2.6128
Carpenter	rat	240	250	2.3802	2.3979
Nagorny	rat	240	478	2.3802	2.6794

n = 1.76
k = 5060814
r^2 = 0.8381

Formaldehyde: Level of Distinct Odor Awareness

The LOA derivation follows the guidance given by van Doorn et al. (2002).

The odor detection threshold (OT_{50}) for formaldehyde was reported to be 0.145 ppm (Berglund et al. 1987).

The concentration C leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function:

$I = k_w \times \log C / OT_{50}) + 0.5$

For the Fechner coefficient, the default of $k_w = 2.33$ will be used due to the lack of chemical-specific data:

$3 = 2.33 \times \log C / 0.145) + 0.5$ which can be rearranged to
$\log C / 0.145) = (3 - 0.5) / 2.33 = 1.266$ and results in
$C = (10^{1.266}) \times 0.145 = 2.675$ ppm

The resulting concentration is multiplied by an empirical field correction factor of 1.33.
LOA = C x 1.33 = 2.675 ppm x 1.33 = 3.6 ppm

The LOA for formaldehyde is 3.6 ppm.

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

March 7-8, 2003

Final Meeting-28 Highlights

Eagle Gate East & West
Best Western Salt Lake Plaza Hotel
122 West South Temple
Salt Lake City, Utah 84101

INTRODUCTION

George Rusch, NAC/AEGL Chair, opened the meeting with brief remarks noting that this off-site meeting was in conjunction with the 42nd Annual Meeting of the Society of Toxicology. At the end of the meeting, George surveyed the committee members regarding their opinion on having the regular quarterly NAC/AEGL meetings in conjunction with other meetings such as SOT. EPA staff scientists, George Woodall and Marquea King, were introduced. George noted the absence of Roger Garrett, AEGL Program Director, due to illness.

Paul Tobin provided an update from EPA on the use of data involving human subjects for development of AEGL values (Attachment 1). In addition, Ernie Falke referred to the Standing Operation Procedures (SOPs) for a statement on human studies. The SOPs state that no data on humans known to be obtained through force, coercion, misrepresentation or any other such means will be used in the development of AEGLs (Attachment 2).

Paul Tobin reported that an internal AEGL web site is under development and will be maintained by Po-Yung Lu. In the near future, draft TSDs and key references will be available on the web site prior to NAC/AEGL meetings. Ursula Gundert-Remy mentioned that the Europe ACUTEX is making good progress and will keep the NAC/AEGL updated in the future.

The draft NAC/AEGL-27 meeting highlights were reviewed; two minor changes were suggested. John Morawetz asked for clarification on whether the meeting had discussed if the health effects found in toluene studies below 200 ppm were considered AEGL 1 effects. He also was concerned about how the committee should proceed if a member raises a question on the accuracy of the description of a paper used in the TSD section on the derivation of AEGL values. He proposed that the committee either reach a consensus on the description of the paper or postpone discussion on the derivation section and withhold judgment until there is a consensus. A motion was made by Mark McClanahan and seconded by John Hinz to accept the meeting highlights as presented with

the aforementioned revisions. The motion passed unanimously by a voice vote. The final version of the NAC/AEGL-27 meeting highlights is attached (Appendix A) and was distributed to the NAC/AEGL by e-mail on March 28, 2003.

The highlights of the NAC/AEGL-28 meeting are summarized below along with the Meeting Agenda (Attachment 3) and the Attendee List (Attachment 4). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-28 Agenda.

STATUS REPORTS

NRC/COT/AEGL Subcommittee Review Meeting of January 27-29, 2003

Ernie Falke reported that a total of 13 (new and revisited) TSDs were reviewed in January at Irvine, CA. They are Acrylic acid, Allylamine, Carbon monoxide, Chlorine dioxide, Crotonaldehyde, Cyclohexylamine, Ethylenediamine, Ethyleneimine, HFE-7100, Hydrogen sulfide, Methanol, Phenol, and Propyleneimine. In addition to reviewing the TSDs, the concept of LOA was introduced to COT/AEGL subcommittee. The COT/AEGL supported the concept of LOAs. LOA methodology will be incorporated into the SOPs in the near future.

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

Roger Garrett and George Alexeeff had a number of discussions on the TSDs of concern. A summary status report (Attachment 5) was prepared by Po-Yung Lu and distributed to the NAC/AEGL for information and any further discussion. It appeared that no more clarification is warranted and a motion was made by George Alexeeff and seconded by Bill Bress to accept the status report. The motion was approved by a unanimous voice vote (Appendix B).

TECHNICAL ISSUE DISCUSSIONS

LOA Subcommittee Report: Data Quality Report
Mark McClanahan

Mark McClanahan summarized the odor subcommittee's February 13, 2003 conference call. George Alexeeff discussed three tables he had developed showing chemical specific sub-AEGL-1, AEGL-1 and AEGL-2 signs/symptoms identified in the TSDs. Most of the discussion focused on the AEGL-1 table. The AEGL-1 table includes those signs/symptoms used to define the AEGL-1 level as well as those classified as more severe than AEGL-1 but not AEGL-2 signs/symptoms. The participants expressed some confusion with the AEGL-1 table. George Alexeeff will revise the AEGL-1 signs/symptoms table. He may produce two separate tables or designate those signs/symptoms which have not been used to define AEGL-1 but have been identified in the TSDs

as below AEGL-2 with an asterisk. George Alexeeff will revise this table and present all three tables at the June meeting. He will also produce a more compact set of tables (not chemical specific) with just signs/symptoms for these three levels: less than AEGL-1, AEGL-1 (but less than AEGL-2) and AEGL-2.

The subcommittee also discussed a paper about NOAELs/LOAELs published by George Alexeeff that led to the suggestion that George present his findings at the June meeting. With approval of the NAC/AEGL a description of George's findings along with how the NAC/AEGL will use this information will be placed in the SOPs.

Overview of Fundamental Principles of Industrial Hygiene
John Morawetz

John Morawetz gave a presentation on Basic Occupational Exposure Assessment, noting the variability in exposures in the work environment, the different types of occupational samples and collection devices, and the variable sampling times. He compared the constant exposure to all subjects in animal and human chamber studies to the variability in occupational exposures, the basic sources of occupational variation, and the various types of exposure measurements (area, personal, short-term, time-weighted-averages, bulk) (Attachment 6). He then presented a draft proposal for the evaluation of human exposure measurements in the occupational setting (Attachment 7). The committee agreed with the first two points of his proposal that breathing zone samples are preferable and that the type of sample should be clearly described in the TSD (Appendix C). Discussions on the rest of John Morawetz's proposal was deferred to the June meeting when Ed Bishop of the NRC/COT will be attending. A working team was formed to explore these issues further.

AEGL Applications: Relevance to Occupational Exposures
George Rusch

A revised draft of the application of Acute Exposure Guideline Levels was distributed at the meeting (Attachment 8) representing input from several committee members. It was briefly discussed before the decision was made to defer further discussion to the NAC/AEGL-29 meeting.

Iron pentacarbonyl
CAS Reg. No. 75-55-8

Chemical Manager: Ernie Falke, EPA
Staff Scientist: Bob Young, ORNL

Ernie Falke reviewed the values that were originally approved by the NAC/AEGL in NAC/AEGL-25 (June 2002) (Attachment 9). The point-of-departure (POD) for the AEGL-3 was 2.91 ppm for 6 hours which resulted in the death of 1/10 rats (a second exposure resulted in 50% mortality). The NAC/AEGL decided to revisit the AEGL-3 because it was based on a "LOAEL." There was uncertainty as to how many deaths actually resulted from the single exposure as deaths may not occur for several days. Ernie did a benchmark dose analysis (log probit) of the BASF (1995) rat data using two scenarios: 1 of 10 or 5 of 10 animals would have died from the exposure to 2.91 ppm. Assuming 1/10 deaths, the resulting MLE LC_{01} and BMDL LC_{05} were 2.4 and 1.7 ppm, respectively. Assuming 5/10 deaths, the resulting respective values were 1.9 and 0.80 ppm (Attachment 9). Normally the more conservative BMDL LC_{05} of 0.80 ppm would apply. However, no deaths occurred when 10 rats were exposed to 1.0 ppm for 6 hours/day for up to 28 days. Therefore, 1.0 ppm was chosen as a more reasonable POD. Because the rat is 2-3 times more sensitive than the mouse (based on the data of Sundeman et al. 1959) and a very conservative endpoint was used (no deaths for 28 days), an interspecies uncertainty factor of 1 is reasonable. An intraspecies uncertainty factor of 3 as used in the original derivation was retained. Time-scaling utilized n = 1. Steve Barbee noted that the Sundeman et al. (1959) experiment was for only 5 days, a more reasonable acute exposure (the data involved an exposure to 118 ppm and a suggested total UF of 30). It was decided to use the Sundeman et al. (1959) data for support. It was moved Loren Koller and seconded by Mark McClanahan to accept the rederived AEGL-3 values of 3.6, 1.2, 0.60, 0.15, and 0.075 ppm. The motion passed unanimously (YES: 18; NO: 0; Abstain: 0) (Appendix D). There was comment about the 8-hour AEGL-3 value being lower than the ACGIH-TLV.

The original AEGL-2 values were calculated by dividing the AEGL-3 values by 3 (supported by the steep dose-response curve). Tom Hornshaw suggested a larger factor such as 6, based on the 3 for the steep dose-response curve and 2 for bad data. He also suggested looking at nickel carbonyl to derive a structure-activity relationship. The discussion was tabled at this point. When the discussion was resumed, the consensus was that nickel carbonyl was not a good surrogate for iron pentacarbonyl (this included differences in species sensitivity). It was moved by Bob Benson and seconded by Bob Snyder to retain the original AEGL-2 values. The motion passed (YES:15; NO: 0; Abstain: 1) (Appendix E). It was noted that the reduction factor of 3 must be justified.

REVIEW AND RESOLUTION OF COT/AEGL COMMENTS

Ethyleneimine
CAS Reg. No. 107-15-3
&
Propylenimine
CAS Reg. No. 75-55-8

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

TSDs of Ethyleneimine and Propylenimine were reviewed by COT/AEGL in January 2003. They were approved by COT/AEGL pending the availability of data to develop an LOA. Kowetha Davidson presented the available odor information (Attachement 10) used to develop LOA values for these two chemicals. Marc Ruijten provided the calculation of the LOA based upon an odor threshold (OT_{50}) for ethyleneimine of 0.698 ppm. This gave an LOA, under field conditions, of 10.8891 which to two figures is 11 ppm. The 10 and 90 percent population response estimates are 2.1 to 56 ppm, respectively. (Under laboratory conditions the default values gives a factor of 12 times the OT_{50} while under field conditions the factor is 16.) A motioned was made by Ernie Falke to accept the LOA of 11 ppm; the motion was seconded by Richard Thomas. The motion passed (YES: 16; NO: 0; Abstain: 1) (Appendix F).

There are no odor threshold data for propylenimine so an LOA value could not be calculated.

Piperidine
CAS Reg. No. 110-89-4

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

The NAC/AEGL committee initially considered piperidine at the June 1997 meeting at which time there was insufficient data on which to base development of either AEGL-2 or AEGL-3 values. Since that time, BASF has made available two studies upon which to base AEGL values.
A motion was proposed by John Hinz and seconded by Nancy Kim to set aside AEGL-1 values developed in Sept. 1998. The motioned was unanimously approved (Appendix G). Kowetha Davidson presented data analyses of the two studies (Attachment 11).

The AEGL-1 values were based on the lowest concentration (50 ppm) that caused nasal irritation in rats (nasal secretions and bloody encrustation) during and after a 6-hour exposure; there was no eye irritation at this concentration (BASF, 1990). Uncertainty factors (UF) of 3 for interspecies sensitivity and 3 for intraspecies variability (total UF = 10) were applied to the 50-ppm exposure. The rationale for selecting interspecies and intraspecies UFs of 3 is as follows: (1) the effect observed at 50 ppm was mediated by direct contact of piperidine (corrosive agent) with the nasal epithelium without involvement of other regions of the respiratory tract, and (2) the composition of the nasal mucosa is similar among species and among individuals within the population. After applying a total uncertainty factor of 10, the resulting value of 5 ppm was time scaled based on ten Berge's equation, $C^n \times t = k$. Scaling was based on regression of LC_{50} values for the mouse, guinea pig, and rat (n = 1.5). The 6-hour exposure was scaled to other time points except that the 30-minute value was retained for 10 minutes. It was proposed by Bob Snyder and seconded by Bob Benson to adopt the proposed AEGL-1 of 10, 10, 6.6, 2.6, and 1.7 ppm for 10-, 30-minutes, 1-, 4- and 8-hours, respectively. The motion passed (YES:14; NO:1; Abstain:0) (Appendix G).

The initially proposed AEGL-2 values were based on the concentration of piperidine (200 ppm) that caused nasal irritation along with salivation and evidence of some eye irritation within a 6-hour exposure duration. This value was considered a NOAEL for severe irritation. Uncertainty factors and the time scaling procedure were the same as described for derivation of AEGL-1 values. The 30-minute value was retained for 10 minutes because of scaling from a 6-hour exposure. It was proposed by Bob Snyder and seconded by John Hinz to adopt the proposed AEGL-2 of 100, 100, 66, 26 and 17 ppm for 10-, 30-minutes, 1-, 4- and 8-hours, respectively. The motion failed (YES:8; NO: 6; Abstain:1) (Appendix G). A new endpoint was considered in which the AEGL-2 values were based on the concentration (100 ppm) of piperidine that had no effect on CNS, but caused some irritation (nasal crusts) within a 6-hour exposure duration. Uncertainty factors and the time-scaling procedure were the same as described for derivation of AEGL-1 values. A motion was made by Richard Thomas and seconded by John Hinz to accept the new set of AEGL-2 values: 50, 50, 33, 13, and 8.3 for 10 and 30 minutes and 1, 4 and 8 hours, respectively. The motion passed (YES:11; NO: 2; Abstain:2) (Appendix G).

The AEGL-3 values were based on the LC_{01} calculated from 4-hour lethality data in rats. The LC_{01} of 448 ppm for a 4-hour exposure is lower than the lowest concentration that caused one death among 20 rats (5% lethality) and higher than the concentration that caused no deaths or clinical signs indicative of death. Uncertainty factors of 3 for interspecies sensitivity and 3 for intraspecies variability (total UF = 10) were applied to the LC_{01}. The data for comparing species sensitivity to lethal concentrations of piperidine are very scarce. The reported LC_{50} values for 4-hour exposures was 5996 mg/m^3 for the mouse and 4800 mg/m^3 for the rat, which is only 20% lower than that for the mouse. These data support an uncertainty factor for interspecies sensitivity of 3. The uncertainty factor for intraspecies variability is 3, because an uncertainty factor of 10 would produce AEGL values for 1, 4, and 8 hours lower than the irritation threshold of 26 ppm. The time scaling procedure was the same as described for AEGL-1. It was proposed by George Alexeeff and seconded by John Hinz to adopt the proposed AEGL-3 values of 370, 180, 110, 45, and 28 ppm for 10 and 30-minutes and 1, 4 and 8 hours, respectively. The motion carried (YES:13; NO: 0; Abstain: 2) (Appendix G).

Proposed AEGL Values for Piperidine (ppm)						
Classification	10 minutes	30 minutes	1 hour	4 hours	8 hours	Endpoint/ Reference
AEGL-1 (Nondisabling)	10	10	6.6	2.6	1.7	nasal irritation/ BASF, 1990
AEGL-2 (Disabling)	50	50	33	13	8.3	nasal irritation, signs of eye irritation, salivation /BASF, 1990
AEGL-3 (Lethal)	370	180	110	45	28	threshold for lethality/ BASF, 1980

The level of distinct odor awareness under field conditions (LOA) for piperidine, based on an OT_{50} of 0.37 ppm is 5.7775 or 5.8 ppm and the estimated 10 and 90 percent population response values

are 1.127 or 1.1 ppm and 29.6176 or 30 ppm. A motion was made by Richard Thomas and seconded by Nancy Kim to accept this value and population response estimates for piperidine. The motion carried (YES:12; NO: 1; Abstain:2) (Appendix G).

REVIEW of PRIORITY CHEMICALS

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

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

The chemical review on carbon disulfide (CS_2) was presented by Jens-Uwe Voss (Attachment 12). AEGL-1 and AEGL-3 values had already been derived in September 2002 (NAC/AEGL-26). The derivation of AEGL-3 was based on data from a study (Du Pont 1966) that was available from secondary sources at that time. Therefore, it was noted at the meeting that the original study is necessary to check the acceptability of the data. The original study was provided by Du Pont and the acceptability was confirmed.

With respect to possible AEGL-2 relevance, effects on the central nervous system (CNS) and effects on the developing embryo/fetus were discussed. Developmental effects (malformations) were observed in animal studies with repeated administration of carbon disulfide for at least one third of the whole gestational period, but no developmental toxicity study with a single exposure was available. The data base was inconsistent as effects reported in Yang et al. 1993 (abstract) and in Tabacova et al. 1978 were not seen in several other studies at higher exposure levels (e.g. Saillenfait et al. 1989). Carbon disulfide reacts with the NH_2-group of endogenous compounds (e.g., amino acids) forming dithiocarbamates. Since some dithiocarbamate chemicals are reproductive and/or developmental toxins in animals, it was discussed whether endogenously formed dithiocarbamates could play a role in the occurrence of developmental effects following carbon disulfide exposure. Although this cannot be ruled out, it has to be taken into account that while carbon disulfide itself is rapidly eliminated from the body after ceasing exposure, the so-called "acid-labile" pool of bound carbon disulfide containing thiocarbamates has a long half-life and increases with daily repeated exposures. Therefore, it is unclear whether developmental effects observed after repeated exposure to carbon disulfide are of relevance for single acute exposures. For the reasons noted above, it was agreed that developmental effects should not be used for the derivation of AEGL-2 values for carbon disulfide.

Regarding effects on the CNS, a single exposure of rats for 4 hours to 2000 ppm led to an inhibition of the escape response (pole climbing in response to a buzzer to avoid electrical shock); no such effect was seen at 1000 ppm (NOAEL). This concentration was used as a starting point to derive AEGL-2 values. A total uncertainty factor of 10 was applied. The interspecies uncertainty factor was reduced to 3 based on the similarity of acute effects on the CNS produced by CNS-depressing

agents in rodents and humans. Moreover, use of a default interspecies uncertainty factor of 10 would have resulted in values which are contradicted by experimental human studies in which no serious or escape-impairing effects were reported during or following 6-8 hours of exposure to 80 ppm. An intraspecies uncertainty factor of 3 was applied to account for sensitive individuals because the threshold for CNS impairment is not expected to vary much among individuals. Time scaling was performed according to the equation $C^n \times t = k$, using the default of $n = 3$ for shorter exposure periods (30 minutes and 1 hour) and $n = 1$ for longer exposure periods (8 hours), due to the lack of suitable experimental data for deriving the concentration exponent. For the 10-minute AEGL-3 the 30-minute value was used because the derivation of AEGL-3 values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response. A motion was made by John Hinz and seconded by George Rodgers to adopt the proposed AEGL-2 values for carbon disulfide for 10 minutes to 8 hours of 200, 200, 160, 100, and 50 ppm, respectively. The motion passed (YES: 16; NO: 2; Abstain:0) (Appendix H).

Regarding odor annoyance, no study was available that could be used to derive a level of distinct odor awareness (LOA). The odor of carbon disulfide depends on the purity of the compound. Purest carbon disulfide has a chloroform-like pleasant smell. However, due to decomposition products, commercially available carbon disulfide typically has an unpleasant repulsive odor of decaying radish. The quality and intensity of the odor will vary with the amount of these decomposition products that are rapidly formed by the exposure of carbon disulfide to light and air. A motion was made by Thomas Hornshaw and seconded by John Hinz that a LOA should not be derived. The motion passed unanimously (YES: 17; NO: 0; Abstain: 0) (Appendix H).

Summary of AEGL Values For Carbon Disulfide [ppm]						
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	5.0	5.0	4.0	2.5	2.0	Increase in blood acetaldehyde in humans with moderate intake of alcohol (Freundt et al. 1976b)
AEGL-2 (Disabling)	200	200	160	100	50	Inhibition of escape response in behavioral study in rats (Goldberg et al. 1964)
AEGL-3 (Lethal)	600	600	480	300	150	Lethality in rats after 4 hours (0/6 at 3000 ppm; 6/6 at 3500 ppm) (Du Pont 1966)

Formaldehyde
CAS Reg. No. 50-00-0

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

Sylvia Talmage reviewed the data base on formaldehyde (Attachment 13). There were approximately 22 studies with human subjects involving controlled exposures. The data base on animal studies involving acute exposures is less robust. Because formaldehyde is a carcinogen in the rat, most animal studies involved chronic exposures. The discussions for each AEGL level were long and covered ranges of topics including the threshold for sensory irritation, the range of variability in the population, and formaldehyde-induced sensory irritation in mobile homes.

Initially, AEGL-3 values of 127, 88, 70, 35, and 18 ppm for the 10-minute through 8-hour exposure durations, respectively, were proposed. The basis was no deaths in rats exposed to 350 ppm for 4 hours (Nagorny et al. 1979). Interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were used. No data on time-scaling were available so the default n values of 3 and 1 were applied. It was moved by Richard Thomas and seconded by Steve Barbee to accept these values. Later, during a discussion of a proposed AEGL-2 value of 13.8 ppm across time, it was noted that the 8-hour AEGL-3 value might be too similar to the AEGL-2 value. Therefore, the original AEGL-3 values were withdrawn and new numbers were proposed. It was decided to use the two LC_{50} values for the rat (from two different studies) to derive an n value of 3.9. The 350 ppm value was divided by a total uncertainty factor of 10 and time scaled using n = 3.9. The resulting values were 79, 60, 50, 35, and 29 ppm for the 10-minute through 8-hour exposure durations, respectively. It was moved by Richard Thomas and seconded by Steve Barbee to accept these values. The motion passed (YES: 17; NO: 1; Abstain: 0) (Appendix I).

The proposed AEGL-2 value of 8 ppm across time was discussed (as were values based on other studies), but rejected by the NAC in favor of a 30-minute exposure of human subjects to 13.8 ppm (Sim and Pattle 1957). The endpoint was nasal and eye irritation with mild lacrimation; there was adaptation to the eye irritation. It was moved by John Hinz and seconded by Richard Thomas to adopt 14 ppm (rounded up from 13.8 ppm) for all time points. The motion passed (YES: 14; NO: 2; Abstain: 2) (Appendix I). Animal cancer studies with chronic exposures to 14 ppm would be used as support. The Douglas (1974) study with exposures to 8 and 13 ppm via goggles and a mouthpiece was to be located to see if it would be relevant as a support document (only an abstract was available at the present time).

An AEGL-1 of 1 ppm for all time points, based on the weight-of-evidence from multiple studies was initially proposed. It was moved by George Rodgers and seconded by Ernie Falke to accept this value. The motion failed (YES: 8; NO: 9; Abstain:1)(Appendix I). It was then moved by Bob Benson and seconded by Marinelle Payton to use 0.4 ppm across all time points. This value was reported as irritating in two of the many human studies. Other studies showed more severe irritation at higher exposures. The motion passed (YES: 13; NO: 3; Abstain: 1) (Appendix I).

Summary of AEGL Values for Formaldehyde						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1[a]	0.40 ppm	0.40 ppm	0.40 ppm	0.40 ppm	0.40 ppm	Eye irritation and rhinitis - humans (Pazdrak et al. 1993; Krakowiak et al. 1998)
AEGL–2	14 ppm	14 ppm	14 ppm	14 ppm	14 ppm	Mild lacrimation with adaptation (Sim and Pattle 1957)
AEGL–3	79 ppm	60 ppm	50 ppm	35 ppm	29 ppm	Highest non-lethal value - rat (Nagorny et al. 1979)

Acetone
CAS Reg. No. 67-64-1

Chemical Manager: Mark McClanahan, CDC
Staff Scientist: Jens-Uwe Voss/Gerhard Rosner, Germany

The chemical review on acetone was presented by Jens-Uwe Voss (Attachment 14). Acetone is the most widely used ketone in industry. In 1994, worldwide production capacity was about 3.8 million tonnes. Acetone is used primarily as a solvent and to synthesize methacrylates, bisphenol A, and other ketones. Owing to its high volatility and flammability (explosive limits in air, lower: 2.6 %, upper: 12.8 % v/v), acetone poses an acute fire and explosion hazard.

In humans and other mammalians, acetone is a minor metabolite of normal intermediary metabolism. Consequently, small quantities may occur in exhaled air. Endogenous acetone formation is closely linked with ketogenesis in the catabolism of body fat. Concentrations above normal levels in body tissues build up during fasting and especially in diabetic patients in the ketoacidotic state.

The primary effects in humans are irritation and effects on the central nervous system (CNS). CNS effects are also observed in animals following acute inhalation exposure. Acetone is not genotoxic *in vitro* and *in vivo*. Carcinogenicity studies are lacking, but dermal carcinogenicity studies in which acetone is used as vehicle control did not provide evidence of tumorgenic activity. Isopropanol which is primarily metabolized to acetone in mammals was not considered carcinogenic in a two-year inhalation carcinogenicity study with rats. In developmental toxicity studies with repeated exposure, reduced maternal and fetal weight was observed but the incidence of malformations was not significantly increased.

The AEGL-1 derivation is based on observations in four studies with human volunteers exposed for 3-5 minutes (Nelson et al. 1943), 2 hours (Ernstgard et al. 1999), 6 hours (Matsushita et al. 1979a) and 7.5 hours (Stewart et al. 1975). At 200 ppm, subjective symptoms (feeling of eye/throat

irritation) were not reported more often than in controls (Stewart et al. 1975). At 250 ppm, no irritative symptoms on mucous membranes or effects on the CNS were observed in one study (Ernstgard et al. 1999); in a second study, slight irritation and subjective discomfort (feeling of tension, general weakness, heavy eyes, lacking in energy) was felt at 250 ppm, and these subjective symptoms were felt by most volunteers at 500 ppm and 1000 ppm (Matsushita et al. 1969a). Slight feeling of irritation at 300 ppm and subjective irritation in the majority of exposed volunteers at 500 ppm were reported in a further study (Nelson et al. 1943). Therefore, 200 ppm were selected to derive AEGL-1. Because this concentration represents a NOAEL for local effects and effects at higher concentrations were weak, an intraspecies factor of 1 was applied. The value of 200 ppm was used for all time points since accommodation to slight irritation occurs and the complaints about subjective discomfort at higher concentrations were reported not to increase during 6 hour or 7.5 hour exposure. A motion was made by Nancy Kim and seconded by Tom Hornshaw to adopt 200 ppm as AEGL-1 for all time points. The motion passed unanimously (YES: 18; NO: 0; Abstain: 0) (Appendix J).

The AEGL-2 is based on the NOAEL for ataxia in rats following exposure to 6000 ppm acetone for 4 hours (Goldberg et al. 1964). At the next higher concentration of 12,000 ppm, reversible ataxia was observed. Reversible ataxia also was observed in another study at exposure of rats to 12,600 ppm for 3 hours, but a no-effect level was not determined in that study (Bruckner and Peterson 1981a). A total uncertainty factor of 4.2 was applied. An intraspecies uncertainty factor of 4.2 was applied to account for sensitive individuals. This substance-specific factor was derived from a study with rats of different ages in which it was observed that the lethal dose of acetone via intraperitoneal injection was 4.2-fold lower in newborn than in adult rats (Kimura et al. 1971). Additionally, in humans it is consistently observed for volatile anesthetics that newborns are the most sensitive age group (NRC 2001). An interspecies factor of 1 was used: toxicokinetic studies show that following inhalation the concentration of acetone in blood is similar or lower in humans than in rats. Furthermore, with respect to toxicodynamics, effects of substances such as acetone that are non-specific acute CNS-depressants in general do not show much variation between species. Finally, an interspecies factor of 3 which is often used in the derivation of AEGLs for CNS-depressant volatile solvents like acetone would (together with an intraspecies factor of 4.2) have resulted in AEGL-2 values of 480 ppm for 4 hours and of 320 ppm for 8 hours. These values are not supported by data from controlled human studies in which higher exposures for up to 7.5 hours resulted in irritation and slight headaches but no more severe effects. Furthermore, available toxicokinetic data for humans show that an exposure to such concentrations would lead to acetone concentrations in blood below 50 mg/L. Such concentrations are still in the physiological range which can be observed in healthy fasting humans. A substance specific intraspecies uncertainty factor of 4.2 was applied to account for sensitive individuals. The experimentally derived exposure values were scaled to AEGL time frames using the equation $c^n \times t = k$ with $n = 1.7$ as outlined below for AEGL-3. A motion was made by Richard Thomas and seconded by John Hinz to adopt AEGL-2 values for acetone for 10 min., 30 min., 1 h, 4 h, and 8 h of 9300, 4900, 3200, 1400, and 950 ppm, respectively. The motion passed (YES: 15; NO: 1; Abstain: 1) (Appendix J).

The AEGL-3 is based on a study in rats in which no deaths of animals occurred at exposure to 12,600 ppm for 3 hours (Bruckner and Peterson 1981a). In that study, also no deaths were observed in animals exposed to 19,000 and 25,300 ppm, but since 1 of 6 animals died at 16,000 ppm in another study (Smyth et al. 1962), the findings at 12,600 ppm exposure for 3 hours were taken as basis for the derivation of AEGL-3. A total uncertainty factor of 4.2 was applied. An interspecies uncertainty factor of 1 was used because the same toxic effects (CNS-depression) which are relevant for AEGL-2 are also relevant in case of AEGL-3. The experimentally derived exposure values were scaled to AEGL time frames using the equation $c^n \times t = k$ with a value of $n = 1.7$ that was derived by extrapolation from 4-hour and 8-hour LC_{50} data (Pozzani et al. 1959). A motion was made by John Hinz and seconded by Tom Hornshaw to adopt AEGL-2 values for acetone for 10 min., 30 min., 1 h, 4 h, and 8 h of 16000, 8600, 5700, 2500, and 1700 ppm, respectively. The motion passed (YES: 16; NO: 2; Abstain: 0) (Appendix J).

The AEGL-2 values for 10 minutes, 30 minutes and 1 hour and the AEGL-3 values for 30 minutes, 1 hour and 4 hours are higher than 1/10 of the lower explosive limit (LEL) of acetone in air. The AEGL-3 value for 10 minutes is higher than 1/2 of the LEL of acetone in air. It was discussed and proposed to mark values higher than 1/10 of the LEL by an asterisk and to indicate in a footnote that safety considerations against hazard of explosion must be taken into account at these levels. Similarly, it was proposed to replace values higher than 1/2 of the LEL in the table by a remark „see below" and to present the value in a footnote together with a note that extreme safety considerations against hazard of explosion must be taken into account at these levels. Both proposals were accepted by specific count of hands for or against not recorded.

As additional information for emergency responders, a level of distinct odor awareness (LOA) was derived. The LOA is based on a median odor detection threshold of 41 ppm (Wysocki et al. 1997) and a threshold of 0.16 ppm for the reference chemical n-butanol in the same study. Wysocki et al. (1997) reported that no correlation was observed between acetone and n-butanol olfactory thresholds in that study. However, since the reference odor threshold of 0.04 ppm for n-butanol is based on a large number of data, it was discussed to use a corrected odor threshold of 41 x (0.04/0.16) ppm. Using a default factor of 16, a LOA of 170 ppm was calculated. A motion was made by Richard Thomas and seconded by John Hinz to adopt a LOA of 170 ppm provided that no objection will be made by Mark Ruijten who will be asked as an expert for the calculation of odor values. The motion passed unanimously (YES:17; NO: 0; Abstain:0) (Appendix J).

SUMMARY TABLE OF AEGL VALUES FOR ACETONE [ppm] [a]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	200	200	200	200	200	NOAEL for slight irritation (Ernstgard et al. 1999; Matsushita et al., 1969a; Nelson et al. 1943; Stewart et al. 1975)
AEGL-2	9,300*	4,900*	3,200*	1,400	950	Ataxia in rats (Bruckner and Petersen 1981a; Goldberg et al. 1964)
AEGL-3	see below #	8,600*	5,700*	2500*	1,700	No lethality in rats (Bruckner and Petersen 1981a; Smyth et al. 1962)

a: Cutaneous absorption of liquid acetone may occur. Since liquid acetone is an eye irritant, eye contact must be avoided.

#: The AEGL-3 value of 16,000 ppm (39,000 mg/m³) for 10 minutes is higher than 50 % of the lower explosive limit of acetone in air (2.6 % = 26,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

*: Concentrations are higher than 1/10 of the lower explosive limit of acetone in air (2.6 % = 26,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

Level of distinct odor awareness: 170 ppm (Odor detection threshold in humans; Wysocki et al. 1997).

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

Chemical Manager: Bob Benson, EPA
Staff Scientist: Fritz Kalberlah, Germany

Susan Ripple, liaison for the American Chemistry Council to the NAC/AEGL fulfilled the request to provide insight on the issue of whether headaches in a few individuals can be attributed to vinyl chloride exposure (Attachment 15). Susan Ripple pointed out that there are 3 studies: Lester et al. 1963, Baretta et al. 1969, and further supported by Patty et al. 1930. These three studies found that at least some individuals developed headaches that lasted only 30 minutes at higher exposure-levels. This is consistent with anecdotal information from industry assessments. A detailed explanation of the carcinogenicity issue was presented, providing numbers of exposed workers in the cohort studies by Ward et al. 2000 and Mundt et al. 1999. Overall, there were 12,700 subjects in the vinyl chloride cohort study by Ward, with an SMR of 62 in 10,961 workers of less than 3 years exposure that developed liver cancer (ASL). Another way to look at these values is to calculate the ppm.years, where the ASL incidence in the unknown exposure population was 67, and for 1-734 ppm.years was an SMR of 107. Mundt likewise was presented in terms of length of exposure, with an SMR of 83 incidence of ASLs in the 1-4-year exposure time frame. The discussion of higher sensitivity in young and newborn rats as a possible cancer risk assessment approach was presented as highly uncertain as the studies by Maltoni et al. 1981 had study-design and reporting flaws. Chemical Manager, Bob Benson, responded to Susan Ripple's comments on the derivation of AEGL-1, AEGL-2, and the cancer assessment. For AEGL-2 Susan Ripple suggested that the NAC consider using a higher exposure (16,000 ppm for 5 minutes) from Lester et al. (1963) as the

starting point for the derivation. Bob Benson later indicated that the effects observed at this exposure (dizziness, light headedness, some nausea, and dulling of visual and auditory cues) were beyond the "threshold" for effects meeting the definition of AEGL-2. The NAC/AEGL used the next lower exposure of 12,000 ppm exposure as the equivalent of the "threshold" for effects that would impair the ability to escape and there was no need to reconsider this decision. For AEGL-1 Susan Ripple suggested that the NAC/AEGL consider using the same study and exposure as originally used (Baretta et al., 1969) but use 7 hours as the exposure duration. The justification was based on the fact that the original study did not make clear whether the headache occurred during the first 3.5 hours or the subsequent 3.5 hours of exposure. Bob Benson later responded and agreed that the wording in the publication did not make it absolutely clear when the headaches occurred but a reasonable interpretation of the text was that headache occurred in some individuals during both exposures. The wording in the text is "The only complaints were those of two subjects who reported mild headache and some dryness of their eyes and nose during the 500 ppm exposure experiments." A logical interpretation is that the authors consider there were two experiments - one with an exposure duration of 3.5 hours, and the other with an exposure duration of 7.5 hours (3.5 hours, a break of 0.5 hours, and then additional exposure of 3.5 hours) - and that headache was noted by two individuals during both exposures. Therefore it was logical to use 3.5 hours as the time required for headache as the NAC/AEGL had previously done. Therefore, there was no need to reconsider this decision. Susan Ripple also presented a discussion of another epidemiological study of workers exposed to vinyl chloride and occurrence of cancer (Ward et al., 2000). There appeared to be no increase in cancer following short term exposure. However, it was not clear whether actual exposure to VC was known. Susan Ripple agreed to provide a brief summary of this information for inclusion in the Technical Support Document.

Fritz Kalberlah presented a discussion of the cancer assessment (Attachment 16). The appendix included a cancer calculation for continuous lifetime exposure using the default procedure in the SOP; a cancer calculation based on childhood exposure using the unit risk estimate for childhood exposure derived by EPA; a cancer calculation based on derivation of a unit risk estimate from a five-week animal study from Maltoni et al. (1981); and a calculation based on the occurrence of DNA adducts after a single in vivo exposure of adult animals. There was considerable discussion about these calculations and how best to draw attention to the calculations in the Executive Summary of the Technical Support Document. Bob Benson and Fritz Kalberlah agreed to consider various alternatives and present these at a future NAC/AEGL meeting. The NAC/AEGL also requested that information on transplacental carcinogenicity be added to the document.

Hydrogen Bromide
CAS Reg. No. 10035-10-6

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

Sylvia Talmage reviewed the sparse data base for hydrogen bromide (Attachment 17). The AEGL-1 was based on the only available clinical study in which subjects were exposed to concentrations between 2 and 6 ppm for short periods of time (Conn. Dept. of Health 1955). 3 ppm was the NOAEL for notable discomfort as evidenced by nose and throat irritation (assumed to be slight) in 1 of 6 subjects. The 3 ppm value was divided by an intraspecies uncertainty factor of 3. No time scaling was applied because adaptation occurs to the slight irritation that defines the AEGL-1. It was moved by John Hinz and seconded by Nancy Kim to accept the AEGL-1 value. The motion passed (YES: 16; NO: 0; Abstain: 0) (Appendix K).

In the absence of chemical-specific data, it was proposed that the HBr AEGL-2 values be based on a structure-activity relationship with other hydrogen halides. The proposal to base the HBr AEGL-2 on hydrogen fluoride (HF) was rejected in favor of basing the values on the more chemically similar hydrogen chloride (HCl). It was moved by Mark McClanahan and seconded by Nancy Kim to accept the HCl values for the 10-minute to 8-hour time periods of 100, 43, 22, 11, and 11. The motion passed (YES: 15; NO: 0; ABSTAIN: 0) (Appendix K).

In response to earlier Committee suggestions, the benchmark concentration approach was used to develop AEGL-3 values. One-hour rat lethality data generated by MacEwen and Vernot (1972) were used. The $BMCL_{01}$ was suggested, but this suggestion was rejected in favor of the $BMCL_{05}$ (the $BMCL_{05}$ is the suggested approach in the SOPs). After much discussion it was moved by Ernie Falke and seconded by John Hinz to accept the $BMCL_{05}$ values of 740, 250, 120, 31, and 31 ppm. The 4-hour and 8-hour values were set equal as was done for HCl and HF, because all of these hydrogen halides are well scrubbed at lower concentrations. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix K).

SUMMARY OF AEGL VALUES FOR HYDROGEN BROMIDE (ppm)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	1	1	1	1	1	NOAEL for notable discomfort - humans
AEGL-2	100	43	22	11	11	Analogy with hydrogen chloride
AEGL-3	740	250	120	31	31	Benchmark concentration - rat lethality data

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

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

Experimental data will be available in later part of the year; then the TSD will be revisited accordingly.

Titanum tetrachloride
CAS Reg. No. 7550-45-0

Chemical Manager: Tom Hornshaw, Illinois EPA
Staff Scientist: Claudia Troxel, ORNL

The chemical review was presented by Claudia Troxel (Attachment 18). The AEGL-3 values were based on one-third of the rat LC_{50} values reported by Kelly (1980). The adjusted, empirical values (1/3 of the values) for the 30, 60, and 240-minute exposure durations were used for the respective AEGL time points. Using an n=0.88, the adjusted, 15-minute LC_{50} value was used to extrapolate to 10 minutes, while the adjusted 240-minute LC_{50} value was used to extrapolate to 480 minutes. A total uncertainty factor of 10 was applied to be consistent with available toxicity data. A motion was made by Loren Koller and seconded by Richard Thomas to adopt the proposed AEGL-3 values. The motion passed unanimously (YES: 17; NO: 0; Abstain: 0) (Appendix L).

The AEGL-2 was based on the exposure concentration of 1.3 ppm titanium tetrachloride for 6 hours/day, 5 days/week for 4 weeks (Kelly, 1979). Although no clinical signs were observed at this concentration, using the next higher exposure concentration of 6.5 ppm for 6 hours/day, 5 days/week for 4 weeks (Kelly, 1979) results in values approaching the lethality threshold. A total uncertainty factor of 10 was applied to be consistent with available toxicity data. The value was then scaled across time using the derived value of n=0.88. The 10-minute value was initially set equal to the 30-minute value because the NAC considers it inappropriate to extrapolate from an exposure duration of 6 hours to 10 minutes. A motion was made by Loren Koller and seconded by Richard Thomas to adopt the proposed AEGL-2 values. However, it was brought out at the end of the meeting that the AEGL-2 starting value could be scaled to the 10-minute time-period because the derived value of n used time points encompassing that particular time point. Therefore, the motion was amended so that the 10-minute AEGL-2 value would now be 7.6 ppm (instead of 2.2 ppm) following scaling across time. The motion passed (YES:17; NO: 0; Abstain: 0) (Appendix L).

No acute toxicity data relevant to the definition of an AEGL-1 endpoint are available. Therefore, the 0.7 ppm exposure for 6 hours/day was used to provide a general baseline of an exposure concentration at which no one should experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. A total uncertainty factor of 10 was applied (3 for interspecies and 3 for intraspecies) because the endpoint selected is below the endpoint defined for the AEGL-1 tier and because the study was a multiple exposure study. The value, 0.070 ppm, was then set equal across time. A motion was made by Loren Koller and seconded by Richard Thomas to adopt the proposed AEGL-1 values. The motion passed (YES:16; NO: 0; Abstain:0) (Appendix L).

Because titanium tetrachloride forms an aerosol upon contact with moist air, the AEGL values should be presented only in terms of mg/m^3, as was done for the chemical boron trifluoride.

Summary of Proposed AEGL Values for Name of Titanium Tetrachloride [mg/m^3]-						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	0.54	0.54	0.54	0.54	0.54	No clinical signs observed in rats exposed to 0.7 ppm for 6 h/d, 5 d/wk for 4 wks (Kelly, 1979)
AEGL-2 (Disabling)	59	17	7.8	1.6	0.73	Exposure of rats to 1.3 ppm for 6 h/d, 5 d/wk for 4 wks resulted in no clinical signs, but next exposure level approaches lethality threshold (Kelly, 1979)
AEGL-3 (Lethal)	290	100	44	16	7.1	One-third the rat LC_{50} values (Kelly, 1980)

Administrative Matters

The site and time of the next meeting, NAC/AEGL-29, was decided to be June 17-19, 2003 in Washington. D.C. The date for NAC/AEGL-30 has been set tentatively as September 16-18, 2003 in Washington, D.C. The NAC/AEGL-31 has two options (1) early December in San Antonio or (2) Dec. 15-17, 2003 in Washington, D. C. More information regarding the NAC/AEGL-29 hotel information will be coming from Po-Yung Lu as soon as the arrangement 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. Status update from EPA on Human Subject Studies
Attachment 2. Excerpt from SOP on selection of Human Studies for TSD Preparation
Attachment 3. NAC/AEGL-27 Meeting Agenda
Attachment 4. NAC/AEGL-27 Attendee List
Attachment 5. Status Report of Category V chemicals: Critical Health Effect Starting Points for AEGL Determination: LOAEL vs. NOAEL
Attachment 6. Basic Occupational Exposure Assessment
Attachment 7. Proposal of Information Be Included in Exposure Assessment of TSDs
Attachment 8. Application of Acute Exposure Guideline Levels
Attachment 9. Data Analysis of Iron pentacarbonyl
Attachment 10. Data Analysis of Ethyleneimine and Propylenimine
Attachment 11. Data Analysis of Piperidine
Attachment 12. Data Analysis of Carbon Disulfide
Attachment 13. Data Analysis of Formaldehyde
Attachment 14. Data Analysis of Acetone
Attachment 15. Data Analysis of Vinyl Chloride, ACC, Susan Ripple
Attachment 16. Data Analysis of Vinyl Chloride, Fritz Kalberlah
Attachment 17. Data Analysis of Hydrogen Bromide
Attachment 18. Data Analysis of Titanium Tetrachloride

LIST OF APPENDICES

Appendix A. Revised meeting highlights of NAC/AEGL-26 (sent to NAC/AEGL on 3/28/2003 by E-mail).
Appendix B. Ballot for Acceptance of the Status Report of NOAEL vs LOAEL (March 3, 2003)
Appendix C. Ballot for Acceptance of Occupational Exposure Measurement Information (proposals: 1 and 2).
Appendix D. Ballot for Iron Pentacarbonyl
Appendix E. Ballot for Iron Pentacarbonyl
Appendix F. Ballot for Ethyleneimine
Appendix G. Ballot for Piperidine
Appendix H. Ballot for Carbon Disulfide
Appendix I. Ballot for Formaldehyde
Appendix J. Ballot for Acetone
Appendix K. Ballot for Hydrogen Bromide
Appendix L. Ballot for Titanium Tetrachloride

NAC/AEGL Meeting 29: June 16-18, 2003

Chemical: Nickel Carbonyl **CAS Reg. No.:** 13463-39-5

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff		Y			Nancy Kim		Y		
Steven Barbee		N			Loren Koller		N		
Lynn Beasley		Y			Glenn Leach		Y		
David Belluck		A			Mark McClanahan		Y		
Robert Benson		Y			John Morawetz		Y		
Jonnthan Borak		A			Richard Niemeier		A		
William Bress		Y			Marinelle Payton		A		
George Cushmac		A			Zarena Post		A		
Al Dietz		A			George Rodgers		A		
Ernest Falke		N			George Rusch, Chair		Y		
Larry Gephart		A			Robert Snyder		Y		
John Hinz		Y			Thomas Sobotka		A		
Jim Holler		Y			~~Kenneth Still~~				
Thomas Hornshaw		Y			Richard Thomas		A		
					TALLY		13/16		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	[redacted] , ( )	[redacted] , ( )	, ( )	, ( )	, ( )
AEGL 2	0.10, ( )	0.072, ( )	0.036 ( )	0.0090, ( )	0.0045 , ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
LOA					

AEGL 1 Motion by: _____ **Second by:** _____

AEGL 2 Motion by: * Benson **Second by:** Hornshaw

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

LOA Motion by: _____ **Second by:** _____

* Keep AEGL-3 values and ballot new AEGL-2 values.

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/18/03

NAC/AEGL Meeting 29: June 16-18, 2003

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

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	Y				Nancy Kim	Y			
Steven Barbee	N				Loren Koller	A			
Lynn Beasley	Y				Glenn Leach	N			
David Belluck	A				Mark McClanahan	N			
Robert Benson	Y				John Morawetz	Y			
Jonathan Borak	A				Richard Niemeier	Y			
William Bress	N				Marinelle Payton	A			
George Cushmac	A				Zarena Post	A			
Al Dietz	A				George Rodgers	A			
Ernest Falke	Y				George Rusch, Chair	N			
Larry Gephart	A				Robert Snyder	N			
John Hinz	N				Thomas Sobotka	A			
Jim Holler	N				~~Kenneth Still~~				
Thomas Hornshaw	N				Richard Thomas				
					TALLY	7/16			

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

* Delete ref. to Greenberg 1926 + 1939 from derivation of AEGL-3 values

AEGL 1 Motion by: _____ **Second by:** _____

AEGL 2 Motion by: Morawetz **Second by:** Alexeeff

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

LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/18/03

NAC/AEGL Meeting 29: June 16-18, 2003

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

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff		N	P		Nancy Kim		Y	Y	
Steven Barbee		Y	Y		Loren Koller		Y	Y	
Lynn Beasley		P	Y		Glenn Leach		Y	Y	
David Belluck		A	A		Mark McClanahan		Y	Y	
Robert Benson		Y	Y		John Morawetz		N	N	
Jonathan Borak		A	A		Richard Niemeier		Y	Y	
William Bress		Y	Y		Marinelle Payton		A	A	
George Cushmac		A	A		Zarena Post		A	A	
Al Dietz		A	A		George Rodgers		A	A	
Ernest Falke		Y	Y		George Rusch, Chair		Y	Y	
Larry Gephart		A	A		Robert Snyder		Y	Y	
John Hinz		Y	Y		Thomas Sobotka		A	A	
Jim Holler		Y	Y		Kenneth Still		A	A	
Thomas Hornshaw		Y	Y		Richard Thomas		A	A	
					TALLY		14/16		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	[redacted], (2000)	[redacted], (1100)	800, ( )	400, ( )	200, ( )
AEGL 3	9700, ( )	5600, ( )	4000, ( )	2000, ( )	990, ( )
LOA					

AEGL 1 Motion by: _____ **Second by:** _____

AEGL 2 Motion by: Hinz **Second by:** Bress

AEGL 3 Motion by: " **Second by:** Mac ?

LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 6/18/03

NAC/AEGL Meeting 29: June 16-18, 2003

Chemical: CHLORINE PENTAFLUORIDE **CAS Reg. No.:** 13637-63-3

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	N	P	Y		Nancy Kim	Y	Y	Y	
Steven Barbee	Y	Y	Y		Loren Koller	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Glenn Leach	Y	Y	Y	
David Belluck	A	A	A		Mark McClanahan	N	N	Y	
Robert Benson	Y	Y	Y		John Morawetz	N	Y	Y	
Jonathan Borak	A	A	A		Richard Niemeier	Y	N	Y	
William Bress	Y	Y	Y		Marinelle Payton	A	A	A	
George Cushmac	A	A	A		Zarena Post	A	A	A	
Al Dietz	A	A	A		George Rodgers	A	A	A	
Ernest Falke	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Larry Gephart	A	A	A		Robert Snyder	Y	Y	Y	
John Hinz	Y	Y	Y		Thomas Sobotka	A	A	A	
Jim Holler	Y	Y	Y		Kenneth Still	A	A	A	
Thomas Hornshaw	N	Y	Y		Richard Thomas	A	A	A	
					TALLY	13/17	14/16	17/17	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.30 ,( )	0.30 ,( )	0.30 ,( )	0.30 ,( )	0.30 ,( )
AEGL 2	3.0 ,( )	2.0 ,( )	1.0 ,( )	0.50 ,( )	0.36 ,( )
AEGL 3	20 ,( )	11 ,( )	8.0 ,( )	4.0 ,( )	2.8 ,( )
LOA					

AEGL 1 Motion by: Benson **Second by:** Hinz

AEGL 2 Motion by: Hinz **Second by:** Snyder

AEGL 3 Motion by: Hinz **Second by:** Falke

LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/18/03

NAC/AEGL Meeting 29: June 16-18, 2003

Chemical: BROMINE PENTAFLUORIDE **CAS Reg. No.:** 7789-30-2

NAC Member	AEGL 1	AEGL 2	AEGL 3	LOA *	NAC Member	AEGL 1	AEGL 2	AEGL 3	LOA
George Alexeeff	Y	Y	Y	P	Nancy Kim	Y	Y	Y	N
Steven Barbee	N	Y	Y	Y	Loren Koller	P	Y	Y	N
Lynn Beasley	Y	Y	Y	N	Glenn Leach	Y	Y	Y	Y
David Belluck	A	A	A	A	Mark McClanahan	N	Y	Y	N
Robert Benson	Y	P	Y	P	John Morawetz	Y	Y	P	N
Jonathan Borak	A	A	A	A	Richard Niemeier	N	Y	Y	Y
William Bress	Y	Y	Y	P	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	A	A	A	A
Ernest Falke	Y	Y	Y	P	George Rusch, Chair	Y	Y	Y	Y
Larry Gephart	A	A	A	A	Robert Snyder	Y	Y	Y	Y
John Hinz	P	Y	Y	N	Thomas Sobotka	A	A	A	A
Jim Holler	Y	Y	Y	Y	Kenneth Still	A	A	A	A
Thomas Hornshaw	Y	Y	Y	N	Richard Thomas	A	A	A	A
					TALLY	12/15	16/16	16/16	6/13 *

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	3.0, ( )	2.0, ( )	1.0, ( )	0.50, ( )	0.36, ( )
AEGL 3	79, ( )	55, ( )	33, ( )	8.3, ( )	4.2, ( )
LOA					

NR = not recommended due to absence of data

AEGL 1 Motion by: Alexeeff **Second by:** Nancy Kim

AEGL 2 Motion by: Hornshaw **Second by:** Bress

AEGL 3 Motion by: Benson NIEMEIER **Second by:** Hinz HOLLER *

LOA Motion by: _____ **Second by:** _____

* Add notation below table that ClF_5 + ClF_3 could be referred to for AEGL-1 (DOES NOT CARRY).

Approved by Chair: George M Rusch **DFO:** Paul S Tobin **Date:** 6/18/03

NAC/AEGL Meeting 29: June 16-18, 2003

Chemical: NITRIC ACID * **CAS Reg. No.:** 7697-37-2

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

* Carries unanimously

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.53 ,( )	,( )	,( )	,( )	,( )
AEGL 2	43 ,( )	30 ,( )	24 ,( )	6.0 ,( )	3.0 ,( )
AEGL 3	~~160~~ 170 ,( )	~~110~~ 120 ,( )	92 ,( )	23 ,( )	11 ,( )
LOA					

AEGL 1 Motion by: Benson / Barbee **Second by:** McClanahan

AEGL 2 Motion by: McClanahan **Second by:** Snyder

AEGL 3 Motion by: Koller **Second by:** Niemeier

LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/18/03

NAC/AEGL Meeting 29: June 16-18, 2003

Chemical: Nitric Acid **CAS Reg. No.:** 7697-37-2

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

* Carries unanimously

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.53 ,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	~~160~~ 170 ,( )	~~110~~ 120 ,( )	92 ,( )	23 ,( )	11 ,( )
LOA					

AEGL 1 **Motion by:** Benson **Second by:** McClanahan

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

AEGL 3 **Motion by:** Koller **Second by:** Niemeier

LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/18/03

NAC/AEGL Meeting 29: June 16-18, 2003

Chemical: HYDROGEN SELENIDE **CAS Reg. No.:** 7783-07-5

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	*	N	Y		Nancy Kim		N	Y	
Steven Barbee		Y	Y		Loren Koller		Y	Y	
Lynn Beasley		A	A		Glenn Leach		Y	Y	
David Belluck		A	A		Mark McClanahan		Y	Y	
Robert Benson		P	Y		John Morawetz		N	Y	
Jonathan Borak		A	A		Richard Niemeier		Y	Y	
William Bress		N	N		Marinelle Payton		A	A	
George Cushmac		A	A		Zarena Post		A	A	
Al Dietz		A	A		George Rodgers		A	A	
Ernest Falke		Y	Y		George Rusch, Chair		Y	Y	
Larry Gephart		A	A		Robert Snyder		Y	Y	
John Hinz		A	A		Thomas Sobotka		A	A	
Jim Holler		Y	Y		Kenneth Still		A	A	
Thomas Hornshaw		P	Y		Richard Thomas		A	A	
					TALLY		9/13	14/15	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	1.8, ( )	1.0, ( )	0.73, ( )	0.37, ( )	0.26, ( )
AEGL 3	5.4, ( )	3.1, ( )	2.2, ( )	1.1, ( )	0.78, ( )
LOA					

* Unanimous for NR, based on no data.

AEGL 1 Motion by: McClanahan **Second by:** Benson

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

AEGL 3 Motion by: Benson **Second by:** Barbee

LOA Motion by: _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/18/03

NAC/AEGL Meeting 29: June 16-18, 2003

Chemical: METHYL THIOCYANATE **CAS Reg. No.:** 556-64-9

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

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

*Motion not to develop

AEGL 1 Motion by: Falke **Second by:** Koller

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

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

LOA Motion by: _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/19/03

NAC/AEGL Meeting 29: June 16-18, 2003

Chemical: BROMINE TRIFLUORIDE **CAS Reg. No.:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	N *				Nancy Kim	Y			
Steven Barbee	Y				Loren Koller	Y			
Lynn Beasley	A				Glenn Leach	Y			
David Belluck	A				Mark McClanahan	Y			
Robert Benson	Y				John Morawetz	Y			
Jonathan Borak	A				Richard Niemeier	Y			
William Bress	Y				Marinelle Payton	A			
George Cushmac	A				Zarena Post	A			
Al Dietz	A				George Rodgers	A			
Ernest Falke	Y				George Rusch, Chair	Y			
Larry Gephart	A				Robert Snyder	Y			
John Hinz	A				Thomas Sobotka	A			
Jim Holler	Y				Kenneth Still	A			
Thomas Hornshaw	Y				Richard Thomas	A			
					TALLY	14/15			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.12, ( )	0.12, ( )	0.12, ( )	0.12, ( )	0.12, ( )
AEGL 2	62, ( )	6.2, ( )	3.1, ( )	0.77, ( )	0.39, ( )
AEGL 3	81, ( )	27, ( )	14, ( )	3.4, ( )	1.7, ( )
LOA					

* Ballot on all 3 levels (as simple equiv. to ClF_3)

AEGL 1 Motion by: Falke **Second by:** McClanahan

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

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

LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/18/03

NAC/AEGL Meeting 29: June 16-18, 2003

Chemical: FORMALDEHYDE **CAS Reg. No.:** 50-00-0

NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	A		A	
Steven Barbee	Y		Y	
Lynn Beasley	A		A	
David Belluck	A		A	
Robert Benson	Y		Y	
Jonathan Borak	A		A	
William Bress	N		Y	
George Cushmac	A		A	
Al Dietz	A		A	
Ernest Falke	Y		Y	
Larry Gephart	A		A	
John Hinz	A		A	
Jim Holler	Y		Y	
Thomas Hornshaw	Y		P	

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Nancy Kim	Y		N	
Loren Koller	N		Y	
Glenn Leach	Y		Y	
Mark McClanahan	N		Y	
John Morawetz	Y		P	
Richard Niemeier	Y		Y	
Marinelle Payton	A		A	
Zarena Post	A		A	
George Rodgers	A		A	
George Rusch, Chair	Y		Y	
Robert Snyder	Y		Y	
Thomas Sobotka	A		A	
Kenneth Still	A		A	
Richard Thomas	A		A	
TALLY	11/14		11/13	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.9 , ( )	0.9 , ( )	0.9 , ( )	0.9 , ( )	0.9 , ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	100, ( )	70 , ( )	56 , ( )	35 , ( )	35 , ( )
LOA					

Rescind 0.4 ppm and change to 1 ppm

AEGL 1 Motion by: Benson **Second by:** Barbee

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

AEGL 3 Motion by: * McClanahan **Second by:** Falke

LOA Motion by: _____ **Second by:** _____

* ~~Use n=1,2,6 with same 4 hr, 8 hr value~~
Use default n=3 + 1

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 6/19/03