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

Final Meeting 20 Highlights

U. S. Department of Transportation
DOT Headquarters/Nassif Building, Rooms 8236-8240
400 7th Street, S.W., Washington, D.C.
January 8-10, 2001

INTRODUCTION

Welcoming remarks were provided by George Rusch (NAC/AEGL Chairperson) and George Cushmac (meeting host, Department of Transportation). The Highlights of the NAC/AEGL Meeting 19 were reviewed and discussed. With regard to approval of the discussion in the minutes concerning the nerve agents GA, GB, GD, GF, and Agent VX, a question was raised by Robert Snyder. He questioned whether the committee had decided to treat the G Agents similar to Agent VX in that the AEGL values would be agreed to for a period of three years, after which the committee would revisit the values and decide if–in the light of any new data–the values should be reconsidered. Bob Snyder agreed to review the NAC/AEGL-19 tapes for discussion content and report back at the next NAC/AEGL meeting. Mark McClanahan made a motion for Bob to review the tapes and approve the meeting highlights excluding pages of meeting highlights pertinent to the development of AEGLs for G agents and VX and was seconded by George Rodgers. Then, the NAC/AEGL-19 highlights will be revised accordingly (Appendix A). The motion passed [YES: 21; NO: 0; ABSTAIN: 2] (Appendix B).

Roger Garrett, AEGL Program Director, announced and invited all in attendance to the U.S. EPA Awards Ceremony at the NAS Auditorium following the afternoon adjournment.

The highlights for the NAC/AEGL-20 are presented below and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached.

GENERAL INTEREST ITEMS

Federal Register Notices submitted for comment in December 2000 were not received by the time of NAC/AEGL Meeting 20. When comments are received telephone conferences will be conducted to address any significant comments and any changes will be voted upon by telephone conference. Note: NAC/AEGL approved the following chemicals: Ethyleneimine, Propylenimine, Methacrylonitrile, Isobutylnitrile, Proprionitrile, and Chlorine trifluoride.

REVIEW OF PRIORITY CHEMICALS FOR AEGL VALUES

Phenol, CAS Reg. No. 108-95-2

Chemical Manager: Robert Snyder, Rutgers University
Chemical Manager: Ursula Gundert-Remy and Juergen Pauluhn, German SFK Expert Group
Staff Scientist: Peter Griem, FoBiG Staff Scientist

Peter Griem presented an overview of the Technical Support Document (Attachment 3) which contained very little quantitative inhalation data for humans. An odor threshold was set at 0.06 ppm (AIHA, 1989). Piotrowski (1971) did not report on effects in a toxicokinetic study, in which subjects were exposed to 1.3-6.5 ppm for 8 hours. Likewise, Ogata et al. (1974) in a toxicokinetic field study did not mention any effects on workers exposed to a TWA 1.22-4.95 ppm. Animal studies included continuous exposure of rhesus monkeys, rats and mice to 5 ppm phenol for 90 days, which did not cause effects (Sandage, 1961). After exposure of rats to 0.5, 5, and 25 ppm for 6 h/d, 5 d/w for 2 weeks no clinical, hematological or histopathological effects were found (CMA, 1998). However, red nasal discharge was reported mostly in males and increased in occurrence from the first to the second week.

It was proposed by Steve Barbee that the AEGL-3 be established first. Robert Snyder moved and seconded by Robert Benson that Committee accept the values as proposed and obtained from the Flickinger (1976) study, in which exposure of rats to a phenol aerosol concentration of 900 mg/m³ phenol (equivalent to 234 ppm phenol vapor) for 8 hours resulted in tremors, incoordination in all and prostration in 1 of 6 animals, but not in death. Time extrapolation was done according to the Standard Operating Procedures (SOP) (n=3 for shorter exposure periods up to 30 minutes; the value for 30 minutes was used for 10 minutes without further changes). The total uncertainty factor of 10 (interspecies: 3; intraspecies: 3) was based on comparison of the dose equivalent to the derived AEGL-3 values with reports on lethal and non-lethal effects in humans after oral uptake of phenol. The AEGL-3 values were approved [YES: 17; NO: 4; ABSTAIN:0] (Appendix C).

The AEGL-2 values were proposed using the CMA (1998) study, which reported a NOAEL in rats of 25 ppm phenol (highest concentration used) for 6 h/d, 5 d/w for 2 weeks. Time extrapolation was done according to the SOP (n=1 from 6 to 8 hours; n=3 for shorter exposure periods up to 30 minutes; the value for 30 minutes was used for 10 minutes without further changes). A total uncertainty factor of 3 (interspecies: 1; intraspecies: 3) was used because the exposure concentration used was a no-observed-adverse-effect-level in a repeated exposure study. A motion was made by Bob Snyder and seconded by Richard Thomas to accept the proposed values with exception of the 10-minute value. These are: 19, 15, 9.5, and 6.3 ppm for 30 minutes, and 1-, 4- and 8 hours, respectively. The motion passed. [YES: 19; NO: 2; ABSTAIN: 2] (Appendix C). Following further discussion, Robert Benson moved that the

10-minute value be set equal to the 30-minute value which was 19 ppm. John Hinz seconded and it was approved [YES: 18; NO: 5; ABSTAIN: 0] (Appendix C).

The Committee considered the CMA (1998) study appropriate to establish the AEGL-1 values. In this study no clinical, hematological or histopathological effects were observed in rats after exposure to 25 ppm phenol (highest concentration used) for 6 h/d, 5 d/w for 2 weeks. The Committee discussed the relevance of the endpoint red nasal discharge in rats, found in male rats in the CMA (1998) study, and regarded it as a minor, but not relevant effect. Time extrapolation was done according to the SOP (n=1 from 6 to 8 hours; n=3 for shorter exposure periods up to 10 minutes; extrapolation to the 10-minute period was done because data were available for the RD_{50} value in mice). A total uncertainty factor of 10 (interspecies: 3; intraspecies: 3) was used because a multiple exposure study was used and the study reported no effects and thus was below the AEGL-1 effect level. Thomas Hornshaw moved and Richard Niemeier seconded that the Committee accept the proposed AEGL-1 values as 8.3, 5.7, 4.5, 2.9, and 1.9 ppm for 10 minutes, 30 minutes, and 1-, 4-, and 8-hours, respectively. This motion carried [YES: 18; NO: 4; ABSTAIN: 0]. (Appendix C)

There was additional comment that the TSD Table should state that dermal exposure can be as severe as oral or inhalation exposure.

☞**Action Item**: Larry Gephart agreed to provide an update at the next meeting on the relevance/use of RD_{50} values (concentrations that decrease the respiratory rate by 50%) for the derivation of AEGL values.

SUMMARY OF PROPOSED AEGL VALUES FOR PHENOL					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-hour**
AEGL-1	8.3 ppm (32 mg/m^3)	5.7 ppm (22 mg/m^3)	4.5 ppm (17 mg/m^3)	2.9 ppm (11 mg/m^3)	1.9 ppm (7.3 mg/m^3)
AEGL-2	19 ppm (73 mg/m^3)	19 ppm (73 mg/m^3)	15 ppm (58 mg/m^3)	9.5 ppm (36 mg/m^3)	6.3 ppm (24 mg/m^3)
AEGL-3	59 ppm (230 mg/m^3)	59 ppm (230 mg/m^3)	47 ppm (180 mg/m^3)	29 ppm (110 mg/m^3)	23 ppm (88 mg/m^3)

Carbon Monoxide, CAS Reg. No. 630-08-0

Chemical Manager: George Rodgers, AAPCC
Chemical Manager: Hans-Uwe Wolf and Juergen Pauluhn, German SFK Expert Group
Staff Scientist: Peter Griem, FoBiG Staff Scientist

Peter Griem presented the existing pertinent data for possible AEGL values (Attachment 4). Comments immediately centered on a possible concern for children. Peter Griem informed the Committee the levels would be higher in younger people due to inhalation volumes and their smaller sizes. He also informed the Committee that the proposed AEGL-1 values would be at or below present ambient air levels. It was moved by Jonathan Borak and seconded by Mark McClanahan to *not* recommend AEGL-1 values. This motion passed [YES; 22; NO: 1; ABSTAIN: 0]. (Appendix D)

Human data relevant to establishment AEGL-2 values was discussed. Human adults with CAD (coronary artery disease) constitute a sensitive sub-population for the effects of CO. In an experimental study in patients with CAD, a level of 4% COHb (carboxyhemoglobin) concentration caused a reduced time until onset of angina (chest pain) and changes in the electrocardiogram (ST-segment depression of 1 mm or greater) during physical exertion (Allred et al., 1989; 1991). An exposure level of 4% COHb is unlikely to cause a significant increase in the frequency of exercise-induced arrhythmias. In experimental studies, an increase in the frequency of ventricular arrhythmias have been observed at COHb of 5.3%, but not at 3.7% (Sheps et al., 1990; 1991), while in another study no effect of CO exposure on ventricular arrhythmia was found at 3% and 5% COHb (Dahms et al., 1993). The Committee discussed the interindividual variability of the exposure conditions necessary to reach the desired COHb level as reported in these studies. Children were thought to be exposed to greater amounts of CO than adults because due to the higher ratio of minute volume to body size, COHb concentrations rise more rapidly in children than in adults. CO exposure can cause acute neurotoxic effects in children and a threshold for the end-point of syncope at 24.5% COHb was reported (Crocker and Walker, 1985) while symptoms such as headache, nausea, dizziness and dyspnea were found at a mean COHb concentration of 7.0% (Klasner et al., 1998). Long-lasting neurotoxic effects (defects in the cognitive development and behavioral alterations) in children have also been reported (Klees et al., 1985). Using the studies of Allred et al.(1989 a, b; 1991) and Sheps et al. (1990, 1991), a COHb concentration of 4% was used as the basis for AEGL-2 derivation.
A mathematical model by Coburn, Forster, and Kane (CFK model) (Coburn et al., 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations in air resulting in a COHb concentration of 4% at the end of exposure periods of 10- and 30 minutes and 1-, 4- and 8 hours. A total uncertainty factor of 1 (intraspecies: 1) was used because the derivation was based on the most susceptible human sub-population (patients with coronary artery disease).
A motion was made by Judy Strickland and seconded by Loren Koller to accept the AEGL-2 values presented by Peter Griem [YES: 21; NO: 1; ABSTAIN: 0]. This motion passed (Appendix D).

Human data were also discussed for the AEGL-3. Several case reports indicate that in patients with CAD, CO exposure can contribute to myocardial infarction. Anecdotal case reports were discussed but were not considered an adequate basis for the derivation of AEGL-3 values because of uncertainties in the end-of-exposure COHb concentration and the insufficient characterization of the exposure conditions (with repeated and/or prolonged exposures in several cases). Therefore, the experimental studies of Chiodi et al. (1941) and Haldane (1895) that reported no severe or life-threatening symptoms in healthy subjects at COHb concentrations of about 40%–56% were used as the basis for derivation of AEGL-3. The CFK model (Coburn et al., 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations in air resulting in a COHb concentration of 40% at the end of exposure periods of 10- and 30 minutes and 1-, 4-, and 8 hours. The Committee discussed that the use of a ventilation rate of 13200 mL/min in the model adds some additional safety to the uncertainty factor used. A total uncertainty factor of 3 (intraspecies: 3) was based on the available reports on cases of myocardial infarction and stillbirth. Further comments noted that a statement was needed in the rationale that the derived exposure concentrations are protective for pregnant women (15% COHb as one of the therapy criteria) when exposed to CO. Additional comments included concern for the sensitive populations in other countries with Thalassemia; also the mechanism of cytochrome system poisoning. A motion was made by Steve Barbee and seconded by John Hinz to accept values of 1700 ppm, 600 ppm, 330 ppm, 150 ppm and 130 ppm, respectively, for the 10- and 30-minute and 1-, 4-, and 8-hour exposure values. The motion passed [YES:18; NO:3; ABSTAIN:1] (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR CARBON MONOXIDE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	420 ppm (480 mg/m^3)	150 ppm (170 mg/m^3)	83 ppm (95 mg/m^3)	33 ppm (38 mg/m^3)	27 ppm (31 mg/m^3)
AEGL-3	1700 ppm (1900 mg/m^3)	600 ppm (690 mg/m^3)	330 ppm (380 mg/m^3)	150 ppm (170 mg/m^3)	130 ppm (150 mg/m^3)

NR = not recommended due to insufficient data

Sulfur Mustard (Agent-HD)
CAS Res. No. 505-60-2

Chemical Manager: Ken Still, U.S. Navy
Staff Scientist: Bob Young, ORNL Staff Scientist

Presentation of the chemical was given by Bob Young (Attachment 5) who discussed comments from the NAS/COT/AEGL for incorporation into the TSD. The COT agreed with the data but wanted to use an *n* of 3 for time scaling. Following the presentation that the NAC/AEGL Committee revise the AEGL-3 values for 10- and 30-minutes by calculating them using the *n*=3, the resulting values were 0.59 ppm and 0.41 ppm, respectively. George Rodgers moved acceptance of these values and was seconded by Mark McClanahan. The motion passed [YES: 21; NO: 1; ABSTAIN: 0] (Appendix E).

Phosphine, CAS Reg. No. 7803-51-2

Chemical Manager: Ernest Falke, U.S. EPA
Staff Scientist: Cheryl Bast, ORNL Staff Scientist

Cheryl Bast presented an historical update of the phosphine AEGL (Attachment 6) from December 1996 (Draft 1) to the present January 2001 (Draft 6). There was extensive discussion of the *Federal Register* public comments (derivation of the exponent '*n*' for time scaling and use of a repeated-exposure study to derive an acute exposure value) and issues raised by a committee member (proper descriptions of human occupational exposure reports). Additionally, John Morawetz noted that "limited evidence suggested a death may have occurred at lower levels". Loren Koller moved to accept and Mark McClanahan seconded that AEGL-3 values be set as proposed.. The AEGL-3 levels were based on a NOEL for lethality in rats exposed to 18 ppm for 6 hours (Newton, 1991). Since animal lethality data suggested little species variability, an interspecies UF of 3 was applied; and, since human data suggested that children were more sensitive than adults, an intraspecies UF of 10 was applied (total UF=30). An empirically derived value of *n*=1, based on rat lethality data ranging from 1 to 6 hours, was utilized for time scaling. A vote was made on the 10- and 30- minute values and a second vote was made on the 1-, 4-, and 8-hour values. The 10- and 30-minute votes were: [YES: 16; NO: 5; ABSTAIN: 0], and the vote for 1-, 4-, and 8-hours was [YES; 22; NO: 0; ABSTAIN: 0]. All AEGL-3 values were accepted by NAC/AEGL (Appendix F).

SUMMARY OF PROPOSED AEGL VALUES FOR PHOSPHINE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	4 ppm (5.6 mg/m^3)	4 ppm (5.6 mg/m^3)	2.0 ppm (2.8 mg/m^3)	0.5 ppm (0.71 mg/m^3)	0.25 ppm (0.35 mg/m^3)
AEGL-3	7.2 ppm (10 mg/m^3)	7.2 ppm (10 mg/m^3)	3.6 ppm (5.1 mg/m^3)	0.9 ppm (1.3 mg/m^3)	0.45 ppm (0.63 mg/m^3)

NR = not recommended due to insufficient data

Loren Koller moved and Mark McClanahan seconded that the Committee accept the AEGL-2 values as presented based on a decrease in body weight and a threshold for hematological effects in rats exposed to 10 ppm phosphine for 6 hours (Newton et al., 1991). Uncertainty factors and time scaling were as described above for AEGL-3. The vote was [YES: 14; NO: 6; ABSTAIN: 0] for the 10- and 30- minutes and 1-hour values. A second vote was taken on this motion for 4- and 8 hours [YES: 19; NO: 3; ABSTAIN: 0]. All values were accepted. (Appendix F).

The AEGL-1 was not established due to insufficient data.

Monochloroacetic acid, CAS Reg. No 79-11-8

Chemical Manager: Ernest Falke, U.S. EPA
Chemical Manager: Ruediger Bartsch, Horst Hollander and Reinhard Jung, German SFK Expert Group
Staff Scientist: Peter Griem, FoBiG Staff Scientist

Peter Griem presented an overview of the data on monochloroacetic acid (MCAA) to the Committee and covered the properties, production, uses, and toxicity concerns as well as relevant data from human and animal exposures (Attachment 7). Both the Maksimov and Dubinina (1974) study, reporting an irritation threshold of 1.48 ppm in humans, and the Clariant GmbH (2000) communication on occupational exposure were questioned for their inadequate data presentation and lack of effect. It was moved by Robert Benson and seconded by John Hinz to *not* establish AEGL-1 values for MCAA due to insufficient data [YES: 21; NO: 0; ABSTAIN:0] (Appendix G).

An insufficient database was also found for the AEGL-3. The only animal study reporting lethal effects after inhalation exposure (LC_{50} in rats of 46.8 ppm for 4 hours; Maksimov and Dubinina, 1974) was questioned for its inadequate data presentation. Several oral LD_{50} studies in animals were available; however, due to uncertainties regarding possible local effects of MCAA upon inhalation exposure, the group was reluctant to derive AEGL values by route-to-route extrapolation from an oral gavage study (BMD_{05} for lethality of 28.8 mg/kg/day; Hoechst AG,

1979). It was moved by Robert Benson and seconded by Judy Strickland that the AEGL-3 values *not* be established, again due to insufficient data [YES: 20; NO: 0; ABSTAIN: 1] (Appendix G).

For the AEGL-2, an inhalation study in rats (Dow Chemical Co., 1987) in which 12 rats exposed to an analytical concentration of 66 ppm for 1 hour showed eye squint and lethargy was discussed. Points of discussion were the large deviation of the analytical concentration from the nominal concentration of 964 ppm and the effect severity. The Committee considered the study appropriate to establish the AEGL-2 values. Time extrapolation was done by default assumptions (n=1 from 1 to 4 and 8 hours; n=3 for 30- and 10 minutes). A total uncertainty factor of 10 (interspecies: 3; intraspecies: 3) was used because the effect level was considered below that of an AEGL-2 and on basis of comparison with an older experimental study in humans using oral exposure. Judy Strickland moved and Steve Barbee seconded acceptance of the proposed values. The motion passed [YES: 22; NO: 0; ABSTAIN: 1] (Appendix G).

During the discussion a member of the Committee reported that he had done research on the central nervous system effects (damage of the blood-brain barrier) of MCAA and that severe effects had also been found after dermal exposure of rats and mice. This concern led to the proposal to include this information in the TSD and to have a statement in the summary tables concerning the extreme danger of dermal absorption of MCAA.

SUMMARY OF PROPOSED AEGL VALUES FOR MONOCHLOROACETIC ACID					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	12 ppm (47 mg/m^3)	8.3 ppm (33 mg/m^3)	6.6 ppm (26 mg/m^3)	1.7 ppm (6.7 mg/m^3)	0.83 ppm (3.3 mg/m^3)
AEGL-3	NR	NR	NR	NR	NR

NR = not recommended due to insufficient data

Xylenes, CAS Reg. No 1330-20-7

Chemical Manager: Loren Koller, Oregon State University
Staff Scientist: Claudia Troxel, ORNL Staff Scientist

Claudia Troxel presented an overview of the mixed-, ortho-, para-, and meta- xylenes. (Attachment 8). The information presented suggested that blood-xylene concentrations are directly related to the central nervous system toxicity induced by xylene, and that xylene will equilibrate in the body for some period longer than 1 hour. Comments from George Rogers noted that not enough data from different species were available to allow an interspecies uncertainty factor of 1, and that narcosis appeared to be the endpoint of concern. John Morawetz

also noted that these proposed values may not be protective except in a hospital setting. A motion was made by Ernest Falke and seconded by Mark McClanahan to use 130 ppm for the AEGL-1 values from 10 minutes out to 8 hours; AEGL-2 values would be 430 ppm for the 1-, 4-, and 8-hour time points; AEGL-3 values would be 930 ppm for the 1-, 4-, and 8-hour time points. Based upon the data suggesting that blood-xylene concentrations will equilibrate in the body for some period longer than 1 hour, it was proposed to perform pharmacokinetic modeling to extrapolate xylene concentrations to the 10- and 30-minute exposure time points, and the proposal was amended to reconsider these 10- and 30-minute values for AEGL-2 and AEGL-3 at the next meeting. Dr. Ursula Gundert-Remy is to perform the modeling calculations. This motion passed [**AEGL-1:** YES: 16; NO: 4; ABSTAIN: 0; **AEGL-2:** YES: 16; NO: 4; ABSTAIN: 0; **AEGL-3:** YES:15; NO: 5; ABSTAIN: 0] (Appendix H).

SUMMARY OF PROPOSED AEGL VALUES FOR XYLENES					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-hour**
AEGL-1	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)
AEGL-2	–* –	– –	430 ppm (1900 mg/m^3)	430 ppm (1900 mg/m^3)	430 ppm (1900 mg/m^3)
AEGL-3	– –	– –	930 ppm (4000 mg/m^3)	930 ppm (4000 mg/m^3)	930 ppm (4000 mg/m^3)

*Under development by NAC/AEGL committee

Propylene Oxide, CAS Reg. No.75-56-9

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

Claudia Troxel presented data relating to using the original data previously evaluated with reference to epichlorhydrin or ethylene oxide (Attachment 9). A question of concern was that of the proper value of *n* to be used in the calculations. After noting the difference of the three above chemicals, it was moved by Jim Holler and seconded by Richard Thomas to continue with the previously presented AEGL 1-, 2-, and 3-level values based upon the *n* value of 1.2 for ethylene oxide. Having decided which *n* value to use, the issue of adding10-minute values was addressed. The AEGL-1 10-minute value was set equal to the 30-minute value because it was not considered appropriate to extrapolate from 8 hours to 10 minutes. The AEGL-2 and -3 values were extrapolated to the 10-minute exposure duration according to the SOP. This motion passed

[YES: 16; NO: 4; ABSTAIN: 0) (Appendix I). NAC/AEGL noted that additional public comments may be received on the value of *n* when propylene oxide is published in the *Federal Register*. The proposed values are:

SUMMARY OF PROPOSED AEGL VALUES FOR PROPYLENE OXIDE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-hour**
AEGL-1	110 ppm (260 mg/m^3)	110 ppm (260 mg/m^3)	60 ppm (140 mg/m^3)	19 ppm (45 mg/m^3)	11 ppm (26 mg/m^3)
AEGL-2	1300 ppm (3100 mg/m^3)	510 ppm (1200 mg/m^3)	290 ppm (690 mg/m^3)	91 ppm (220 mg/m^3)	51 ppm (120 mg/m^3)
AEGL-3	2700 ppm (6400 mg/m^3)	1100 ppm (2600 mg/m^3)	610 ppm (1400 mg/m^3)	190 ppm (450 mg/m^3)	110 ppm (260 mg/m^3)

ISSUES REVISITED

HYDROGEN SULFIDE: CONFERENCE CALL

A presentation was made by Steve Barbee concerning the December 13, 2000, conference call on hydrogen sulfide (Attachment 10). A goal of the conference call was to finalize the selection of the data package to support AEGL-1 values in response to comments received from the COT AEGL subcommittee. These data sets will be reviewed by Cheryl Bast, Steve Barbee, and Zarena Post and will be discussed at a future AEGL committee meeting. The data set utilized by the WHO for derivation of the WHO hydrogen sulfide value was also discussed; the toxicity endpoint, eye irritation (from a 1939 occupational observation) was not supportable by a single statement of 20 ppm and 10 ppm with an uncertainty factor of 100 to obtain the 100 ppm value.

Tom Hornshaw drafted a letter to solicit any reports or studies documenting health effects meeting the definition of AEGL-1 and associated concentrations of H_2S (Attachment 11). This letter will be sent to members of the State and Territorial Air Pollution Program Administrators and the Association of Local Air Pollution Control Officials (STAPPA/ALAPCO) in January.

HYDROGEN CYANIDE: AEGL- 1

George Rodgers indicated the need to evaluate the data for only the AEGL-1 values (Attachment 12). Values were based on the Leeser et al. (1990) study; however, as pointed out by John Morawetz, the study is unclear at what exposure level the lack of health effects can be attributed to. The health effects are reported as aggregated for all workers in 8 job titles while the exposures are reported for each of 8 job titles (6 of the 8 job titles had geometric mean values at or below 0.5 ppm, one job title had a mean value of 1 ppm) (Attachment 13). The committee agreed the Leeser study generally supported values approved by NAC/AEGL. It is used as a supporting evidence for AEGL-1 values derived from El Ghawabi et al (1975). Two other

studies were also available for evaluation: El Ghawabi et al. (1975) and Grabois (1954). Committee comments included letting the approved values in July stand (values in ascending time order from 10 minutes to 8 hours of 2.5, 2.5, 2.0, 1.3, and 1.0 ppm, respectively), but adding more detailed comments on the sampling methods, in particular emphasizing personal monitoring (TWA samples) over short-term or area samples. It was suggested that additional details on sampling be added to the SOPs. George Rusch (Chair) had to meet a previously scheduled commitment and to facilitate completion of discussion of this chemical George appointed Ernie Falke to preside in his stead. Chairperson Ernie Falke asked for a show of hands to accept the values as passed in July and only clarify the rationale for the values. The show of hands was unanimous. No written ballot was made.

CONSIDERATION OF ODOR IN AEGL-1 DEVELOPMENT

Presentation of the subject on the use of odor in the development of an AEGL-1 was made by Marc Ruijten. Marc presented an organizational outline of the generic issue of whether odor is a valid endpoint for the AEGL-1 (Attachment 14). He outlined current needs to develop or refine the default approach for *n*, and discussed the current SOP. He sought help in various subcommittees in hopes of providing a position paper by end of January by a review in AEGL subcommittee in February or March, and discussion and resolution by NAC/AEGL in May. An update on progress will be in the proposed May meeting.

APPLICATION OF AEGL IN OCCUPATIONAL SETTINGS

The subject was presented by John Morawetz (Attachment 15). He pointed out the use of cases in which the exact exposures were in doubt and how perhaps the AEGL values may be in question due to the methods and ways various types of samples were collected and analyzed . It was commented that AEGLs are considered to be a once-in-a-lifetime exposure event for the general public and do not take the place of STELs in the workforce. John was hopeful that resolution will be available to the AEGL Committee in May. He gave the example of a Bromine release and the use of AEGL-2 values in recommendations to allow the return of workers to areas of work. He also reviewed the major organizations that set occupational limits (OSHA, NIOSH, ACGH) and their applicability in all occupational settings, including emergency response.

VISITORS

Dr. George Woodall presented comments from the American Petroleum Institute on the AEGL values for H_2S. He offered the possibility of using other studies to set the values. Attached is the material Dr. Woodall handed out to accompany his talk (Attachment 16).

Dr. Bill Kojola, Industrial Hygienist, Dept. of Occupational Safety and Health, AFL-CIO,

presented comments represented comments stressing that AEGL values for community exposures should not be used in occupational settings.

Dr. Gerald Kennedy (DuPont) also presented comments on the potential problems in applying AEGL values to occupational settings.

ADMINISTRATIVE ISSUES

The next meeting was considered for May at this same meeting place with the dates and confirmation to be provided at a later time.

Meeting highlights were prepared by Hank Spencer and Po-Yung Lu, Oak Ridge National Laboratory.

LIST OF ATTACHMENTS

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

1. NAC/AEGL Meeting No. 20 Agenda
2. NAC/AEGL Meeting No. 20 Attendee List
3. Phenol: Consideration of data for AEGL values
4. Carbon Monoxide: Consideration of data for AEGL values
5. Sulfur Mustard: Comment incorporation from NAS/AEGL
6. Phosphine: Review of data for AEGL values
7. Xylenes: Review of data
8. Monochloroacetic Acid: Consideration of data for AEGL values
9. Propylene Oxide: Reconsideration of the *n* values
10. Hydrogen Sulfide: Revisit, conference call highlight
11. Solicitation of H2S reports by Thomas Hornshaw
12. Hydrogen Cyanide: Consideration of the data for AEGL-1
13. Hydrogen Cyanide Exposure by Job Title Lesser, 1990
14. Consideration of odor in AEGL-1 development
15. Application of AEGLs in occupational settings
16. Comments of the American Petroleum Institute on AEGL values for Hydrogen Sulfide

LIST OF APPENDICES

A. Ballot for Approval of NAC/AEGL Meeting 19 Highlights
B. Revised NAC/AEGL Meeting18 Highlights
C. Ballot for Phenol
D. Ballot for Carbon Monoxide
E. Ballot for Sulfur Mustard
F. Ballot for Phosphine
G. Ballot for Monochloroacetic Acid
H. Ballot for Xylenes
I. Ballot for Propylene Oxide

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-20
January 8-10, 2001

U.S. Department of Transportation
DOT Headquarters/Nassif Building, Rooms 8236-8240
400 7th Street, S.W., Washington, D. C.

AGENDA

Monday, January 8, 2001

10:00 AM	Introductory remarks and approval of NAC/AEGL-19 Highlights (George Rusch, Roger Garrett, and Paul Tobin)
10:15	Review of Phenol (Robert Snyder/Peter Griem)
12:30 PM	Lunch
1:30	Review of Carbon monoxide (George Rodgers/Peter Griem)
3:00	Adjourn for the day
4:00	US EPA's AEGL Awards Ceremony at NAS Auditorium, 2101 Constitutional Ave., N. W., Washington, D.C.

Tuesday, January 9, 2001

8:00 AM	Review of Carbon monoxide (continued)
9:15	Sulfur Mustard: comments incorporation from NAS/AEGL (Ken Still/Robert Young)
9:45	Review of Phosphine (Ernie Falke/Cheryl Bast)
10:30	Break
10:45	Review of Xylenes (Loren Koller/Claudia Troxel)
12:00 PM	Lunch
1:00	Review of Xylenes (continued)
2:00	Review of Monochloroacetic acid (Ernie Falke/Peter Griem)
3:00	Break
3:15	Review of Monochloroacetic acid (continued)
4:30	Review of Propylene oxide- *n* value (Jim Holler/Claudia Troxel)
5:00	Hydrogen cyanide AEGL-1 (George Rodgers/Sylvia Talmage)
5:30	Adjourn for the day

Wednesday, January 10, 2001

8:30 AM	Administrative matters
9:00	Summary of conference call on Hydrogen sulfide (Steve Barbee)
9:15	Consideration of odor in AEGL-1 development (Marc Ruijten)
10:15	Break
10:30	Application of AEGLs in occupational settings (John Morowetz)
11:00	Review of comments received to date from December 2000 *Federal Register Notice*
12:00 PM	Adjourn meeting

NAC/AEGL-20

Attachment 2

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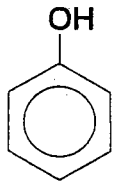
Sara Thurin Rollin	AFL-CIO	
	BNA	202-452-4584

Acute Exposure Guideline Levels (AEGLs)

for

Phenol

(CAS No. 108-95-2)



NAC/AEGL Meeting 20, January 8-10, 2001

FoBiG Staff Scientist:

Peter Griem

Chemical Manager in German Expert Group:

Ursula Gundert-Remy

Industry Reviewer for German Expert Group:

Jürgen Pauluhn

Chemical Manager:

Robert Snyder

Phenol

PROPERTIES

- colorless to pink, hygroscopic solid
- characteristic, sweet, tarry odor
- moderate vapor pressure

PRODUCTION

- distillation from petroleum
- oxidation of cumene or toluene
- vapor-phase hydrolysis of chlorobenzene

USES

- production of various phenolic resins, biphenol A, caprolactam and a wide variety of other chemicals and drugs

TOXICITY MECHANISM AND CONCERNS

- little human inhalation data
- locally, phenol causes irritation by tissue damage
- systemically, phenol causes stimulation of the central nervous system.
  Typical manifestations of phenol ingestion include agitation, muscle tremors, confusion, incoordination, seizures, coma, hypotension, arrhythmias and respiratory arrest

DATA RELEVANT TO AEGL-1

HUMAN

- Odor detection threshold about **0.06 ppm** (AIHA, 1989)

- Piotrowski (1971): human pharmacokinetic study

  face mask exposure of 9 groups of 5 subjects each (total of 8 different subjects) to

  1.3 - 6.5 ppm for 8 hours (2x0.5 h break)

  No statement on the occurrence of effects

- Ogata et al. (1986): 20 workers in toxicokinetic field study

  1.22 - 4.95 ppm mean workshift concentration

  No statement on the occurrence of effects

- Shamy et al. (1994): field study in 20 workers

  5.4 ppm TWA (mean time of job 13 years)

  higher serum levels of alanine and aspartate aminotransferases, higher hemoglobin concentrations and higher numbers of neutrophilic and basophilic granulocytes in the blood; no statement on the occurrence of irritative effects

- Ruth (1986) reported an irritation threshold of 47 ppm in humans, but did not provide the source (48 ppm phenol / 8 ppm HCHO exposure; US DoL, 1978; as source ?)

DATA RELEVANT TO AEGL-1

ANIMAL

– Sandage (1961): inhalation exp. of 10 rhesus monkeys

5 ppm continuously for 90 days

no alterations in hematologic parameters or in histology

– CMA (1998): inhalation exp. of rats (20/sex/group)

0.5, 5 and 25 ppm for 6 h/d, 5 d/w for 2 weeks

no clinical, hematological or histopathological effects

Incidence of red nasal discharge in rats					
Conc. (ppm)	Female:	1st	2nd week	Male:	1st	2nd week
control		0/20	0/20		0/20	0/20
5		0/20	1/20		0/20	0/20
5		1/20	3/20		3/20	7/20
25		0/20	0/20		4/20	10/20

AEGL-1

Keystudy: CMA, (1998)

Endpoint: In rats, exposure to 25 ppm for 6 h/d, 5 d/w for 2 weeks caused no clinical, hematological or histopathological effects

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

30-min value was applied to 10 min because no data are available for short-term human exposure to >5 ppm

Total uncertainty factor: 10

Interspecies: **3**

because a multiple exposure study was used

Intraspecies: **3**

toxicokinetic differences were considered limited for local irritation effects and a factor of 10 would have resulted in concentrations far below those used in pharmacokinetic studies

AEGL-1 Values for Phenol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
5.7 ppm (22 mg/m³)	5.7 ppm (22 mg/m³)	4.5 ppm (17 mg/m³)	2.9 ppm (11 mg/m³)	1.9 ppm (7.3 mg/m³)

Supporting data:

- no effects in rhesus monkeys exposed continuously to 5 ppm for 90 days (Sandage, 1961)
- Piotrowski (1971) exposed subjects for 8 (-1) hours to up to 6.5 ppm and made no statement on health effects
- Shamy et al. (1994) made no statement on irritative effects in workers exposed to 5.4 ppm TWA

DATA RELEVANT TO AEGL-2 (I)

HUMAN

- no relevant inhalation studies available

- Baker et al. (1978): population exp. via drinking water during several weeks
  gastrointestinal symptoms (diarrhea, nausea, burning pain and sores in the mouth) in 17/39 persons after uptake of doses of 10 - 240 mg/d

- Shamy et al. (1994): field study in 20 workers

  5.4 ppm TWA (mean time of job 13 years)

  higher serum levels of alanine and aspartate aminotransferases, higher hemoglobin concentrations and higher numbers of neutrophilic and basophilic granulocytes in the blood; no statement on the occurrence of irritative effects

- Ruth (1986) reported an irritation threshold of 47 ppm in humans, but did not provide the source (48 ppm phenol / 8 ppm HCHO exposure; US DoL, 1978; as source ?)

DATA RELEVANT TO AEGL-2 (II)

ANIMAL

- CMA (1998): inhalation exp. of rats (20/sex/group)

  0.5, 5 and 25 ppm for 6 h/d, 5 d/w for 2 weeks

  no clinical, hematological or histopathological effects.

- Deichmann (1944): inhalation exp. of rabbits/rats/guinea pigs

  26 - 52 ppm for 7 h/d, 5 d/w for 4 - 12 weeks

  guinea pigs: 5/12 died after 20 exposures; rest killed next day
  rabbits: after 88 days of exposure, pneumonia and
  degeneration/necrosis in heart, liver and kidneys
  rats: after 74 days no clinical or histological alterations

- Dalin and Kristofferson (1974): inhalation exp. of rats (n=14)

  26 ppm continuously for 15 days

  after 1 d: increased activity
  during 3rd - 4th d: impaired balance, disordered walking, muscle twitches; symptoms passed off during 5th day

- Brondeau et al. (1989): inhalation exp. of rats (5m/group)

  111, 156 or 211 ppm for 4 hours

  156 and 211 ppm: decrease of numbers of white blood cells
  (interpreted as associative response to sensory irritation)
  111 ppm: no effect on WBC count
  No statement on clinical effects

- De Ceaurriz et al. (1981): inhalation exp. of mice

  166 ppm for 5 min RD_{50}

AEGL-2

Keystudy: not applicable

Endpoint: Derived as fraction of AEGL-3

Scaling: -

Divisor: 3

because a larger divisor would have resulted in an 8-hour concentration to which subjects have been exposed in a toxicokinetic study and which was found at workplaces

AEGL-2 Values for Phenol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
20 ppm (77 mg/m³)	20 ppm (77 mg/m³)	16 ppm (61 mg/m³)	9.7 ppm (37 mg/m³)	7.7 ppm (30 mg/m³)

Supporting data:

- Shamy et al. (1994) reported slight effects on liver and blood parameters (increased serum transaminase activity, increased hemoglobin concentration, increased numbers of white blood cells) in workers exposed to 5.4 ppm TWA (mean time on job 13 years)

- similar values would be derived based on the NOAEL of 25 ppm for 6 h/d in rats (CMA, 1998) using a total UF of 3

DATA RELEVANT TO AEGL-3

HUMAN

- no relevant inhalation data are available
- several case reports described lethal poisonings after oral uptake of 106 - 874 mg/kg

ANIMALS

- Flickinger (1976): inhalation exp. of rats (n=6)

  900 mg/m³ phenol aerosol for 8 hours (≈ 234 ppm)

  after 4 hours: ocular and nasal irritation, slight loss of coordination with spasms of isolated muscles and
  after 8 hours additionally tremors and prostration in 1 animal

- Anonymous (1986): inhalation exp. of rats (n=6)

  312 ppm for 15 minutes

  inactivity and lacrimation

- Brondeau et al. (1989): inhalation exp. of rats (5m/group)

  111, 156, 211 ppm for 4 hours

  111 and 156 ppm: decrease of numbers of white blood cells (but apparently no severe symptoms)

- Deichmann (1944): inhalation exp. of rabbits/rats/guinea pigs

  26 - 52 ppm for 7 h/d, 5 d/w for 4 - 12 weeks

  guinea pigs: 5/12 died after 20 exposures; rest killed next day
  rabbits: after 88 days of exposure, pneumonia and degeneration/necrosis in heart, liver and kidneys
  rats: after 74 days no clinical or histological alterations

AEGL-3

Keystudy: Flickinger (1976)

Endpoint: No death of rats after 8-hour exposure to 900 mg/m³ phenol aerosol (234 ppm); prostration and tremors in 1/6 rats

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

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

Total uncertainty factor: 10

because this factor was considered adequate based on comparison with oral intoxication cases and because a higher factor of 30 would result in an exposure level for the 8-hour period, for which in toxicokinetic studies no effects were mentioned.

Interspecies: **3**

Intraspecies: **3**

AEGL-3 Values for Phenol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
59 ppm (230 mg/m³)	59 ppm (230 mg/m³)	47 ppm (180 mg/m³)	29 ppm (110 mg/m³)	23 ppm (88 mg/m³)

Supporting data:

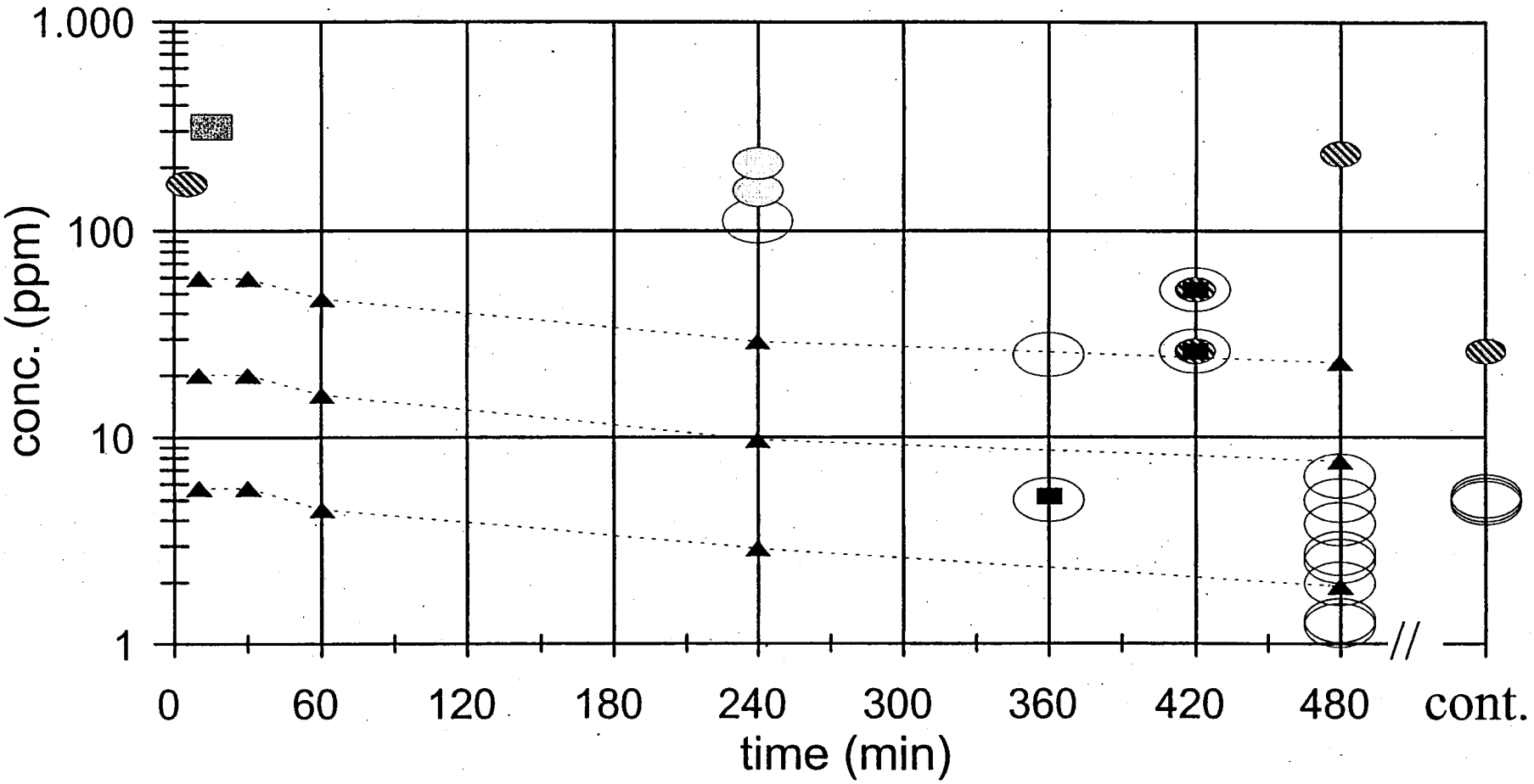
- inhalation exposure in the key study (Flickinger, 1976) is equivalent to a total dose of 321 mg/kg, which is supported by oral toxicity data in rats
- systemic effects: 234 ppm for 8 hours / UF 10 (AEGL-3) is equivalent to 13 mg/kg · d for a 70-kg adult. This is a factor 8 - 48 lower than reported lethal oral doses in humans

SUMMARY OF ACUTE ORAL LETHAL DATA IN ANIMALS					
Species	**Dose (mg/kg)**	**Remarks on administration**	**Total number of animals used**	**Datum**	**Reference**
rabbit	420	solutions with different phenol concentrations were used	35	LOEL for death	Deichmann and Witherup (1944)
rat	400	gavage	not stated	LD_{50}	Berman et al. (1995)
rat	530	gavage, 2 % solution	45	LD_{50}	Deichmann and Witherup (1944)
rat	530	gavage, 5 % solution	45	LD_{50}	Deichmann and Witherup (1944)
rat	540	gavage, 10% solution	40	LD_{50}	Deichmann and Witherup (1944)
rat	340	gavage, 20 % solution	45	LD_{50}	Deichmann and Witherup (1944)
rat	650	gavage	20	LD_{50}	Flickinger (1976)
rat	*321*	*aerosol inhalation exp.*	*6*	*prostration in 1/6 rats*	Flickinger (1976)
mouse	282	not stated	not stated	LD_{50}	Horikawa and Okada, 1975
mouse	300	not stated	not stated	LD_{50}	Von Oettingen and Sharples, 1946
mouse	427	not stated	not stated	LD_{50}	Kostoveckii and Zholdakova, 1971

SUMMARY OF DATA ON LETHAL EFFECTS IN HUMANS			
Subject and exposure route	**Exposure information and estimated dose**	**Effect**	**Reference**
1-day-old newborn inhalation	about 5.2 ppm for 5-6 h, subsequently about 1.3 ppm for 14-15 h; add. 25 - 40 ppm HCHO dose n.d.	cyanosis, tachypnea, death 4 days later	Heuschkel and Felscher, 1983
65-year-old female oral	70 ml of 42-52 % phenol solution dose 490 - 606 mg/kg	after 1 h respiratory arrest, coma (survived)	Kamijo et al., 1999
50-year-old male oral	approx. 60 ml of an 88 % phenol emulsion dose 754 mg/kg	after 45 min stuporous, tachycardia, stertorous breathing, rales in the lungs (survived)	Bennett et al., 1959
19-year-old female oral	15 ml liquefied phenol dose 250 mg/kg	90 min later nausea, vomiting, diarrhea, cyanosis, stuporous, death after 17.5 h	Bennett et al., 1959
adult female oral	10-20 g phenol dose 166 - 333 mg/kg	coma, absence of reflexes, tachypnea, tachycardia, death after 1 h due to cardiac and respiratory arrest	Stajduhar-Caric, 1968
27-year-old male oral (+ dermal)	unknown dose 106 - 874 mg/kg based on tissue concentration	found dead next day	Tanaka et al., 1998
1-day-old newborn dermal	2 % phenol solution in umbilical bandage dose 125 - 202 mg/kg based on tissue concentration	cyanosis, death after 11 h	Hinkel and Kintzel, 1968

AEGL Values for Phenol					
	10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1	5.7 ppm (22 mg/m^3)	5.7 ppm (22 mg/m^3)	4.5 ppm (17 mg/m^3)	2.9 ppm (11 mg/m^3)	1.9 ppm (7.3 mg/m^3)
AEGL-2	20 ppm (77 mg/m^3)	20 ppm (77 mg/m^3)	16 ppm (61 mg/m^3)	9.7 ppm (37 mg/m^3)	7.7 ppm (30 mg/m^3)
AEGL-3	59 ppm (230 mg/m^3)	59 ppm (230 mg/m^3)	47 ppm (180 mg/m^3)	29 ppm (110 mg/m^3)	23 ppm (88 mg/m^3)

Chemical Toxicity - TSD All Data
Phenol



Acute Exposure Guideline Levels (AEGLs)

for

Carbon Monoxide

(CAS No. 630-08-0)

CO

NAC/AEGL Meeting 20, January 8-10, 2001

FoBiG Staff Scientist:

Peter Griem

Chemical Manager in German Expert Group:

Hans-Uwe Wolf

Industry Reviewer for German Expert Group:

Jürgen Pauluhn

Chemical Manager:

George Rodgers

Carbon monoxide

PROPERTIES

- tasteless, odorless, colorless, non-irritating gas

PRODUCTION

- by-product of combustion of fuels in industry, homes and motor vehicles
- most important fire effluent
- considerable exposure through smoking

USES

- reducing agent in steel production

TOXICITY MECHANISM AND CONCERNS

- CO binds to hemoglobin forming carboxyhemoglobin.

  This decreases the oxygen transport capacity of the blood and can lead to tissue hypoxia. Organs with a high oxygen demand, such as heart and brain, are especially sensitive.
- until very severe toxic symptoms occur, none or only nonspecific symptoms (e.g. headache, increased respiration, dimmed vision) are noted
- CO exposure occurs not only in hazardous incidences, but in everyday life

Symptoms in healthy adult humans (WHO, 1999)		Findings in sensitive subgroups	
[COHb] (%)	**Symptoms**	**[COHb] (%)**	**Symptoms**
1	physiological background (3 - 8 % in smokers)	2 - 4	electrocardiogram signs of myocardic ischemia and angina pectoris in subjects with CAD
		5 - 6	increase in cardiac arrhythmias in CAD patients
		7	headache, nausea, dizziness in children
10	no appreciable effect, except shortness of breath on vigorous exertion, possible tightness across the forehead, dilation of cutaneous blood vessels	13	cognitive development deficits in children
20	shortness of breath on moderate exertion, occasional headache with throbbing in temples	15	myocardial infarction in subjects with CAD
		25	syncopes in children
30	decided headache, irritable, easily fatigued, judgement disturbed, possible dizziness, dimness of vision	25	stillbirths
40 - 50	headache, confusion, collapse, fainting on exertion		
60 - 70	unconsciousness, intermittent convulsion, respiratory failure, death if exposure is long continued		
80	rapidly fatal		

DATA RELEVANT TO AEGL-1

HUMAN

- In healthy adult individuals, subclinical effects (such as decrements in neurobehavioral function and decreases in work capacity) start at [COHb] of about **5 %** (WHO, 1999; EPA, 2000)
- In school children, headache, nausea, dizziness, dyspnea and vomiting was found at a [COHb] of **7 %** (Klasner et al., 1998)
- In patients with coronary artery disease (CAD), the time to onset of angina and the time to 1-mm ST-segment depression in the electrocardiogram during physical exercise are significantly reduced at [COHb] of **2 - 4 %**

Additional Information

Time	**US National Ambient Air Quality Standard (1994)**	**WHO Ambient Air Quality Guideline Values (1999)**	**EU Limit Value (1999)**
15 min		100 mg/m³ (87 ppm)	
30 min		60 mg/m³ (52 ppm)	
1 h	35 ppm	30 mg/m³ (26 ppm)	
8 h	9 ppm	10 mg/m³ (9 ppm)	10 mg/m³
		set in such a way that [COHb] of 2.5 % is not exceeded, even when a normal subject engages in light or moderate exercise	

AEGL-1

Derivation of AEGL-1 values cannot be recommended

- because CO a tasteless, non-irritating, odorless and colorless toxic gas, which can cause lethal poisonings with few and late occurring warning signs
- because in CAD patients effects, such as significant electrocardiogram changes and reduced time to angina onset during physical activity, occur at ambient air quality guideline levels
- because AEGL-1 values would have to be derived in a concentration range encountered in everyday life:
  - physiologic background level 0.1 - 0.8 % [COHb]
  - 3 - 8 % [COHb] are found in smokers
  - CO concentrations between 10 and 50 ppm can be found on heavily traveled roads, inside motor vehicles and homes with gas-, coal-, wood- or kerosene-fired heaters and stoves

10 minutes	30 minutes	1 hour	4 hours	8 hours
N.R.	N.R.	N.R.	N.R.	N.R.

DATA RELEVANT TO AEGL-2 (I)

HUMAN: CAD patients

- Allred et al. (1989a; b; 1991) experimental study using

  [COHb] of **2 and 4 %** in 63 patients with stable exertional angina pectoris

Parameter	**[COHb]**	**Overall finding**	**Results in individual test centers**
Time to 1-mm ST-segment change	2 % 4 %	significant 5 % decrease significant 12 % decrease	+ (+) - + + +
Time to onset of angina	2 % 4 %	significant 4 % decrease significant 7 % decrease	+ + - + (+) -
Total exercise time	2 % 4 %	no effect significant decrease	
Heart rate - blood pressure product	2 % 4 %	no effect significant decrease	

- Sheps et al. (1990; 1991) experimental study

  41 established CAD patients and differing arrhythmia levels

  Significantly increased frequency of ventricular premature depolarizations at [COHb] of **6 %**, but not at **4 %** in all groups, during exercise

- further studies evaluating same endpoints

Parameter	**[COHb]**	**Findings**	**Reference**
Depression of ST-segment	3.8 % 3.9 %	not found not found	Sheps et al., 1987 Kleinman et al., 1998
Reduced time to onset of angina	2.5 - 3.0% 3.0 % 2.9 + 4.5 % 3.8 % 3.9 %	found found found not found found	Aronow et al., 1972 Kleinman et al., 1989 Anderson et al., 1973 Sheps et al., 1987 Kleinman et al., 1998
Increased cardiac arrhythmia	3 + 5 %	not found	Dahms et al., 1993

DATA RELEVANT TO AEGL-2 (II)

HUMAN: children

- Klasner et al. (1998): mass poisoning by gas leak

  504 school children (mean age 8.7 years) were potentially exposed; **7.0 %** [COHb] measured in 147 with symptoms about 1 h (up to 2 h) after removal from CO atmosphere; 179 children were examined in hospital:

  headache (139), nausea (69), dizziness (30), dyspnea (19), vomiting (13), abdominal pain (11), drowsiness (9), other (0)

- Crocker and Walker (1985): exposure through faulty gas furnaces/stoves

  analysis of CO poisonings in 16 children with [COHb] **>15 %**

Symptom	**Threshold [COHb] (%)**	**Average [COHb] (%)**	**patients experiencing this symptom**
None	<15	<15	12/12
Nausea	16.7	27.1	16/16
Vomiting	19.8	29.4	12/16
Headache	16.7	28.3	13/14
Lethargy	18.6	25.9	11/16
Visual symptoms	24.5	32.5	3/14
Syncope	**24.5**	**31.6**	**9/16**
Seizures	36.9	36.9	1/16

2/16 children showed long-lasting recurrent headaches or memory difficulties (**36.1** and **36.9 %** [COHb])

DATA RELEVANT TO AEGL-2 (III)

– Klees et al. (1985): exposure through faulty furnaces or fires

analysis of psychological sequelae of CO poisoning in children

2 - 11 years after poisoning (14 children):			
No. of Children	**Age (years)**	**[COHb] (%)**	**Findings**
6 /14	7.8 (2.8 - 12.1)	13, 19, 19, 32, -, -	spatial organization problems, constructive apraxia, deterioration of lexical and arithmetic activity
7 / 14	9.8 (3.4 - 14.4)	16, 20, 22, 23, 24, 25, 26	slight impairment of visual memory and concentration

3 months after poisoning (20 children):			
No. of Children	**Age (years)**	**[COHb] (%)**	**Findings**
5/6	< 3 (2.0 - 2.9)	16, 20, 27, -, -	were more nervous, more irritable, more anxious; possibly caused by situation surrounding intoxication
1/6	< 3 (2.6)	37	developmental level regression, violent anger, nervosity
6/8	4 - 9	4, 6, 25, 27, -, -	perturbed visuo-spatial perceptions, topographical memory and auditory memory
3/6	>10 (10.0 - 10.9)	26, 27, 36	perturbed visuo-spatial perceptions, auditory memory
1/6	>10 (14.3 - 15.7)	30	serious balance problems, spatial organization impairment

– Meert et al. (1998): exposure through fires in 95/106 cases

7 children ([COHb] **31 - 45 %**) with neurologic deficits or delayed neurologic syndromes of a total of 37 with [COHb] > 25 % (severe intoxication)

DATA RELEVANT TO AEGL-2 (IV)

ANIMAL

- Purser and Berrill (1983): cynomolgus monkeys (n=3)

  at **1000 ppm**, no effects were observed during the first 16 - 20 min; then animals became less active and sat down; at about 25 min, the animals went into a state of severe intoxication within 1- 2 min, in which animals were lying down with eyes closed, they sometimes vomited and were virtually unable to perform coordinated movements (total exp. time **30 min**)

  at **900 ppm**, animals layed down, but did not collapse; no signs occurred until 20 - 25 min (corresponding to [COHb] of about 16 - 21 %) (total exp. time **30 min**)

- Mactutus and Fechter (1985): pregnant rats

  after continuous CO exposure throughout gestation (mean maternal [COHb] was **15.6 %**), a significant memory impairment in behavioral tests was found in 120-day-old offspring

- Morris et al. (1985): pregnant pigs

  after continuous CO exposure for the last 5 days of gestation (maternal [COHb] **22 %**), impaired negative geotaxis behavior and reduced open field activity in offspring at 1-2 d

AEGL-2

Keystudy: Allred et al. (1989a; b; 1991); Sheps et al. (1990; 1991)

Endpoint: At 4 % [COHb], a reduced time to ST-segment depression in the electrocardiogram and a reduced time to the onset of angina pectoris during physical exercise were found. At 5.3 % [COHb], but not at 3.7 %, a increased frequency of exercise-induced arrhythmias was found.

AEGL-2 values were derived on a [COHb] of 4 %

Mathematical model (incl. time scaling):

The CFK model was used to calculated CO exposure concentrations that would result in a [COHb] of 4 % at the end of relevant exposure periods

Total uncertainty factor: 1

Intraspecies: 1

because the values are based on observations in the most sensitive human subpopulation (CAD patients)

AEGL-2 Values for CO				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
420 ppm (480 mg/m³)	150 ppm (170 mg/m³)	83 ppm (95 mg/m³)	33 ppm (38 mg/m³)	27 ppm (31 mg/m³)

Supporting data:

- derived values should protect children against syncopes (inability to escape), for which a LOEL of 24.5 % [COHb] has been reported by Crocker and Walker (1985)

- derived values should protect children against long-lasting cognitive developmental defects, for which a LOEL of 13 % [COHb] has been reported by Klees et al. (1985)

DATA RELEVANT TO AEGL-3 (I)

HUMAN

- In apparently healthy people that died from CO poisoning, usually [COHb] of **60 %** or higher are found

- Haldane (1895); Chiodi et al. (1941): healthy adults

  experimental exposure to **40 - 55 %** [COHb] led to hyperpnea, confusion of mind, dim vision and unsteady/inability to walk, but not to lethal effects

- Koren et al. (1991): pregnant women

  2 cases of stillbirths and 1 case of cerebral palsy due to postanoxic encephalopathy after CO poisoning of pregnant women with [COHb] ≥**25 %**

- Caravati et al. (1988): pregnant women

  3 cases of stillbirths (one stillbirth of a malformed fetus delayed for 20 weeks) with maternal [COHb] of **32, 40 and 24 %**; 3 other cases (10, 23 and 39 %) with no effects on fetal outcome

- Case reports about CO-caused myocardial infarction

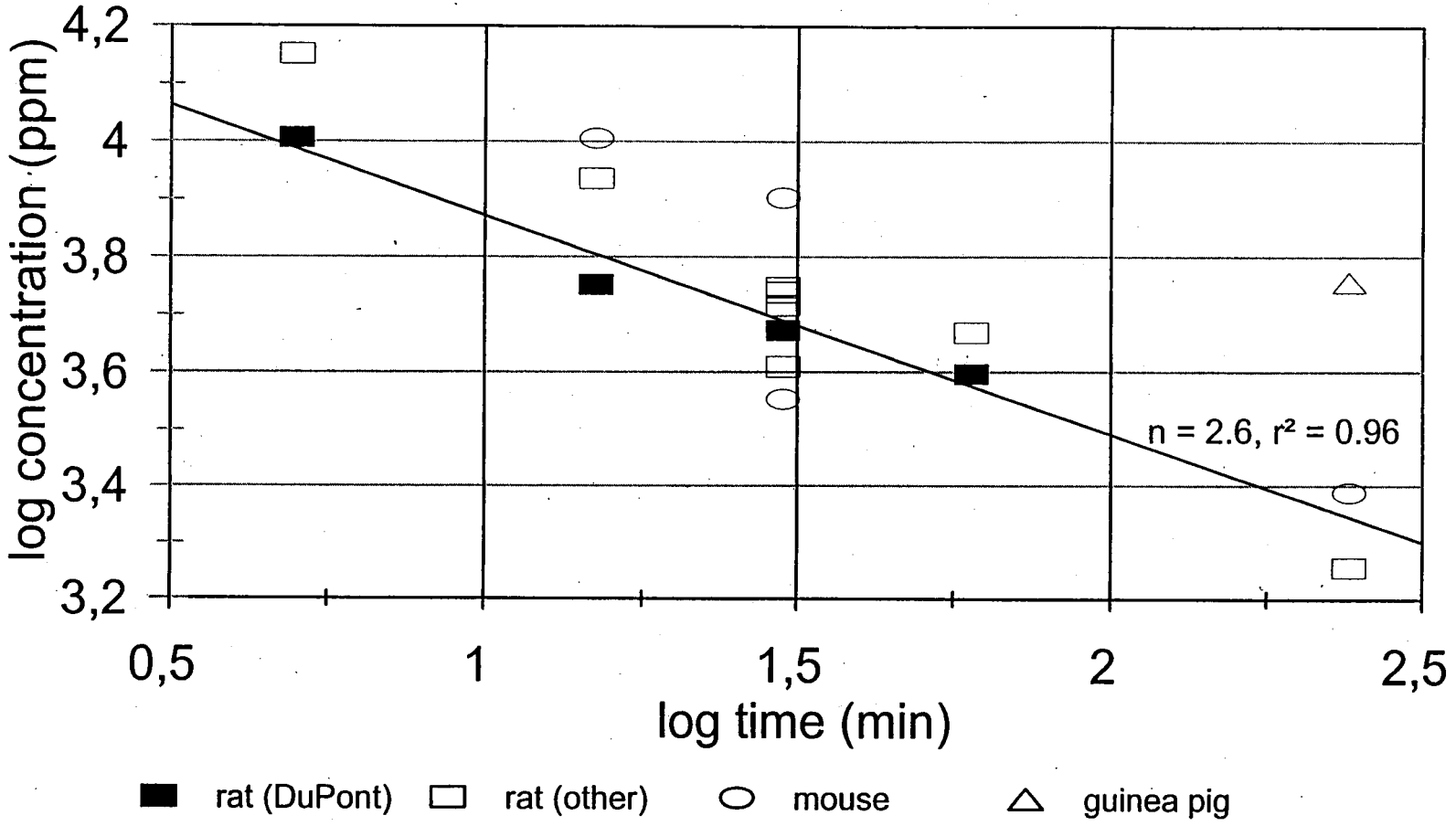
Subject	Exposure	[COHb]	Reference
m, 67, CAD?, survived m, 69, CAD?, survived	repeated/prolonged exposure through faulty furnaces at home	15.6 % about 30 %	Grace and Platt (1981)
m, age?, CAD, died m, age?, CAD, died	exposure at workplace through furnace/forklift	30 % 23 %	Atkins and Baker (1985)
m, 28, no CAD, survived	accidental exposure at workplace through bast furnace	21 %;	Ebisuno et al. (1986)
m, 46, no CAD, survived	exposure through apartment fire	52 %	Marius-Nunez (1990)

DATA RELEVANT TO AEGL-3 (II)

ANIMAL

LC_{50} data in animals			
Species	**Conc. (ppm)**	**Time (min)**	**Reference**
Rat	14200	5	Darmer et al., 1972
Rat	10151	5	E.I. du Pont de Nemours and Co., 1981
Rat	8636	15	Hartzell et al., 1985
Rat	5664	30	E.I. du Pont de Nemours and Co., 1981
Rat	5607	30	Herpol et al., 1976
Rat	5500	30	Kimerle, 1974
Rat	5207	30	Hartzell et al., 1985
Rat	4710	30	E.I. du Pont de Nemours and Co., 1981
Rat	4070	30	Haskell Laboratories, 1978
Rat	4670	60	Kimerle, 1974
Rat	3954	60	E.I. du Pont de Nemours and Co., 1981
Rat	1807	240	Rose et al., 1970
Mouse	10127	15	Kishitani et al., 1979
Mouse	3570	30	Hilado et al., 1978
Mouse	8000	30	Hilado et al., 1978
Mouse	2444	240	Rose et al., 1970
Guinea pig	5718	240	Rose et al., 1970

LC50 values in different species



analysis of all data: n = 2.8, r^2 = 0.64

DATA RELEVANT TO AEGL-3 (III)

ANIMAL

Increased stillbirths/fetal mortality in animals			
Species	**Exposure**	**Maternal [COHb]**	**Reference**
Pig	continuously for 3 d	23 %	Dominick and Carson, 1983
Rabbit	continuously during gestation	16 - 18 %	Astrup et al., 1972
Rabbit	12 puffs of cigarette smoke, 2700 - 5400 ppm CO during gestational days 16 - 18	about 16 %	Rosenkrantz et al., 1986
Rat	750 ppm 3 h on gestational day 7, 8 or 9	n.d.	Choi and Oh, 1975
Mouse	125, 250, 500 ppm (NOEL 65 ppm) continuously on gestational days 6 - 17	n.d.	Singh and Scott, 1984

AEGL-3

Keystudy: Grace and Platt (1981); Atkins and Baker (1985); Ebisuno et al. (1986); Marius-Nunez (1990)

Endpoint: Lowest reported [COHb] of 15 % for death by myocardial infarction (in this case the man was exposed repeatedly during several weeks).

A level of 15 % [COHb] is a factor 3 lower than [COHb] that do not cause lethal effects in healthy individuals.

A threshold for the induction of myocardial infarction in this subpopulation cannot be defined because myocardial infarction can als occur spontaneously and by trigger effects (e.g. psychologic stress, physical exertion), which have no relevant effects on healthy individuals.

Mathematical model (incl. time scaling):

The CFK model was used to calculated CO exposure concentrations that would result in a [COHb] of 15 % at the end of relevant exposure periods

Total uncertainty factor: 1

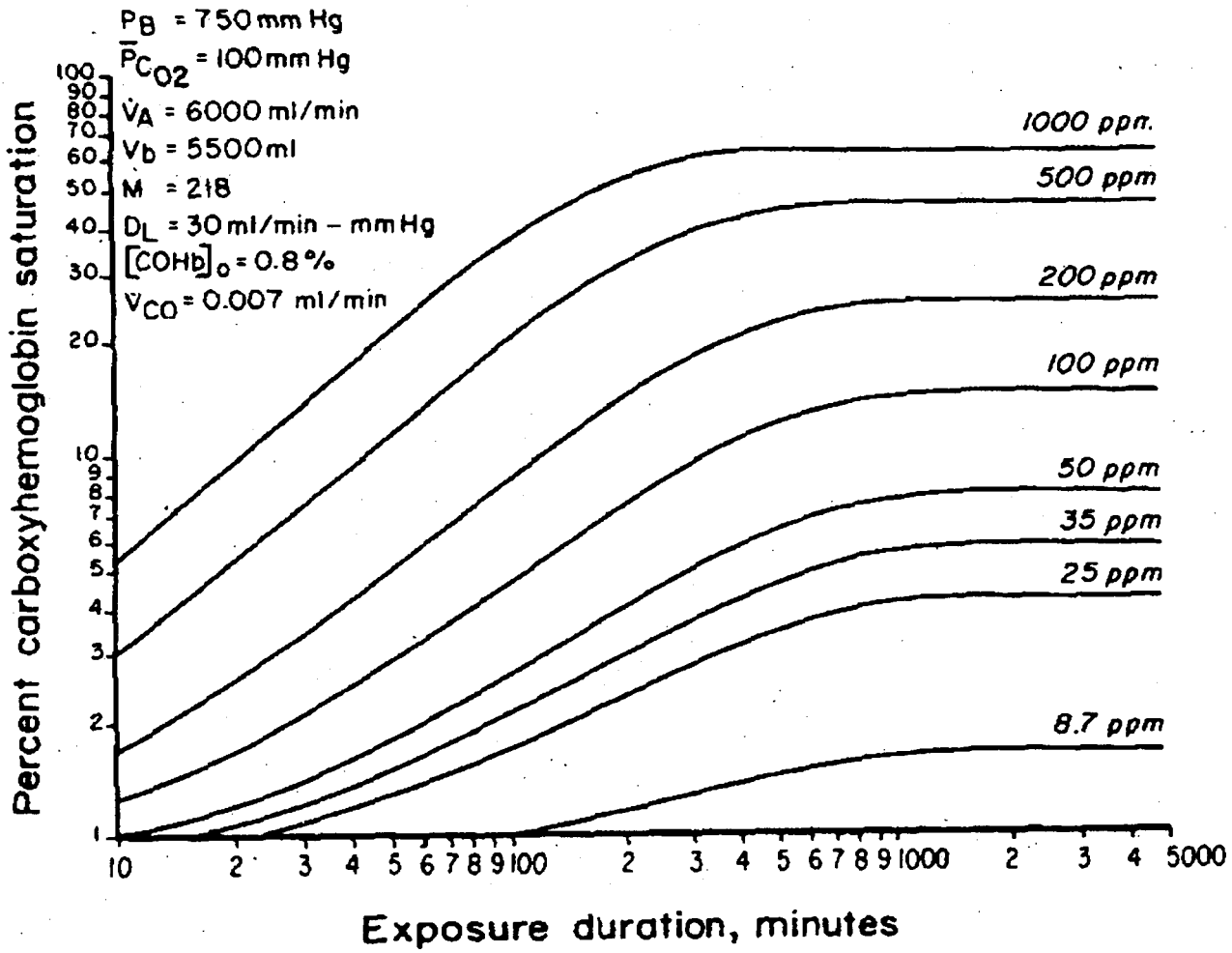
Intraspecies: **1**

because values are based on observations in the most sensitive human subpopulation and the measured [COHb] of 15 % as a basis for the calculation of exposure concentrations is conservative as the end of exposure [COHb] was probably higher than the concentration measured after transport to the hospital.

AEGL-3 Values for CO				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1900 ppm (2200 mg/m³)	650 ppm (740 mg/m³)	350 ppm (400 mg/m³)	140 ppm (160 mg/m³)	110 ppm (130 mg/m³)

[COHb] FOR DIFFERENT EXPOSURE CONCENTRATION-TIME COMBINATIONS

(from Peterson and Stewart, 1975)



Mathematical Model for Calculating [COHb] and Exposure Concentrations (I)

Study describing model: Coburn et al. (1965); Peterson and Stewart (1975)

- Since this model in the formulation of Peterson and Stewart (1975) calculates [COHb] larger than 100 % at high exposure concentrations, the following correction proposed by Peterson and Stewart (1975) was used: $[OHb]_t = [OHb]_{max} - [COHb]_t$.

- Since with this correction the CFK equation can only be solved iteratively, calculations were done using time steps (Δt) of 1 min for the period of 0 - 10 min, steps of 5 min between 10 and 60 min, steps of 15 min between 60 and 240 min, and steps of 20 min between 240 and 480 min. In each step, the [COHb] of the step before was used to calculate $[OHb]_t$. For the first step, a background [COHb] of 0.75 % was assumed.

- The alveolar ventilation rate was calculated as: $V_A = V_E - f\,V_D$ (Peterson and Stewart, 1975); with
  - V_E = total rate of ventilation (ml/min),
  - f = respiration rate (min^{-1}) and
  - V_D = dead space (ml).

  Derivations were done for a 70-kg man, assuming a blood volume of 5500 ml (Coburn et al., 1965) and a daily inhalation volume (V_E) of 23 m^3 (8 h resting and 16 h light/non-occupational activity; WHO, 1999b), a respiration rate (f) of 18 min^{-1} and a dead space (V_D) of 2.2 ml/kg (Numa and Newth, 1996)

Mathematical Model for Calculating [COHb] and Exposure Concentrations (II)

Calculations using the following equation were carried out in a spreadsheet computer program:

$$\Delta[COHb]_t = \left(\frac{V_{CO}}{Vb} - \frac{[COHb]_{t-1}\, P_{O2}}{M\, B\, Vb\, ([OHb]_{max} - [COHb]_{t-1})} + \frac{P_{CO}}{B\, Vb} \right) \Delta t$$

- $[COHb]_t$ = ml of CO per ml blood at time t (min)
  Conversion: % carboxyhemoglobin = [COHb] 100 / $[OHb]_{max}$
- V_{CO} = rate of endogenous CO production = 0.007 ml/min
- Vb = blood volume
- M = Ratio of affinity of blood for CO to that for = 218
- $B = 1 / D_L + P_L / V_A$
  - D_L = diffusivity of the lung for CO = 30 ml/min mm Hg
  - P_L = the vapor pressure of water at 37 °C = 713 mm Hg
  - V_A = alveolar ventilation rate;
- $[OHb]_{max}$ = ml of O_2 per ml blood (normal conditions) = 0,2
- P_{O2} = av. partial pressure of O_2 in the lung = 100 mm Hg
- P_{CO} = partial pressure of CO in the air inhaled (mm Hg);
  Conversion: P_{CO} (mm Hg) = P_{CO} (ppm) / 1316
- t = exposure duration (min)

Calculation of alveolar ventilation rates:

- V_A (70-kg man) = 23 m^3/d x 1 · 10^6 ml/m^3 x 1/1440 min/d - 18 /min x 2,2 ml/kg x 70 kg
  V_A (70-kg man) = 13200 ml/min

Mathematical Model for Calculating [COHb] and Exposure Concentrations (II)

Calculations

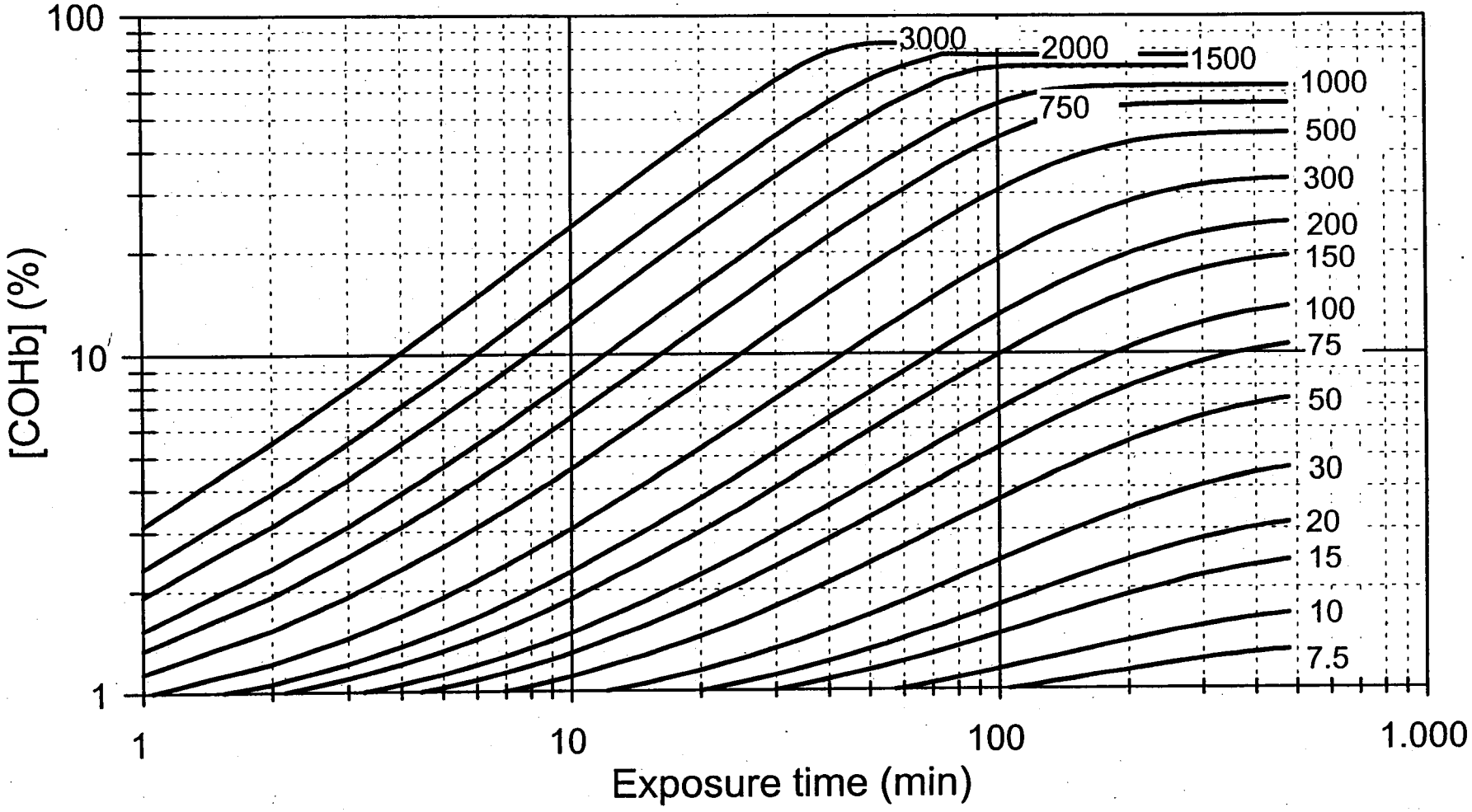
For the derivation of AEGL-2 values, exposure concentrations were calculated that would result in a [COHb] of 4 %.

CONCENTRATION-TIME COMBINATIONS RESULTING IN 4 % [COHb]		
Exposure time (min)	**for a 70-kg adult man**	
	Exposure concentration (ppm)	**Exposure concentration (ppm), rounded**
10	424	420
30	150	150
60	83	83
240	33	33
480	27	27

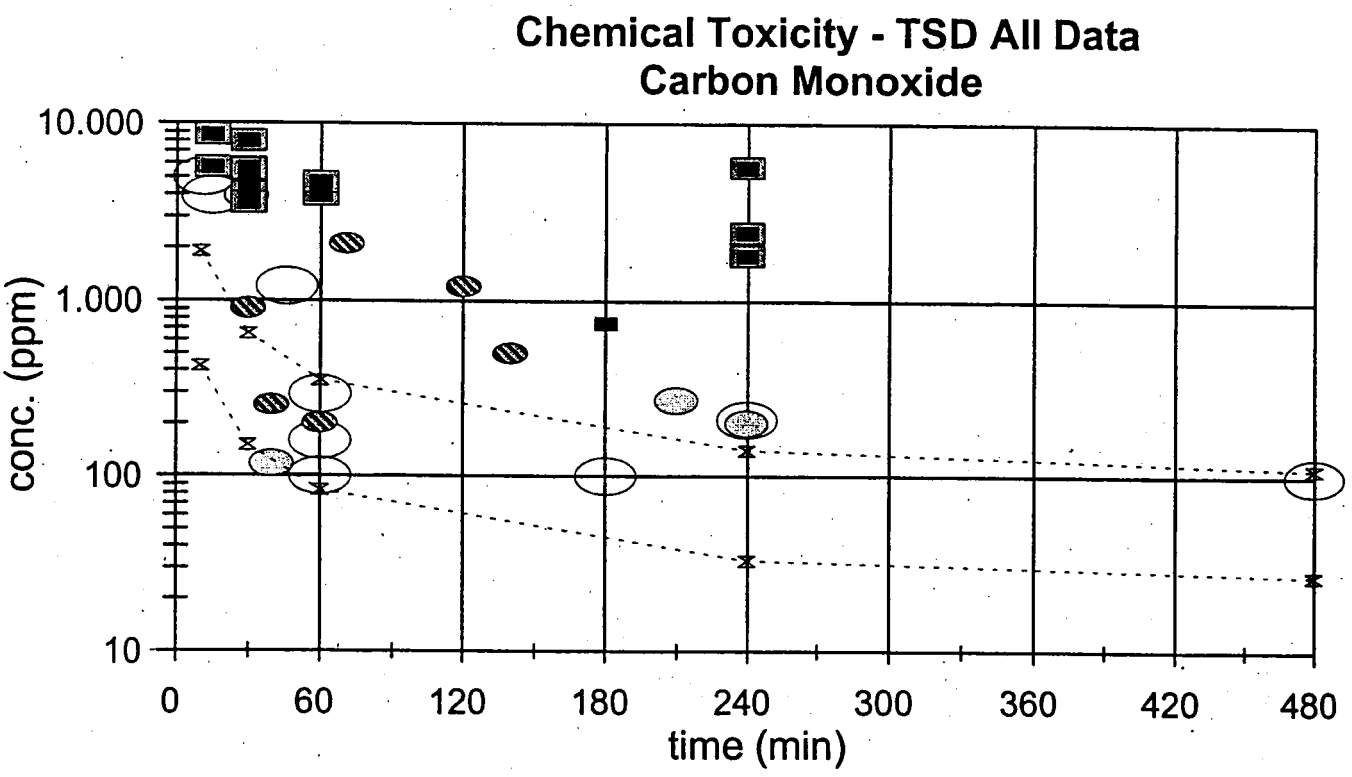
For the derivation of AEGL-3 values, exposure concentrations were calculated that would result in a [COHb] of 15 %.

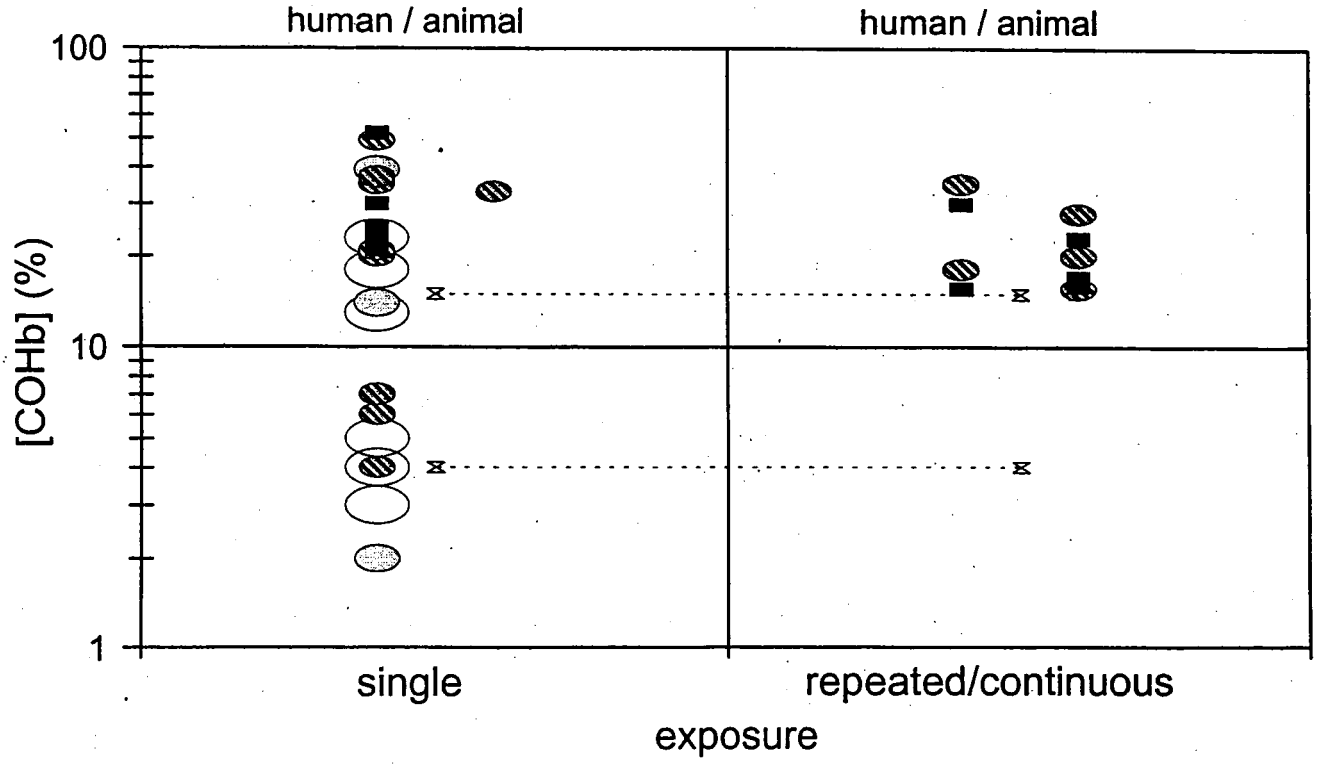
CONCENTRATION-TIME COMBINATIONS RESULTING IN 15 % [COHb]		
Exposure time (min)	**for a 70-kg adult man**	
	Exposure concentration (ppm)	**Exposure concentration (ppm), rounded**
10	1850	1900
30	648	650
60	352	350
240	137	140
480	111	110

[COHb] VS. EXPOSURE-TIME PLOTS FOR DIFFERENT CO CONCENTRATIONS (ppm)
(for a 70-kg adult)



AEGL Values for Carbon Monoxide					
	10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1	N.R.	N.R.	N.R.	N.R.	N.R.
AEGL-2	420 ppm (480 mg/m^3)	150 ppm (170 mg/m^3)	83 ppm (95 mg/m^3)	33 ppm (38 mg/m^3)	27 ppm (31 mg/m^3)
AEGL-3	1900 ppm (2200 mg/m^3)	650 ppm (740 mg/m^3)	350 ppm (400 mg/m^3)	140 ppm (160 mg/m^3)	110 ppm (130 mg/m^3)





no or minimal effect discomfort disabling

SULFUR MUSTARD (AGENT HD)

- **Technical Support Document, selection of key studies, and data analysis approved by NAS/COT at November 13-14, 2000 meeting.**

- **NAS/COT acknowledged concurrence with Interim AEGL values for sulfur mustard following minor adjustment to 10-minute and 30-minute AEGL-3 values to maintain methodological consistency with NAC/AEGL Standing Operating Procedures.**

Attachment 5

AEGL-3 Values for Sulfur Mustard					
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-3	0.91 ppm 6.1 mg/m^3	0.63 ppm 4.2 mg/m^3	0.32 ppm 2.1 mg/m^3	0.08 ppm 0.53 mg/m^3	0.04 ppm 0.27 mg/m^3

- All values except 10-min value were developed using an *n* of 1, estimated 1-hr lethality threshold (mice) of 21.2 mg/m^3, and total UF of 10 (3 x 3)

- 10-min values scaled from 30-min value using an *n* of 3

AEGL-3 Values for Sulfur Mustard					
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-3	~~0.91 ppm~~ ~~6.1 mg/m^3~~ 0.59 ppm 3.9 mg/m^3	~~0.63 ppm~~ ~~4.2 mg/m^3~~ 0.41 ppm 2.7 mg/m^3	0.32 ppm 2.1 mg/m^3	0.08 ppm 0.53 mg/m^3	0.04 ppm 0.27 mg/m^3

NAS/COT request:

- **Follow SOPs and use of *n* of 1 or 3; derived *n* of 1 based on ocular response not lethality**

Result

- **No effect on 1, 4, and 8-hour values (already developed using an *n* of 1)**
- **10-min and 30-min values slightly lower**

AEGL Values for Sulfur Mustard						
Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	0.06 ppm 0.40 mg/m^3	0.02 ppm 0.13 mg/m^3	0.01 ppm 0.067 mg/m^3	0.003 ppm 0.017 mg/m^3	0.001 ppm 0.008 mg/m^3	conjunctival injection and minor discomfort with no functional decrement in human volunteers (Anderson, 1942)
AEGL-2	0.09 ppm 0.60 mg/m^3	0.03 ppm 0.20 mg/m^3	0.02 ppm 0.10 mg/m^3	0.004 ppm 0.025 mg/m^3	0.002 ppm 0.013 mg/m^3	well marked, generalized conjunctivitis, edema, photophobia, and eye irritation in human volunteers (Anderson, 1942)
AEGL-3	0.59 ppm 3.9 mg/m^3	0.41 ppm 2.7 mg/m^3	0.32 ppm 2.1 mg/m^3	0.08 ppm 0.53 mg/m^3	0.04 ppm 0.27 mg/m^3	lethality estimate in mice (Kumar and Vijayaraghavan, 1998)

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

PHOSPHINE

NAC/AEGL-20

JANUARY 8-10, 2001

ORNL Staff Scientist: Cheryl Bast
Chemical Manager: Ernest Falke
Chemical Reviewers: Robert Benson, Mark McClanahan, John Morawetz

ISSUES- PHOSPHINE

- **REGRESSION OF RAT LETHALITY DATA SUGGESTS THAT THE VALUE OF THE EXPONENT 'n' IS APPROXIMATELY 1. THE DEFAULT VALUES OF n=1 OR n=3 ARE NOT CORRECT.**

- **DERIVATION OF ACUTE EXPOSURE VALUES FROM REPEATED EXPOSURE STUDIES IS INAPPROPRIATE.**

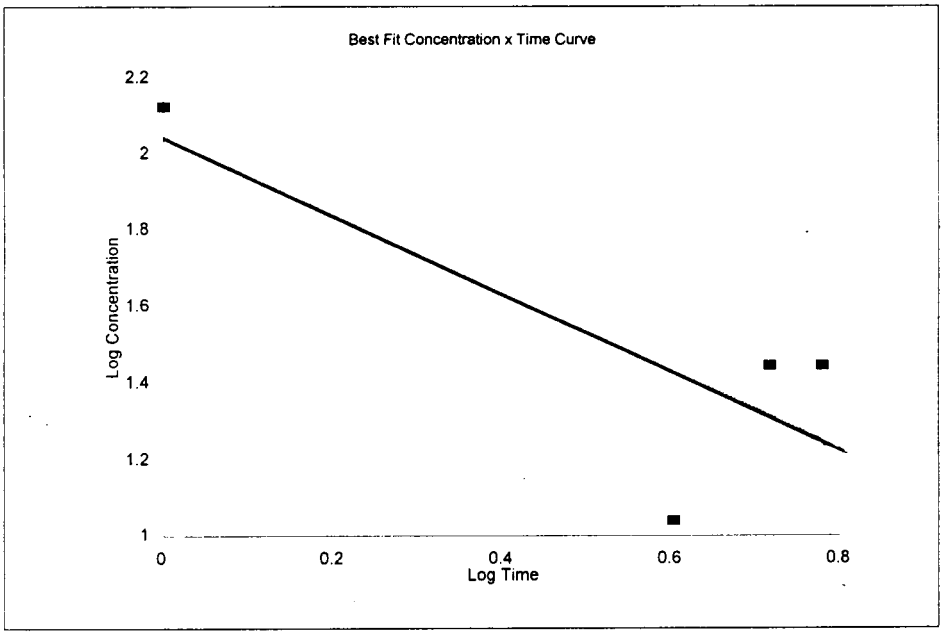
Time	Conc.	Log Time	Log Conc.
1	134	0.0000	2.1271
6	28	0.7782	1.4472
5.2	28	0.7160	1.4472
4	11	0.6021	1.0414

Regression Output:	
Intercept	2.0478
Slope	-1.0153
R Squared	0.6477
Correlation	-0.8048
Degrees of Freedom	2
Observations	4

n =	0.98
k =	103.97

Minutes	Conc.
30	3.53
60	1.75
240	0.43
480	0.21

Hours	Conc.
0.5	225.64
1.0	111.63
4.0	27.32
8.0	13.52



Selected Lethality Data from Animals Exposed to Phosphine					
Endpoint	**Species**	**Concentration (ppm)**	**Time (Hr)**	**C X T (ppm-hr)**	**Reference**
LC_{50}	*rat*	*11*	*4*	*44*	*Waritz & Brown, 1975*
LC_{50}	**rat**	**134**	**1**	**134**	**Muthu et al., 1980**
LC_{50}	**rat**	**28**	**5.2**	**146**	**Muthu et al., 1980**
LC_{50}	**rat**	**28**	**6**	**168**	**Newton, 1991**
LC_{50}	**mouse**	**26.5-33.4**	**4**	**106-134**	**Omae et al., 1996**
LC_{95}	**rat**	**45**	**6.2**	**279**	**Muthu et al., 1980**
LC_{95}	**rat**	**33.3**	**8.8**	**293**	**Muthu et al., 1980**

AEGL-2 FOR PHOSPHINE (ppm [mg/m^3])					
AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	4.0 [5.6]	4.0 [5.6]	2.0 [2.8]	0.50 [0.71]	0.25 [0.35]

Species: Rat
Concentration: 10 ppm
Time: 6 hr.
Endpoint: Red nasal mucoid discharge
References: Newton et al., 1993

n = 1

Uncertainty Factor: 3 x 10 =30

Interspecies = 3 (Rat, rabbit, guinea pig, and cat lethality data suggest little species variability)

Intraspecies = 10 (Human data suggest that children are more sensitive than adults)

INTER SPECIES UF = 3

RAT, RABBIT, GUINEA PIG, AND CAT LETHALITY DATA SUGGEST LITTLE SPECIES VARIABILITY

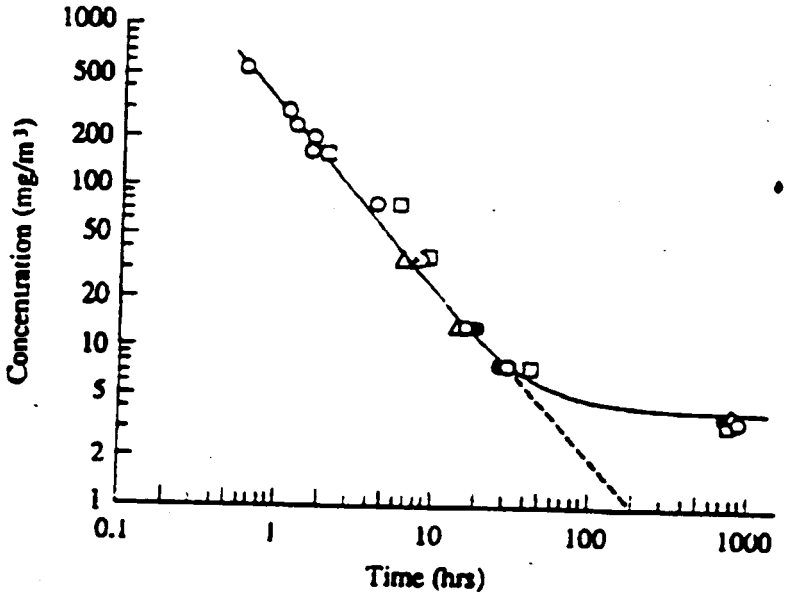


FIGURE 1. Phosphine concentration vs. Average time to death of rats (○), rabbits (△), guinea pigs (●), and cats (□).
(Gehring, 1991 from analysis of the data of Klimmer, 1969)

INTRA SPECIES UF = 10:

- **Children may be more sensitive than adults when exposed to presumably similar phosphine concentrations.**

    - **Two female children (ages 2 and 4.5 years) and 31 adult crew members were exposed to phosphine aboard a grain freighter. All adults and the 4 year-old child survived. The two-year old died as a result of the exposure. (Wilson et al., 1980).**

    - **Four males (ages 12, 35, 39, and 52 years) were discovered in a box car containing loose bulk lima beans that had been fumigated with aluminum phosphide. When discovered, the 12-year old was dead, while the three adults survived the exposure. (MMWR, 1994)**

AEGL-3 FOR PHOSPHINE (ppm [mg/m^3])					
AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	7.2 [10]	7.2 [10]	3.6 [5.1]	0.90 [1.3]	0.45 [0.63]

Species: Rat
Concentration: 18 ppm
Time: 6 hr.
Endpoint: NOEL for death
References: Newton, 1991

n = 1

Uncertainty Factor: 3 x 10 =30

Interspecies = 3 (Rat, rabbit, guinea pig, and cat lethality data suggest little species variability)

Intraspecies = 10 (Human data suggest that children are more sensitive than adults)

RELATIONAL COMPARISON OF AEGL VALUES FOR PHOSPHINE (ppm [mg/m^3])					
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	-	–	–	–	–
AEGL-2 (Disabling)	**4.0 [5.6]**	**4.0 [5.6]**	**2.0 [2.8]**	**0.50 [0.71]**	**0.25 [0.35]**
AEGL-3 (Lethality)	**7.2 [10]**	**7.2 [10]**	**3.6 [5.1]**	**0.90 [1.3]**	**0.45 [0.63]**

TWA PEL (OSHA): 0.28 ppm
TLV TWA (ACGIH, 1991): 0.3 ppm
TLV STEL (ACGIH, 1991): 1.0 ppm

ERPG-1 (AIHA, 1999): Not Appropriate
ERPG-2 (AIHA, 1999): 0.5 ppm (1 hour)
ERPG-3 (AIHA, 1999): 5 ppm (1 hour)

AEGL-2 VALUES				
10 min.	**30 min.**	**1 hr.**	**4 hr.**	**8 hr.**
0.38 ppm	**0.38 ppm**	**0.30 ppm**	**0.19 ppm**	**0.13 ppm**

Reference: Newton et al. 1993. Inhalation toxicity of phosphine in the rat: acute, subchronic, and developmental. Inhalation Toxicol. 5: 223-239.

Test Species/Strain/Number: B6C3F1 mice/ 4 males/concentration

Exposure Route/Concentrations/Durations: Inhalation: 0, 1.0, 5.0, or 10 ppm, 6 hr/day for 4 days.

Effects:

1.0 ppm	No effects
5.0 ppm	No effects (determinant for AEGL-2)
10 ppm	Anemia, decreased leukocyte counts, increased serum ALT and SDH activities, increased urine nitrogen, degeneration and necrosis of renal tubule epithelium, myocardial degeneration, and liver foci and degeneration

Endpoint/Concentration/Rationale: 5 ppm, Exposure was for 6 hours/day for 4 days. Values calculated assuming a single 6 hour exposure

Uncertainty Factors/Rationale:

Total uncertainty factor: 30

Interspecies: 3; Lethality data from rats, mice, rabbits, and guinea pigs suggest little species variability.

Intraspecies: 10- Children appear to be more sensitive than adults to the effects of phosphine. There were two case reports where exposed children died but adults exposed under similar conditions survived.

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: None; insufficient data

Time Scaling: The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge, 1986). To obtain conservative and protective AEGL values for the 30-minute, 1-, 4-, and 8-hour time points in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $c^n \times t = k$ equation. The 30-min AEGL-2 value was also adopted as the 10-minute value due to the fact that reliable data are limited to durations ≥4 hours, and it is considered inappropriate to extrapolate back to 10-minutes.

Confidence and Support for AEGL values: Data for effects defined by AEGL-2 are limited. Confidence is moderate at best.

AEGL-3 VALUES				
30 min.	**30 min.**	**1 hr.**	**4 hr.**	**8 hr.**
1.4 ppm	**1.4 ppm**	**1.1 ppm**	**0.69 ppm**	**0.45 ppm**

Reference: Newton, P.E. 1991. Acute inhalation exposures of rats to phosphine. Bio/Dynamics, Inc. East Millstone, NJ. Project No. 90-8271.

Test Species/Strain/Sex/Number: Sprague-Dawley rats, 5/sex/concentration or 10 males/concentration

Exposure Route/Concentrations/Durations: Inhalation: 0, 1.3, 6.0, or 28 ppm for 6 hr (5/sex/group); 0, 3.1, 10, or 18 ppm for 6 hr (10 males/group)

Effects: Exposure was for 6 hours.

Concentration	Mortality
0 ppm	0/10
1.3 ppm	0/10
3.1 ppm	0/10
6.0 ppm	0/10
10 ppm	0/10
18 ppm	0/10 (determinant for AEGL-3)
28 ppm	5/10

LC_{50}: 28 ppm

Endpoint/Concentration/Rationale: No-effect-level for death; 18 ppm, 6 hr./This study was chosen because 10 animals per dose group were used and data were for exposures over a range of phosphine concentrations.

Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Interspecies: 3- Lethality data from rats, mice, rabbits, and guinea pigs suggest little species variability.
Intraspecies: 10 - Children appear to be more sensitive than adults to the effects of phosphine. There were two case reports where exposed children died but adults exposed under similar conditions survived.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge, 1986). To obtain conservative and protective AEGL values for the 30-minute, 1-, 4-, and 8-hour time points in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $c^n \times t = k$ equation. The 30-min AEGL-3 value was also adopted as the 10-minute value due to the fact that reliable data are limited to durations ≥4 hours, and it is considered inappropriate to extrapolate back to 10-minutes.

Confidence and Support for AEGL values: Study is considered appropriate for AEGL-3 derivation since exposures are over a wide range of phosphine concentrations and utilize a sufficient number of animals.

XYLENES

- Mix of 3 isomers: *meta* (m), *para* (p), *ortho* (o)
- Majority of mixed xylenes produced by catalytic reforming of petroleum; this process usually results in ~44% m-xylene, 20% each of o- and p-xylene, and 15% ethylbenzene
- Prior to 1940s, produced from coal tar
- Consumer products: solvents, paints or coatings, blend in gasoline (BTX)
- U.S. production of mixed xylenes in 1990: 6.2 to 12.1 billion pounds; individual isomers: p-xylene > o-xylene > m-xylene
- Odor threshold: 0.7 to 40 ppm; aromatic hydrocarbon odor
- Two primary effects of acute exposure
  - irritation
  - central nervous system toxicity (narcosis)

AEGL-1 Derivation

Key study:

Hastings et al., 1986.

Effects:

Subjects exposed to 0, 100, 200, or 400 ppm mixed xylene for 30 min (via olfactory hood) Mild eye irritation noted by 56, 60, 70, and 90% of the subjects, respectively. Number of eye blinks/min and respiration rate not affected

Uncertainty factors:

Interspecies UF: 1

Intraspecies UF: 3 effect was that of an irritant

Time scaling:

Irritation is threshold effect and should not vary over time; threshold value is applied to all times

AEGL-1 Values for Xylenes (ppm)				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
130	**130**	**130**	**130**	**130**

AEGL-1

130 ppm value supported by:

- 150 ppm p-xylene for 7.5 hr - eye irritation in contact lens wearer (Hake et al., 1981)

- 230 ppm mixed xylene for 15 min - mild eye irritation and dizziness in 1/7 individuals (Carpenter et al., 1975)

- No effect levels at:

  200 ppm m- or p-xylene for 3 hr (Ogata et al., 1970)

  200 ppm m-xylene for 4 hr (Savolainen et al., 1981)

  200 ppm m-xylene for 5.5 hr (Laine et al., 1993)

Key Study for AEGL-2 and AEGL-3

Carpenter et al., 1975 Male albino rats: mixed xylene for 4 hr		
Conc. (ppm)	**Mortality**	**Other effects**
580	0/10	none observed
1300	0/10	poor coordination after 2 hours, returned to normal
2800	0/10	irritation; all rats prostrate 2-3.5 hr but recovered within 1 hr, coordination returned to normal next day
6000	4/10	rats prostrate within 30 min; all survivors prostrate but recovered promptly
9900	10/10	none stated

AEGL-2 and -3: Uncertainty Factors:

- Interspecies UF - 1
  - based on similar exposure effects in humans as compared with animals
  - pharmacokinetic data: interspecies UF for toxicokinetic differences < 1 using rat data to derive exposure values for humans
  - pharmacodynamic data: little difference in interspecies sensitivity: lethality data for mice and rats identical
- Intraspecies UF - 3
  - MAC for volatile anesthetics should not vary by more than factor of 2-3-fold in humans.
  - A 3-fold factor also adequate to account for moderate physical activity during exposure, resulting in greater uptake of the chemical

AEGL-2 and -3: Time Scaling

- Data inappropriate for calculation of n
- Available data indicate that concentration, not duration, is prime determinant in CNS toxicity
  - Xylene-blood conc. key in CNS toxicity
    - Readily crosses blood:brain barrier; distribution studies confirm immediate presence in CNS; elimination by 1 hr
    - Pharmacokinetic modeling in rats and humans: rapid increase in blood conc. first 15 min with minimal increases thereafter (hyperbolic curve)
    - Human data: initial rapid increase in blood conc., but then levels off

      while
    - Human and animal data indicate that increasing exposure conc. correlate with increases in venous blood conc.

AEGL-2 Derivation

Key study:

Carpenter et al., 1975.

Effects:

Poor coordination resulted when rats exposed to 1300 ppm mixed xylene for 4 hours. Represents threshold for reversible equilibrium disturbances.

Uncertainty factors:

Interspecies UF: 1

Intraspecies UF: 3

Time scaling:

Data indicate concentration, not duration, is prime determinant in xylene-induced CNS toxicity, so threshold value applied to all times

AEGL-2 Values for Xylenes (ppm)				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
430	**430**	**430**	**430**	**430**

AEGL-3

930 ppm value supported by:

- 15 min exposure to 690 ppm resulted in eye irritation and dizziness and/or lightheadedness in human volunteers (Carpenter et al., 1975)

- 30 min exposure to concentrations as high as 700 ppm xylene resulted in headache, nausea, vomiting, dizziness or vertigo, eye irritation, or nose or throat irritation (Klaucke et al., 1982)

Summary of AEGL Values for Xylenes (ppm)					
Level	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1	**130**	**130**	**130**	**130**	**130**
AEGL-2	**430**	**430**	**430**	**430**	**430**
AEGL-3	**930**	**930**	**930**	**930**	**930**

Acute Exposure Guideline Levels (AEGLs)

for

Monochloroacetic Acid

(CAS No. 79-11-8)

$Cl\text{-}CH_2\text{-}COOH$

NAC/AEGL Meeting 20, January 8-10, 2001

FoBiG Staff Scientist:

Peter Griem

Chemical Manager in German Expert Group:

Helmut Greim (Vertreter: Rüdiger Bartsch)

Industry Reviewer for German Expert Group:

Horst Hollander, Reinhard Jung

Chemical Manager:

Ernest Falke

Monochloroacetic Acid

PROPERTIES

- colorless crystalline material with pungent odor
- moderate vapor pressure at room temperature (1hPa)
- very soluble in water and wide range of organic solvents

PRODUCTION

- capacity about 0.4 million tons in 1987

USES

- industrial production of different products (carboxymethylcellulose, herbicides, plastics, pharmaceuticals, cosmetics)

TOXICITY CONCERNS

- mechanism involves inhibition of enzymes of the glycolytic pathway and tricarboxylic acid cycle
- effects on central nervous system and heart
- local irritation due to acidity
- skin resorption
- lack of inhalation studies

DATA RELEVANT TO AEGL-1

HUMAN

- odor thresholds reported:

  0.01 ppm AIHA (1993)
  (unpubl. correspondence, no details)

  0.045 ppm Oelert and Florian (1972)
  (unclear if determined or cited, no details)

- Maksimov and Dubinina (1974): experimental study in humans

  1.48 ppm irritation threshold in humans

  (inadequate data presentation, no details reported)

- Clariant GmbH (2000): occupational surveillance

  0.31 ppm (maximum workplace exposure)

  no irritation or other effects

ANIMALS

- Maksimov and Dubinina (1974): inhalation study in rats

  6.16 ppm irritation threshold

  respiration rate changes; inadequate data presentation

DATA RELEVANT TO AEGL-1

RESULTS OF MCAA MEASUREMENTS AT WORKPLACE adopted from Clariant GmbH, 2000			
Plant	**Workplace situation**	**Individual MCAA concentrations measured between 1991 and 2000**	**No. workers and exposure time per workshift**
SMCA [a] production	area of rollers for production of MCAA flakes	area sampling; MCAA measured 1, <1, <1, 1, 1, 1, 1 mg/m³ (0.26, <0.26, <0.26, 0.26, 0.26, 0.26, 0.26 ppm)	1 person for 1 hour
SMCA production	filling of MCAA flakes	personal sampling; MCAA measured <1, 1.2, 1, <1, 1 mg/m³ (<0.26, 0.31, 0.26, <0.26, 0.26 ppm)	max. 4 persons for 7 hours
SMCA production	SMCA mixer	area sampling; SMCA measured 0.81, 0.89 mg/m³ (0.21, 0.23 ppm)	1 person for 1 hour
SMCA production	filling of bags with SMCA	personal sampling; SMCA measured 0.49, 0.45, <0.40 mg/m³ (0.13, 0.12, <0.10 ppm)	1 person for 6 hours
MCAA production	round and sampling men workarea in five different buildings	personal sampling;MCAA measured <1, <1, <1,<1,<1, <1, <1, <1,<1,<1, 0.8, <0.5, <0.5, <0.5, <0.5, <0.5, <0.5 mg/m³ (<0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, 0.21, <0.13, <0.13, <0.13, <0.13, <0.13, <0.13 ppm)	8 persons for 3 hours

[a] SMCA; sodium monochloroacetate

AEGL-1

Keystudy: Clariant GmbH (2000)

Endpoint: No effects after occupational exposure to concentrations of up to 0.31 ppm

Scaling: it was considered adequate to apply the same exposure concentration to all time periods

because application of an UF of 3 to the 1-min irritation threshold of 1.48 (supportive evidence by Maskimov and Dubinina, 1974) would result in a value close to the derivation basis of 0.31 ppm

Total uncertainty factor: 1

Interspecies: not applicable

Intraspecies: **1**

because the exposure concentration was a no-observed-effect-level and thus was below the severity level which could be tolerated for the AEGL-1 level and because MCAA is a direct acting toxicant, which does not require metabolism into a reactive intermediate

AEGL-1 Values for MCAA				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
0.31 ppm (1.2 mg/m^3)	0.31 ppm (1.2 mg/m^3)	0.31 ppm (1.2 mg/m^3)	0.31 ppm (1.2 mg/m^3)	0.31 ppm (1.2 mg/m^3)

DATA RELEVANT TO AEGL-2

HUMAN

- Morrison and Leake (1941): exp. oral study

  daily oral exposure for 60 days of 3 subjects to 300 mg of a 0.05 % MCAA solution in water did not result in adverse effects (about **2.1 mg/kg · d**)

ANIMAL

- Dow Chemical (1987): inhalation study in rats

  1-h inhalation exposure of rats (12 animals)
  target conc. 1000 ppm
  nominal conc. 964 ppm
  analytical conc. **66 ppm**
  all rats squinted and were slightly (?) lethargic

- Maksimov and Dubinina (1974): inhalation study in rats and guinea pigs

  1.5 and 5.4 ppm (probably continuously) for 4 months

  inflammatory changes in respiratory organs, bronchitis, bronchopneumonia in the high dose group, not significant in the low dose group

AEGL-2

Keystudy: -

Endpoint: Derived as fraction of AEGL-3 due to the lack of adequate inhalation studies

Divisor: 2

because of the very steep dose-response relationship of MCAA after oral exposure:

rat: LD_{50} 80.9 mg/kg (mean value)
NOAEL 30 mg/kg · d, subchronic (Bryant et al., 1992)
LOAEL 30 mg/kg · d, subchronic (Daniel et al., 1991)

mouse: LD_{50} 227 mg/kg (mean value)
NOAEL 100 mg/kg · d, subchronic (Bryant et al., 1992)

AEGL-2 Values for MCAA				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
8.0 ppm (31 mg/m³)	8.0 ppm (31 mg/m³)	6.0 ppm (24 mg/m³)	3.9 ppm (15 mg/m³)	3.1 ppm (12 mg/m³)

Supporting data:

- 1-hour inhalation of rats 66 ppm (Dow Chemical Co., 1987) led to slight lethargy, but not to severe effects. Using a total UF of 3 (as for AEGL-3) would result in 22 ppm for 1 hour

- as to systemic toxicity, the AEGL-2 exposure level corresponds to a dose of about 1.6 mg/kg, which is lower than the oral dose of 2.1 mg/kg · d (60 exp.) that caused no adverse effects in humans (Morrison and Leake, 1941)

DATA RELEVANT TO AEGL-3

HUMAN

- no relevant inhalation data available

- dermal penetration is rapid and fatal intoxications have been observed when 10 % or more of the body surface was involved (Christofano et al., 1970; Kulling et al., 1992; Ruty et al., 1987)

- Feldhaus et al. (1993); Rogers (1995): case report
  death of a 5-year old girl after ingestion of 4.0 - 4.8 g MCA, about **200 - 240 mg/kg** (assuming 20 kg b.w.)

- Morrison and Leake (1941): exp. oral study
  dialy oral exposure for 60 days of 3 subjects to 300 mg of a 0.05 % MCAA solution in water did not result in adverse effects (**about 2.1 mg/kg · d**)

ANIMAL

- Maksimov and Dubinina (1974): inhalation study in rats

  180 mg/m³ (**46.8 ppm**) (4 h) LC_{50}

  no details were reported; exposure corresponds to a dose of 29.8 mg/kg

- Hoechst (1979a): oral gavage study in rats (10/group)

Dose (mg/kg)	Mortality
0	0/10
40	0/10
63	2/10
100	5/10
160	10/10

LD_{50}: 90.4 mg/kg
MLE_{01}: 42.5 mg/kg
BMD_{05}: 28.8 mg/kg

Symptoms: restlessness, crouching, balance disturbance, passiveness, drowsiness, incomplete eyelid closure, discharge from the eyes and dyspnea

SUMMARY OF ACUTE ORAL LETHAL DOSES IN LABORATORY ANIMALS

Species	Dose (mg/kg)	Remark	Exposure	Signs and Symptoms	Reference
cattle	100 / 150	1 animal/dose	(gastric tube)	GI symptoms, survived / dead	Dalgaard-Mikkelsen and Rasmussen, 1961
rabbit	≈ 90	LD_{50}	neutr. sol.	apathy	Woodard et al., 1941
guinea pig	79.8	LD_{50}	neutr. sol.	apathy	Woodard et al., 1941
rat	102	LD_{50}	non-neutr. sol.	CNS effects, death (1-4 h)	Berardi, 1986
rat	90.4	LD_{50}	1 % solution	crouching, imbalance, dyspnea	Hoechst AG, 1979a
rat	76.2	LD_{50}	neutr. sol.	apathy	Woodard et al., 1941
rat	55 / 580	LD_{50}	non-neutr. / neutr. sol	not reported	Maksimov and Dubinina, 1974
mouse	260	LD_{50}	non-neutr. sol.	ataxia, tremors, dyspnea	Berardi and Snyder,1983
mouse	255	LD_{50}	neutr. sol.	apathy	Woodard et al., 1941
mouse	165	LD_{50}	no details reported	respiratory paralysis	Morrison and Leake, 1941
goose	50 / 75	same 2 animals	no details reported	no symptoms / incoordination, seizures, death	Christiansen and Dalgaard-Mikkelsen, 1961

AEGL-3

Keystudy: Maksimov and Dubinina (1974)

Endpoint: 180 mg/m³ (**46.8 ppm**) (4 h) LC_{50} in rats

Rationale: Local effects of MCAA may contribute to lethality:

- pKa 2.85, strong acid
- possible local depletion of sulfhydryl groups in respiratory tract
- possible local enzyme inhibition and tissue damage in respiratory tract
- inhalation exposure of rats to MCAA causes irritation of eyes and nose and local effects in lungs
- MCAA solution is corrosive to skin and eyes
- the LC_{50} corresponds to a body dose about 3fold lower than oral LD_{50}

LC_{01} extrapolation: Divisor of 2

because of the very steep dose-response relationship and support by Dow Chemical Co. (1987) study (1h, 66 ppm)

Time Scaling: $C^n \times t = k$ with default n = 3 for shorter periods and n = 3 for extrapolation to 8 hours because n = 1 was considered too conservative.
The 30-min value was applied to 10 min because no data are available for short-term exposure.

Total uncertainty factor: 3

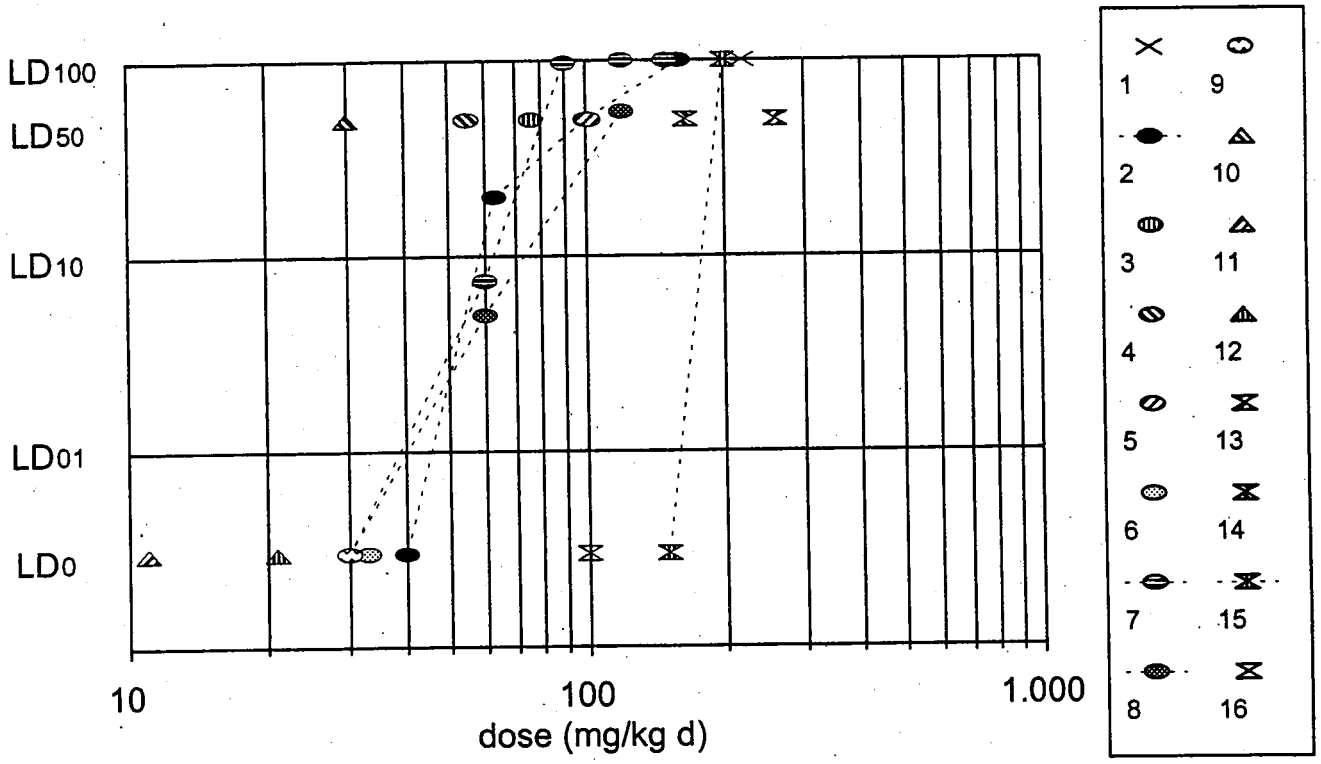
because 1) a total UF of 3x3 would correspond to a dose of 1.0 mg/kg for the 8-hour AEGL-3, which is lower than oral dose of 2.1 mg/kg · d that caused no effects in humans; 2) oral lethal doses are very similar for different species and 3) within each species LD_{50} values differed by less than a factor of 2

Interspecies: 1

Intraspecies: 3

AEGL-3 Values for MCAA				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
16 ppm (63 mg/m³)	16 ppm (63 mg/m³)	12 ppm (47 mg/m³)	7.8 ppm (31 mg/m³)	6.2 ppm (24 mg/m³)

Dose-Response Relationship for Lethality

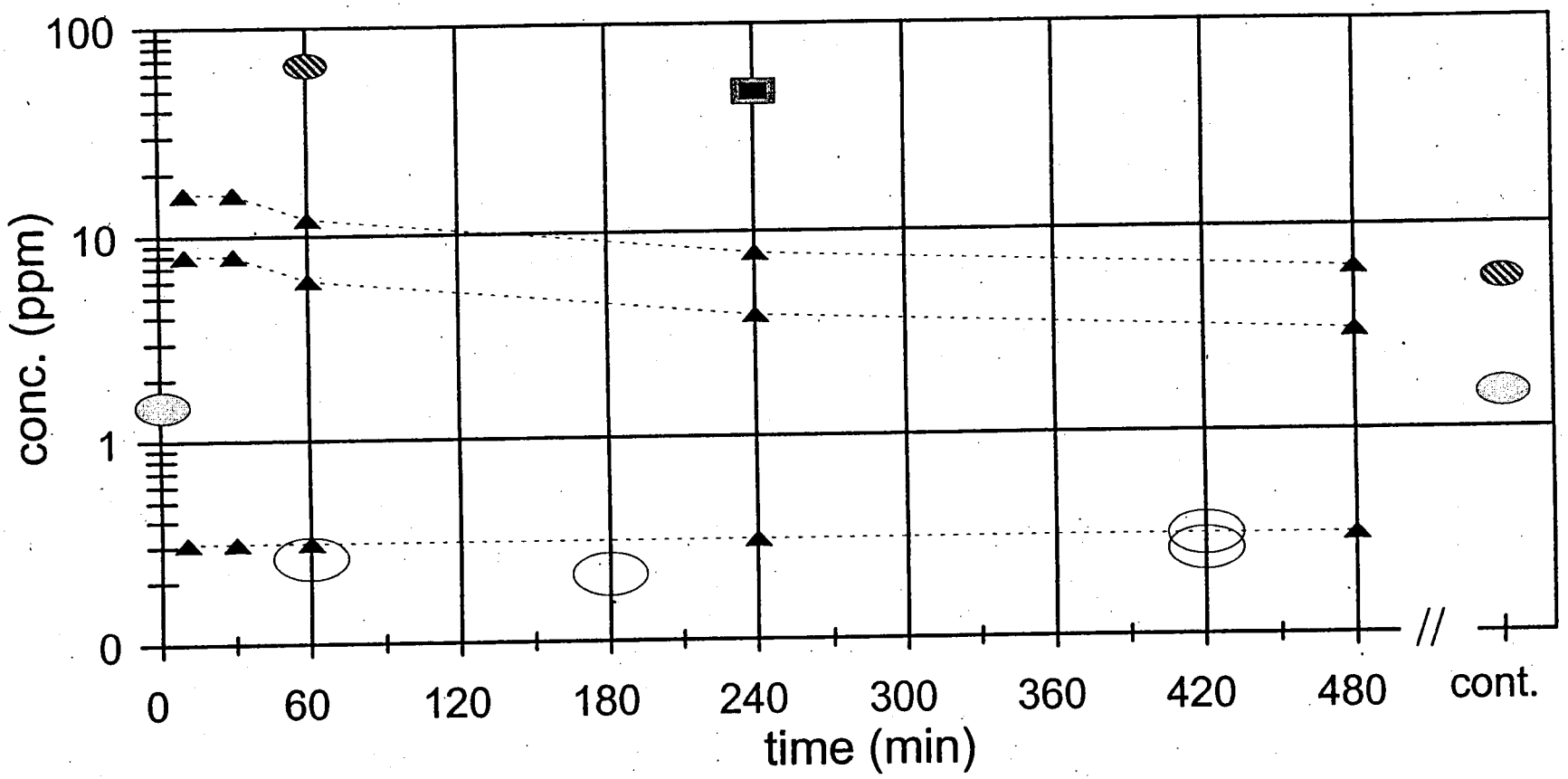


All exposures (including single and repeated inhalation exposures and single oral exposures) were converted to daily doses. LD_0 designates a NOEL for lethality.

1 human case, single oral exposure; Feldhaus et al. (1993); Rogers (1995)
2 rat, single oral exposure; Hoechst AG (1979a)
3 rat, oral LD_{50}; Woodard et al. (1941)
4 rat, oral LD_{50}; Maksimov and Dubinina (1974)
5 rat, oral LD_{50}; Berardi (1986)
6 rat, subacute oral exposure; Johnson et al. (1998)
7 rat, subchronic oral exposure; Bryant et al. (1992); NTP (1992)
8 rat, subchronic oral exposure; Daniel et al. (1991)
9 rat, chronic oral exposure; NTP (1992)
10 rat, inhalation LC_{50}; Maksimov and Dubinina (1974)
11 rat, acute inhalation exposure; Dow Chemical Co. (1987)
12 rat, subchronic inhalation exposure; Maksimov and Dubinina (1974)
13 mouse, oral LD_{50}; Berardi (1986)
14 mouse, oral LD_{50}; Morrison and Leake (1941)
15 mouse, subchronic oral exposure; Bryant et al. (1992); NTP (1992)
16 mouse, chronic oral exosure; NTP (1992)

AEGL Values for Monochloroacetic acid					
	10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1	0.31 ppm (1.2 mg/m^3)	0.31 ppm (1.2 mg/m^3)	0.31 ppm (1.2 mg/m^3)	0.31 ppm (1.2 mg/m^3)	0.31 ppm (1.2 mg/m^3)
AEGL-2	8.0 ppm (31 mg/m^3)	8.0 ppm (31 mg/m^3)	6.0 ppm (24 mg/m^3)	3.9 ppm (15 mg/m^3)	3.1 ppm (12 mg/m^3)
AEGL-3	16 ppm (63 mg/m^3)	16 ppm (63 mg/m^3)	12 ppm (47 mg/m^3)	7.8 ppm (31 mg/m^3)	6.2 ppm (24 mg/m^3)

Chemical Toxicity - TSD All Data
Monochloroacetic acid



no or minimal effect

did not die @ lethal conc

discomfort

lethal

disabling

AEGL

PROPYLENE OXIDE

- Add 10-minute values:
  - AEGL-1: 10 min value set equal to 30-min value because exposure duration ≥ 4 hr
  - AEGL-2 and AEGL-3: extrapolate to 10 min

AEGL Values for Propylene Oxide (ppm) (using n=1.2)						
Level	**10-m**	**30-m**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	110	110	60	19	11	8-hour TWA of 31.8 ppm resulted in no worker complaints
AEGL-2	1300	510	290	91	51	Humans: Strong odor and irritation noted in monitoring study; average of AEGL-2 values using four exposure conc. and durations: 380 ppm for 177 min, 525 ppm for 121 min, 392 ppm for 135 min, 460 ppm for 116 min
AEGL-3	2700	1100	610	190	110	Humans: Highest recorded nonlethal concentration of 1520 ppm for 171 minutes

Propylene Oxide: Derivation of *n*

- Currently use derived value of $n = 1.2$ for ethylene oxide because of similar mechanisms (direct alkylating agent)
  - Ethylene oxide generally 2-3x more toxic than propylene oxide

- Toxicity of propylene oxide may be more like epichlorohydrin ($n = 0.87$):
  - Both affect upper respiratory tract resulting in toxic lesions after single exposure and nasal tumors after repeated exposures.
  - Unlike ethylene oxide, neither epichlorohydrin nor propylene oxide has been found to be a developmental toxicant.
  - Both compounds produce similar clinical signs.
  - However, epichlorohydrin 2-10x more toxic than propylene oxide

AEGL Values (ppm)					
Level	**Exposure Duration**				
	10-min	**30-min**	**1-hour**	**4-hour**	**8-hour**
Based on Ethylene Oxide n=1.2 (currently proposed)					
AEGL-1	110	110	60	19	11
AEGL-2	1400	510	290	91	51
AEGL-3	2700	1100	610	190	110
Based on Epichlorohydrin n=0.87					
AEGL-1	260	260	120	24	11
AEGL-2	2900	830	370	76	34
AEGL-3	6600	1900	840	170	77
Based on Average n=1.0					
AEGL-1	170	170	85	21	11
AEGL-2	2000	660	330	82	41
AEGL-3	4300	1400	720	180	90
Based on Default n=3.0; 1.0					
AEGL-1	27	27	21	13	11
AEGL-2	350	240	190	82	41
AEGL-3	650	450	360	180	90

ISSUE FOR CONSIDERATION FOR PROPYLENE OXIDE AEGLs

Insufficient data currently exist from which to derive an n value for use in the scaling of propylene oxide AEGL values across time. In the current document, because of the lack of data for empirical derivation of *n* for propylene oxide, and based on a similar mechanism of action of propylene oxide as compared to ethylene oxide, the derived value of *n* for ethylene oxide was used in the scaling of propylene oxide AEGL values across time. The value of $n = 1.2$ for ethylene oxide was derived empirically from 1- and 4-hour LC_{50} values for rats. An approximate value of n is supported by data on propylene oxide exposure in guinea pigs (Tables 11 and 14 in TSD - not sufficient for calculation of n).

That being said, it has also been noted in the document that while ethylene oxide is a structurally-related chemical that also is a direct alkylating agent and undergoes similar biotransformation, propylene oxide is not as toxic ethylene oxide. Based on a comparison of the 4-hour LC_{50} values for the two chemicals, propylene oxide is 2-3 times less toxic than ethylene oxide. Ethylene oxide is mutagenic to germ cells as well as somatic cells in species such as rodents, monkeys, and rabbits, and has been found to be 5-10 times more effective than propylene oxide when considering gene conversion, reverse mutations, and sister chromatid conversion in yeast. The two chemicals have about the same potency for inducing *in vitro* point mutations in bacteria and sister chromatid exchanges in human lymphocytes. *In vivo*, ethylene oxide is more effective than propylene oxide at inducing chromosomal aberrations in humans and sister chromatid exchanges and chromosomal aberrations in monkeys. The number of hemoglobin adducts formed following exposure to propylene oxide has been estimated to be 4 times lower than the number formed by ethylene oxide exposure. Following intraperitoneal injection of each chemical, propylene oxide binding in mouse liver DNA was one-twentieth that of ethylene oxide [taken from Section 4.3 of TSD, see section for references if desired].

Kowetha is currently revising the epichlorohydrin AEGL TSD, and was investigating SARs. In her document, she points out that epichlorohydrin is a chloromethyl substituted oxirane (ethylene oxide) or chlorinated methyloxirane (propylene oxide). All three compounds are direct alkylating agents; however, the toxicity of epichlorohydrin is more like that of propylene oxide than ethylene oxide. Both epichlorohydrin and propylene oxide affect the upper respiratory tract resulting in toxic lesions after single exposure and nasal tumors after repeated exposures. Unlike ethylene oxide, neither epichlorohydrin nor propylene oxide has been found to be a developmental toxicant. Both compounds produce similar clinical signs. The LC_{50} values for 4-hour inhalation exposure to epichlorohydrin and propylene oxide, respectively, are as follows: 441–635 ppm and 3205–4197 ppm for rat and 820–1153 and 1160-1740 ppm for the mouse. These data suggest that the rat is 5–10 times more sensitive to epichlorohydrin than propylene oxide; the difference in sensitivity to the mouse, however, is less than a factor of ≤ 2. Although the clinical signs were similar the test concentrations eliciting clinical signs were much lower for epichlorohydrin than for propylene oxide. Therefore these data show that epichlorohydrin are qualitatively similar but quantitatively different. It may be more appropriate to use the n-value for epichlorohydrin rather than for ethylene oxide.

For epichlorohydrinm, the LC_{50} data for inhalation exposure to the rat was used to determine the relationship between concentration of epichlorohydrin and the exposure duration. LC_{50} values for the rat, and are as follows: 2798 (geometric mean of 3617 ppm for males and 2165 ppm for females) for a 1-hour exposure, 635 ppm for a 4-hour exposure, 360 ppm for a 6-hour exposure, and 250 ppm for a 8-hour exposure. A linear log-log relationship was observed over the 1- to 8-hour exposure duration. The calculated value of *n* was 0.87.

Briefing of the H_2S Conference Call

A conference call was held on December 13 to discuss the following items concerning H_2S. Participants on the call were: George Alexeeff, Steven Barbee, Cheryl Bast, David Belluck, Ernest Falke, Larry Gephart, Thomas Hornshaw, Nancy Kim, Po-Yung Lu, Mark McClanahan, John Morawetz, Zarena Post, Thomas Sobotka and Judy Strickland.

Items for discussion on the agenda were:

- Selection of health effects endpoints for the AEGL-1 for H_2S.
- Discussion of the WHO documentation for H_2S-induced eye irritation.
- Discussion of the comments from the COT on scientific support for the H_2S AEGL-1.
- Discussion of the appropriate study(ies) to support the AEGL-1 for H_2S.

Outcome of the discussion of the agenda items

Selection of health effects endpoints for the AEGL-1 for H_2S.

Included in the definition of AEGL-1 health effects listed are notable discomfort, irritation, or certain asymptomatic, non-sensory effects. The discussion focused on whether odor alone, without other health-related effects, should be the primary health criterion upon which to based an AEGL-1 for H_2S. The consensus of the participants was that the presence of odor without other effects, e.g. headache or nausea, should not serve as the basis for establishment of an AEGL-1. Therefore, and based on this consensus, health effects, e.g. headache, irritation or nausea, and not odor alone should be present as qualification for establishment for AEGLs-1 for H_2S.

Discussion of the WHO documentation for H_2S-induced eye irritation

Several references (WHO, 1989; Nordic Working Group, 1982; WHO, 1981) have reported that the threshold for eye irritation is 10-20 ppm. Included in these references is the statement that a concentration of H_2S of 100 ppb would result in no eye irritation. The AEGL Committee has been unable to substantiate this recommendation because these references included no other information of how the values were established. Therefore, we could not determine the significance in the context of use in deriving an AEGL-1. Through library research by ORNL the source of the information has been discovered. It originated from an observation in an occupational setting (rayon factory). The article (Elkins, H. B. 1939. Toxic Fumes in Massachusetts Industries. Industrial Medicine. Vol. 8: 426-432) stated as follows: "We have found that in rayon spinning rooms conjunctivitis or eye irritation is common unless the H_2S is kept below 20 ppm and will not be eliminated if 10 ppm is exceeded." The WHO apparently applied an uncertainty factor of 100 to arrive at the recommended concentration of 100 ppb. The participants concluded that the Elkins statement and hence the WHO recommendation lacked the requisite scientific criteria to support an AEGL for H_2S. The consensus of the participants was that the WHO and Nordic Working Group information is not relevant for and should not be used to support the AEGL-1 value for H_2S.

Comments from COT on scientific support for H_2S AEGL-1 and appropriate study(ies) to support the H_2S AEGL-1

The participants discussed the following studies for support of the AEGL-1:

- Bhambhani et al. 1994. Comparative physiological responses of exercising men and women to 5 ppm hydrogen sulfide exposure. AIHAJ. 55: 1030-1035.
- Bhambhani and Singh. 1991. Physiological effects of hydrogen sulfide inhalation during exercise in healthy men. J. Appl. Physiol. 71: 1872-1877.
- Bhambhani et al. 1996. Effects of 10-ppm hydrogen sulfide inhalation on pulmonary function in healthy men and women. JOEM. 38: 1012-1017.
- Jappinen et al. 1990. Exposure to hydrogen sulfide and respiratory function. Br. J. Ind. Med. 47: 824-828.
- Texas Natural Resources Conservation Commission (TNRCC). 1998. Report entitled, "Real-time gas chromatography and composite sampling, sulfur dioxide, hydrogen sulfide, and impinger sampling."

The participants could not achieve consensus on the study(ies) to use to support the H_2S AEGL-1. A factor in the inability to reach agreement were the questions raised by the COT /Conference Call Participants on the TNRCC report. Since not all participants had the opportunity to review the questions on this report prior to the conference call, there was insufficient time for proper consideration. Consequently, we decided to afford Zarena Post the occasion to respond to them before the entire committee. The time for the response is yet to be determined. It appears that the March or June meeting of the NAC/AEGL Committee is the most likely date. At the same time there will also be a review of the other above listed studies. This plan will offer the full Committee the benefit of a current review of all proposed studies prior to the selection of the appropriate study(ies).

In advance of the response by Zarena the questions concerning the TNRCC report that were raised on the conference call are listed below.

- Why were the health effects experienced by the individuals on the mobile laboratory monitoring trip only described in the summary of the report and not presented in tabular form as were the analytical and meteorological data?
- There were 10 individuals on the monitoring trip. Six of 10 reported health effects, but effects were reported for only 4 individuals. What were the effects of the other 2 individuals?
- Van #753 was the only vehicle containing individuals who reported health effects. Van #940, however, was at sites in which health effects from H_2S may have been anticipated to individuals exposed at these sites. For example, the following concentrations were noted in the TNRCC report:
    - Van #940, 2/1/98, 12:20, site 26, [H_2S] – 5 minute average – 57 ppb, peak value during the 5 minute average – 276 ppb.

- Van #940, 2/1/98, 19:40-19:45, site 26, [H_2S] – 5 minute averages – 67 and 95 ppb, peak values during each 5 minute average – 90 and 101 ppb.
- Van #940, 2/3/98, 19:20-19:45, site 26, [H_2S] – range of values for the 5 minute averages – 38-165 ppb, range of peak values during the 5 minute averages – 103-267
- Van #940, 2/4/98, 16:55-21:50, site 26, [H_2S] – range of values for the 5 minute averages – 56-149 ppb, range of peak values during the 5 minute averages – 67-207.

Did the individuals in van #940 at the above time periods experience any health effects and if so, what were they and why weren't these effects noted? If they didn't experience any health effects, why not since the H_2S concentrations appear to be in the range where individuals in van #753 experienced health effects?

- In the instance of the 4 individuals in which health effects were reported, these individuals were on 2 separate sampling sites on 2/4/98 (26 from 10:05-12:10; 21 from 12:25-17:00). For example, individual (case 2) 2 reported effects only after returning from lunch, yet presumably this individual was present for the morning sampling at site 26. The H_2S concentration at site 26 in the morning and site 21 in the afternoon were comparable (site 26, 5 minute averages between 17-93 ppb, peak values between 24-161; site 21, 5 minute averages 14-98 ppb, peak values between 29-161). Given that the concentrations are comparable, why didn't individual 2 experience effects in the morning?
- Of the 4 individuals who reported health effects, 2 reported no odor and 2 did report odor. Since the H_2S concentration was well above the odor threshold, why didn't the 2 individuals who experienced health effects without odor either fail to report the odor or in fact smell it?
- One individual (case 4) had a pre-existing scratchy throat; therefore, how was the distinction made between this pre-existing condition and effects from H_2S? Individual 4 was one of those who experienced no odor of H_2S.
- Where were the samples collected vis-à-vis the individuals? Can it be documented that the reported concentrations represent the concentration of H_2S in the breathing zone of each individual who reported health effects?

- **ODOR AS SOLE DRIVER FOR AEGL-1**

- **WHO DOCUMENTATION FOR H_2S-INDUCED EYE IRRITATION**

- **SUPPORT STUDIES FOR AEGL-1**

Attachment 11

ACUTE EXPOSURE GUIDELINE LEVELS FOR HYDROGEN SULFIDE

The National Advisory Committee (NAC) for Acute Exposure Guideline Levels (AEGL) has recently proposed AEGLs for hydrogen sulfide (H2S) to the National Academy of Sciences' Committee on Toxicology, Subcommittee on Acute Exposure Guideline Levels. AEGLs are threshold exposure limits for the general public and are applicable to emergency exposure periods from 10 minutes to 8 hours. AEGLs were recommended for three levels of effect, AEGL-1 (nondisabling), AEGL-2 (disabling), and AEGL-3 (lethal), for five time periods, 10 and 30 minutes and 1, 4, and 8 hours. The Subcommittee has returned this proposal with comments regarding the basis for the Level 1 AEGLs. (AEGL-1 is defined as the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.) Since AEGLs for H2S may be important for state and local air programs, this message is a request for data pertaining to Level 1 AEGLs for H2S.

Among the studies of effects on humans are several papers published in peer-reviewed journals and a report by the Texas Natural Resource Conservation Commission (TNRCC) describing effects experienced by field personnel during an air monitoring assignment near several petrochemical facilities. However, after considerable review and discussion by the NAC, none of the studies have emerged as being clearly the most appropriate as the basis for the Level 1 AEGLs.

It is possible that state or local air pollution agencies may have conducted studies similar to the TNRCC study that would not have been discovered during the normal literature searches conducted for the NAC. Therefore, this message is a request for any reports or studies documenting health effects meeting the definition of AEGL-1 and associated concentrations of H2S. Please send appropriate reports or studies by March 1, 2001 (to allow evaluation and discussion at the March NAC meeting) to:

Thomas C. Hornshaw
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Illinois Environmental Protection Agency
P.O. Box 19276
Springfield, IL 62794-9276
(T) 217-785-5735 (F) 217-782-1431 (E) epa8566@epa.state.il.us

HCN: Conversion of AEGLs to Oral Doses

According to review sources, oral exposure to a single dose of 10 mg is noninjurious to the human adult (70 kg). For the average newborn child (7 lb or 3.2 kg), the respective value would by 0.5 mg.

The inhalation rate for adults undergoing light activity is 1.0 m^3/hour and the inhalation rate for infants of <1 year is 4.5 m^3/day or 0.188 m^3/hour (U.S. EPA Exposure Factors Handbook, 2000).

In the following table the inhaled HCN for each AEGL exposure time has been converted to an oral dose. For example, for adults the 10 minute AEGL-1 value would be calculated as follows:

$$1.0\ m^3/hour \times 0.167\ hour \times 2.8\ mg/m^3 = 0.5\ mg$$

Total Dose of Hydrogen Cyanide Inhaled - Adults (inhalation rate: 1.0 m^3/hour)					
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	0.5 mg	1.4 mg	2.2 mg	5.6 mg	8.8 mg
AEGL-2	3.2 mg	5.5 mg	7.8 mg	16 mg	22 mg
AEGL-3	5.0 mg	12 mg	17 mg	39 mg	58 mg

The single oral no-effect dose of 10 mg should be compared to the 10-minute AEGL-1 value. For longer exposures, the detoxification rate should be taken into consideration. The rate of spontaneous detoxification in humans is approximately 1 μg/kg/minute (Schulz et al., 1982). (detoxification: 0.7 mg in 10 minutes, 2.1 mg in 30 minutes, ...etc.)
The average fatal dose is 1.52 mg/kg (100 mg for a 70 kg adult) (ATSDR, 1997).

HCN (con'd)

For infants, the oral dose corresponding to the 10-minute AEGL-1 would be calculated as follows:

$$0.19\ m^3/hour\ x\ 0.167\ hour\ x\ 2.8\ mg/m^3\ =\ 0.088\ mg$$

Total Dose of Hydrogen Cyanide Inhaled - Infant (inhalation rate: 0.19 m^3/hour)					
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	0.1 mg	0.3 mg	0.4 mg	1.1 mg	1.7 mg
AEGL-2	0.6 mg	1.0 mg	1.5 mg	2.9 mg	4.2 mg
AEGL-3	0.9 mg	2.2 mg	3.2 mg	7.3 mg	11 mg

These calculations indicate that the AEGL-1 concentrations are safe for both adults and infants.

Summary Table of AEGL Values for Hydrogen Cyanide [ppm (mg/m^3)]						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Reference**
AEGL-1	2.5 (2.8)	2.5 (2.8)	2.0 (2.2)	1.3 (1.4)	1.0 (1.1)	Leeser et al., 1990 El Ghawabi et al., 1975 Grabois, 1954
AEGL-2	17 (19)	10 (11)	7.1 (7.8)	3.5 (3.9)	2.5 (2.8)	Purser, 1984
AEGL-3	27 (30)	21 (23)	15 (17)	8.6 (9.7)	6.6 (7.3)	E.I. du Pont de Nemours, 1981

Sylvia Talmage
Oak Ridge National Laboratory
January 2001 NAC meeting

Hydrogen Cyanide
AEGL-1 Chronology

- Originally not recommended
- July, 2000 – Set based on Leeser summary (area sample data)
- October, 2000 – Committee agreed to look at Leeser personal sampling data
- November, 2000 – NAS Discussion deferred
- January, 2001 – Need to accurately summarize Leeser, Grabois and El Ghawabi presented to AEGL meeting

Attachment 13

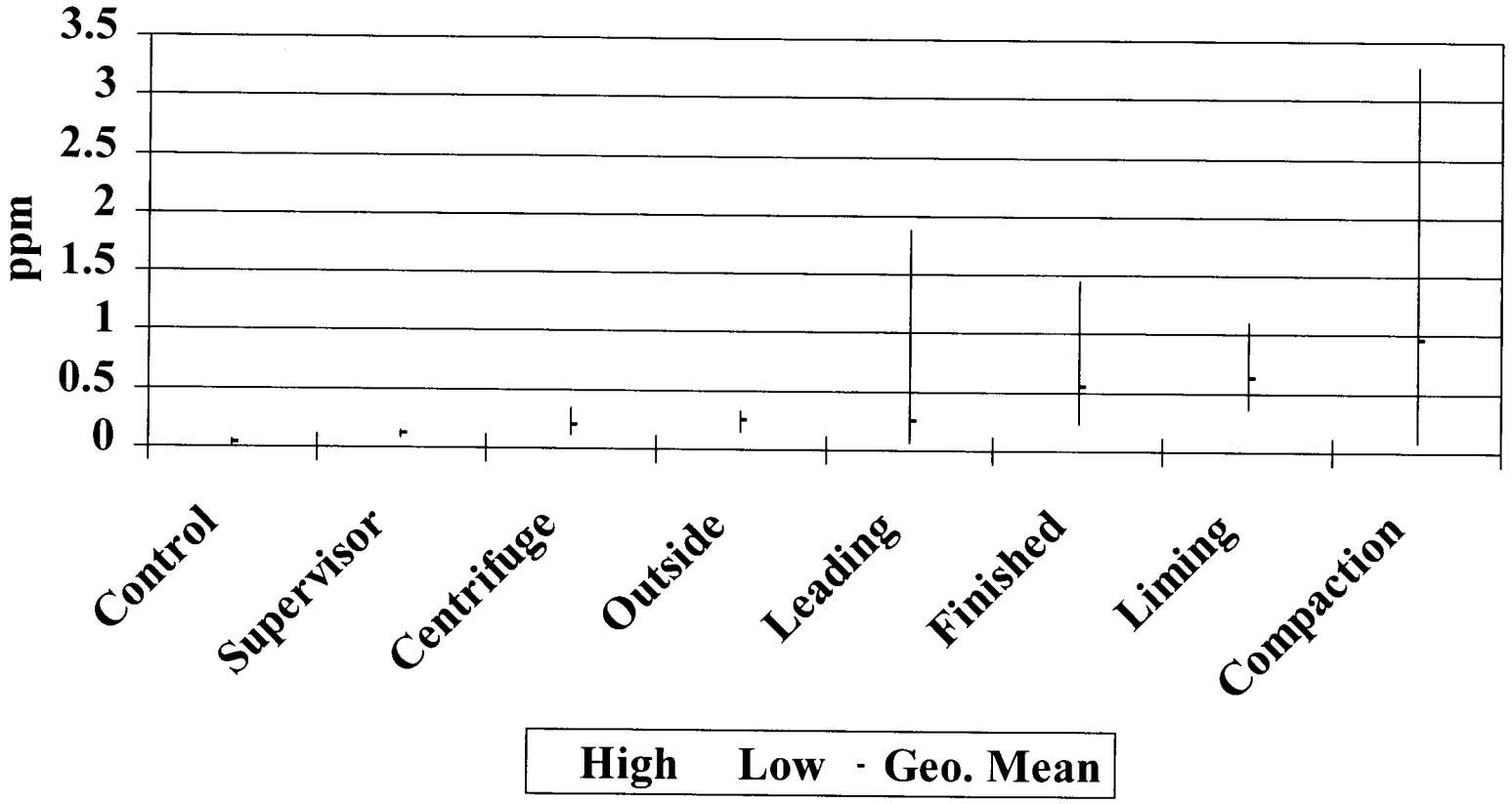
Primary Human Studies – AEGL-1

- **Leeser, 1990**
  - Personal sampling of 8 job titles
  - Medical interviews collected at two times
  - 63 workers in April/May
  - 50 workers in August/September
- **Grabois, 1954**
  - Air sampling: No medical evaluation
- **El Ghawabi, 1975**
  - 15 minute air samples: Health findings above AEGL-1

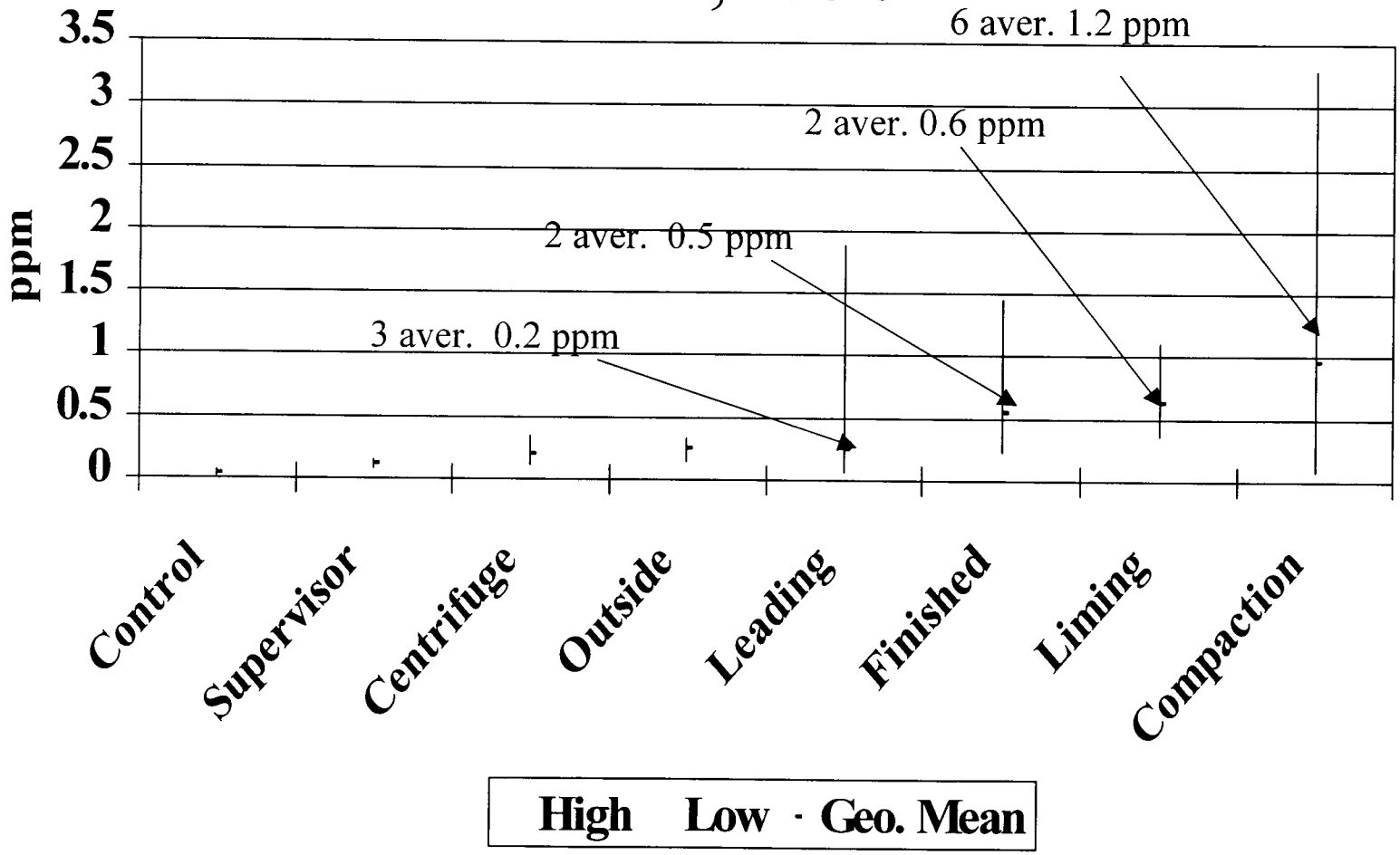
Leeser, 1990 Personal samples (ppm)

Job Title	**G mean**	**Low**	**High**	**N**
Supervisor	**.11**	.09	.15	2
Leading Hand	**.25**	.07	1.89	5
Control Rm Op	**.027**	.009	.064	4
Outside Oper.	**.24**	.15	.33	3
Treatment Op. Liming	**.19**	.11	.34	4
Treatment Op. Centrifuge	**.63**	.36	1.1	4
Compaction Oper.	**.96**	.08	3.3	8
Finished Product	**.54**	.23	1.5	4

Hydrogen Cyanide
Exposures by Job Title
Leeser, 1990



Geometric Average of Remaining Exposures without High and Low Values
Leeser, 1990



Exposure Assessment

- Types of samples
- Time to collect sample
- Variability of exposure in an occupational environment

Types of Samples

- Bulk
  - Processing equipment, storage containers
- Area
- Personal: Breathing Zone

Time to collect sample

- Instantaneous/Grab samples
- Short term: Commonly 15 minutes
- Time Weighted Average
  - Usually 8 hour sample
  - Can range from 15 minutes to 8 hours

Time extrapolation n factor

Current SOP:

1. Use chemical specific data to derive n value
2. In absence of data, use default:
   - n=3 for extrapolation to short time periods.
   - n=1 for extrapolation to longer time periods.
   - flatline 10 min value from 30 min value if no data < 4 hrs available.

Choice of n value has large impact on AEGL numbers.

Odor as an AEGL-1 endpoint

The generic issue:

1. Is odor a valid endpoint for the AEGL-1?
2. If yes, how should we consistently use odor data for consideration in AEGL development?

Time table:

1. Production of position paper (end of january).
2. Review in AEGL subcommittee febr./march
3. Discussion and resolution at may NAC/AEGL.

Opportunities:

1. Join subcommittee.
2. Provide relevant data.

Develop guidance to refine default approach:

1. Identify chemical characteristics as determinant of the n value:
   - Physical/chemical, toxicokinetic or toxicodynamic characteristics.
   - Breakdown by chemical class, critical endpoint or other.
2. Time range for valid extrapolation.

Current needs:

1. Concentration-time-effect data for as many chemicals as possible.
2. Suggestions for chemical characteristics that may determine the n value.
3. Suggestions for search & analysis strategies.

Use of Human studies

- Drafting of TSD
  - Accurately summarize original papers
  - Evaluate each paper's findings

- AEGL committee
  - Determine the usefulness of each paper
  - Recommend final exposure values and rational

Harger, 1958

- 16 year old dies in acetylene plant
- Employed for 6 weeks
- Found at 11 AM on upper floor of the generator building

Bulk Phosphine Measurement

- TSD
- "he was found with his face near an open hopper where the measured phosphine concentration was 75-95 ppm"

- Harger
- "Analyses of gas in generator cylinder and hopper"
- "phosphine concentrations of the hopper gas ranged from 75 to 95 ppm"

Arsine bulk measurement and exposure

- TSD
- "Samples of air over the generators contained concentrations of phosphine between 1 and 14 ppm and less than 3 ppm arsine"

- Harger
- "the raw acetylene contained less than 3 ppm of arsine gas, and since this is diluted at least 10 fold in the air above the hopper…"

Personal Exposure

- TSD
- "Samples of air over the generators contained concentrations of phosphine between 1 and 14 ppm and less than 3 ppm arsine"

  - Harger
  - "we found an average of 8 ppm near the operator's breathing level during the hopper filling period"
  - Two methods of collecting personal samples

Personal Exposure

- Two methods of collecting personal samples

  Both measured two feet above the hopper opening during filling operation

- Scrubbers
  - 6.9 ppm for 3 minute filling operation
  - 9.4 ppm for 2 minute filling operation

- Proportional to bulk sample (Acetylene/phosphine)
  - 3 filling operations; 3 to 8 minutes each
  - 1 to 14 ppm

American Petroleum Institute

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George M. Woodall, Ph.D.
Senior Toxicologist

Attachment 16

Comments of the American Petroleum Institute to The NAC-AEGL Committee on Hydrogen Sulfide January 10, 2001

The American Petroleum Institute (API) is pleased to have the opportunity to provide comment on the Acute Exposure Guideline Levels (AEGLs) for hydrogen sulfide for consideration by the U.S. Environmental Protection Agency (EPA) and the National Advisory Committee (NAC), in response to the Federal Register Notice announcing this meeting of the NAC. API is a national trade association representing more than 400 companies engaged in all aspects of the oil and gas industry. API has long been involved in basic research on the health effects from exposure to hydrogen sulfide and has an active, ongoing research effort attempting to elucidate some of the remaining gaps in understanding of the health effects of this compound. These research efforts include the development of a physiologically-based pharmacokinetic (PB-PK) model for hydrogen sulfide, use of stable isotopes to better track the compound in tissues, and a human chamber study to be conducted in a clinical setting to help determine subtle neurological effects at low exposure levels. API is therefore well aware of the limitations and difficulties inherent in trying to assess the potential risk from exposure to this ubiquitous compound. API has submitted comments on earlier drafts of the hydrogen sulfide AEGLs to which we refer in this document.

API is concerned that the approach being taken in the development of the AEGL values is overly conservative, resulting in unintended impacts upon local communities as they allocate emergency response resources for non-emergency situations. API would like to make three points that we see as important in making a more realistic assessment of risk and more efficiently protecting public health from real hazards.

Human Clinical studies are preferable to other reported exposures in setting the AEGL-1. The most reliable, objective measures of adverse effects due to exposure are through clinical analysis of exposed subjects. These types of studies provide an accurately measured exposure to a single compound with human subjects on which previous health status is known, and where objective clinical analysis is performed following exposure. Additionally, clinical studies using detailed protocols and controlled exposure conditions may be repeated by other researchers, thereby allowing the confirmation of the findings of one researcher by another.

The strengths of clinical studies would be difficult to duplicate in the observations obtained from accidental exposures or field observations. More often in these types of observations, exposure is to more than one compound, as was the case in the TNRCC report, which that noted several other compounds were also present, many of which could also contribute to the symptoms reported. The TNRCC report also relies on self-reported symptoms with no objective analysis of previous health status immediately prior to exposure nor with any accurate diagnosis following exposure. Finally, it is highly unlikely that the exposure conditions in one episode can be duplicated reliably in another, making comparisons between events difficult.

Suggestions for appropriate studies to use in setting the AEGL-1. In API's previous comments (dated April 14, 2000), the study of Jappinen, et al (1990) was suggested in setting the AEGL-1 value; this study was also recommended in the 1998 draft AEGL for hydrogen sulfide from the NAC. In this study, 10 asthmatics were exposed to 2 ppm hydrogen sulfide for 30 minutes. This was a well-controlled study conducted on sensitive individuals, with a rigorous clinical analysis of post-exposure effects. Only 2 individuals had minor effects at this level of exposure (a 30% increase in airway resistance and similar decrease in conductance) that were not significant and within the normal range of individual variation. Using this study as the basis for the AEGL-1 would require no adjustment factor because the study population is a sensitive subgroup. This would result in AEGL-1 values calculated using the 4.36 time scaling factor to be: 2.6 ppm for 10 minutes, 2.0 ppm for 30 minutes, 1.7 ppm for 1-hour, 1.2 ppm for 4-hours, and 1.1 ppm for 8-hours.

A second study that would be appropriate is Bhambhani, et al (1996a), which was mentioned in the 1998 Draft AEGL document produced by the NAC. Using the no observed adverse effects level (NOAEL) of 5 ppm for 30 minutes exposures in healthy exercising males and females and an uncertainty factor of 3x, the AEGL-1 values are calculated to be: 2.1 ppm for 10 minutes, 1.7 ppm for 30 minutes, 1.4 ppm for 1-hour, 1.0 ppm for 4-hours, and 0.9 ppm for 8-hours. These calculated values are strikingly similar to those calculated for Jappinen et al. This concordance between the results from two researchers should lend credence to the use of either one of them as the critical study. Bhambhani and his colleagues have also performed several other studies that show similar results (Bhambahani and Singh, 1991; Bhambahani et al., 1994; Bhambahani et al.,, 1996b; Bhambahani et al., 1997).

Alternative approaches to setting AEGL values. A number of other organizations and governmental agencies have developed guideline levels designed to protect human health from incidental and accidental exposures to hydrogen sulfide. The American Industrial Hygiene Association (AIHA) in 1991 developed the Emergency Response Planning Guideline (ERPG) Level 1 value of 0.1 ppm for one-hour contact with hydrogen sulfide. The goals for the ERPG-1 are similar to those of the AEGL-1 and were adopted following an extensive and comprehensive peer review process. API would encourage the NAC to consider adopting this values when setting the AEGL-1 value. This would be beneficial for the following reasons:

- Concordance of guideline values being used for similar purposes will avoid confusion and will tend to lend support between each of the guideline systems; and
- Values and/or processes used to derive these values have already undergone review and have been judged scientifically credible.

If the ERPG-1 value was to be adopted by NAC, the calculated AEGL-1 values, using the 4.36 time scaling factor, would be calculated as follows: 0.15 ppm for 10 minutes, 0.12 ppm for 30 minutes, 0.10 ppm for 1-hour, 0.07 ppm for 4-hours, and 0.06 ppm for 8-hours.

Thank you for your attention, and for this opportunity to present these comments.

George M Woodall Jr

References:

Bhambhani, Y. and M. Singh. 1991. Physiological effects of hydrogen sulfide inhalation during exercise in healthy men. J. Appl. Physiol. 71:1872-1877.

Bhambhani, Y., R. Burnham, G. Syndmiller, I. MacLean, and T. Martin. 1996a. Effects of 5 ppm hydrogen sulfide inhalation on biochemical properties of skeletal muscle in exercising men and women. AIHA Journal 57:464-468.

Bhambhani, Y., R. Burnham, G. Syndmiller, I. MacLean, and T. Martin. 1996b. Effects of 10-ppm hydrogen sulfide on pulmonary function in healthy men and women. J. Occup. And Environ. Med. 38(10):1012-1017.

Bhambhani, Y., R. Burnham, G. Syndmiller, and I. MacLean. 1997. Effects of 10-ppm hydrogen sulfide inhalation in exercising men and women. J. Occup. And Environ. Med. 39(2): 122-129.

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

Appendix A

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 19 Highlights
U.S. Department of Transportation
DOT Headquarters/Nassif Building, Rooms 6332-6336
400 7th Street, S.W., Washington, D.C
October 23-25, 2000

INTRODUCTION

Welcoming remarks were conveyed by NAC Chairperson, George Rusch and Department of Transportation meeting host, George Cushmac. The Meeting Highlights for the NAC/AEGL Meeting 18 were reviewed and approved after minor changes (Appendix A). These changes are: (1) AEGL Phosgene Development Team (Falke, Bast, Benson, McClanahan, and Morawetz) will come to the NAC/AEGL Meeting 20 (January 2001) with two options: one will be to keep the number as proposed in the *Federal Register*. Another option will be to change it as proposed by the AEGL Development Team prior to the meeting. ORNL will send the original TSD as published in the *Federal Register* along with the proposed version. In a cover letter the AEGL Development Team it should state what they propose to do to respond to the public and committee comments; and (2) Hydrogen cyanide: There was a concern from the NAC/AEGL regarding the absence of the human exposure data in the TSD which reported on the Leeser et al. 1990 study. Following a brief discussion, it was decided to make the human exposure data available and revisit this issue at the NAC/AEGL-20 meeting (January 2001). Roger Garrett (Program Director) provided a perspective of the AEGL Program, its accomplishments, and future directions.

The highlights for NAC/AEGL-19 are presented below and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached.

GENERAL INTEREST ITEMS

Status of SOPs and Final TSDs

A brief overview of the status of the Standing Operating Procedures (SOPs) and the five final Technical Support Documents was given by Ernest Falke and Roger Garrett. These are in final preparation for publication by the National Academy of Sciences Committee on Toxicology, Subcommittee on Acute Exposure Guideline Levels (NAS/COT).

Comments from the NAS/COT on AEGLs

Several issues identified by the NAS/COT regarding AEGL development were briefly commented on by Roger Garrett and referred to the summary sheets distributed prior to the meeting (Attachment 3). Many concerns expressed by the COT/AEGL subcommittee on AEGL's development are listed as follows: (1) choice of effect concentration, (2) choice of endpoint, (3) choice of exposure protocol, (4) AEGL definitions, (5) study quality, (6) TSD format; (7) values to be developed for AEGL-1, and that AEGL values are very low numbers that are not always consistent with the known toxicity of the chemicals and overall human experience.

RESPONSE TO COMMENTS ON THE *FEDERAL REGISTER* NOTICE

There was considerable discussion on how to address *Federal Register* comments. Three proposals were suggested:

Proposal No. 1: The TSD Development Team (author, chemical manager, and reviewers) could make changes to the content of the TSD and AEGL values and present these changes to NAC/AEGL for approval.

Proposal No. 2: The TSD Development Team could make changes to the content of the TSD but *not* AEGL values, and present these changes to NAC/AEGL for approval.

Proposal No. 3: The TSD Development Team could make recommendations to NAC/AEGL for the changes on the content of the TSD and AEGL values. After approval by NAC/AEGL, these recommendations will then be incorporated into the TSD and be ready for NAS/COT AEGL Subcommittee's final review.

Chairman Rusch asked the committee for show of hands for approval. The third proposal was unanimously approved. These was no support for either Proposal No. 1 or No. 2.

DEVELOPMENT OF 10-MINUTE AEGLS

AEGL values for 10-minute durations were proposed for several chemicals for which other AEGL values had already been developed and approved by NAC/AEGL in earlier meetings.

Allyl alcohol (CAS Reg. No. 107-18-6)
Mark McClanahan, chemical manager, presented the proposed 10-minute AEGL values for allyl alcohol and the values for the other time periods using the conservative values for *n* of 1 and 3 according to the SOP (Attachment 4). The AEGL-1 10-minute value based on the odor detection threshold is identical with that for the other time periods. The AEGL-2 10-minute value is identical to the 30-minute value of 1.8 ppm according to the SOP because the data are from a 7-hour exposure study based on irritation in rats. The AEGL-3 10-minute value of 9.6 ppm is an extrapolation of animal data based on a 1-hour exposure animal lethality study. The Committee unanimously approved (motion by George Rodgers, second by Bob Benson) adoption of the values for all three AEGL levels (Appendix B).

Boron trichloride (CAS Reg. No. 10294-34-5)
Mark McClanahan, chemical manager, presented the proposed 10-minute values for AEGL-1, AEGL-2, and AEGL-3 (Attachment 5). The AEGL-1 and AEGL-2 values previously adopted by the committee were derived values recommended as guidance values based on the hydrolysis product of boron trichloride, hydrochloric acid. Because, each mole of boron trichloride produces three moles of hydrochloric acid upon hydrolysis, the previously approved AEGL-1 and AEGL-2 values for hydrochloric acid were divided to obtain the corresponding values for boron trichloride. The hydrochloric acid AEGL-1 value is based on data for exercising humans and is 1.8 ppm for all time values. The boron trichloride value of 0.6 ppm for 30-minute through 8-hour, previously adopted by the NAC/AEGL committee was proposed as the 10-minute value. The proposed AEGL-2 10-minute value (34 ppm) was derived by dividing the hydrochloric acid AEGL-2 value by 3, based on mouse RD_{50} data and rat histopathology findings. The proposed AEGL-3 10-minute value (170 ppm) was developed by

extrapolation based on one-third of the 1-hour boron trichloride LC_{50} value. The extrapolation to 10 minutes used the value of 1 for *n* obtained from hydrogen chloride lethality data. The committee unanimously approved (motion by George Rodgers, second by Steve Barbee) adoption of the three proposed 10-minute values (Appendix C). There was a suggestion that the use of the 3 as a modifying factor for AEGL-2 levels should be explained more throughly in the TSD.

Chloromethyl methyl ether (CAS Reg. No. 107-30-2

The proposed 10-minute AEGL values were accepted (motion by Bob Benson, second by Richard Thomas) (YES: 16; NO: 1; ABSTAIN:0) (Appendix D). Cancer-based AEGLs have been re-calculated using an adjustment factor of 6 instead of 2.8 to account for uncertainty in the stages of the carcinogenic process. Ernie Falke, chemical manager, presented the proposed 10-minute values for AEGL-1 (not recommended), AEGL-2 (0.076 ppm), and AEGL-3 (1.2 ppm) according to SOP guidance of applying *n* of 1 and 3 in the time scale extrapolation. (Attachment 6). It was the consensus of the NAC/AEGL that the cancer risk levels be added as in Appendix section of TSD and that an explanation regarding confidence in these values also be included (motion by Bob Benson, second by Richard Thomas) (Appendix D).

Diborane (CAS Reg. No. 1928-45-7)

Jim Holler, chemical manager, presented the 10-minute AEGL values (Attachment 7). Following discussion on alternative approaches (i.e., use of 15-minute LC_{50} for the 10-minute AEGL-3 value), the following 10-minute AEGL values proposed were accepted: AEGL-1- not recommended due to the lack of data; AEGL-2 value was set at 2.0 ppm; and AEGL-3 value was set at 7.3 ppm. The 10-minute AEGL-2 & 3 values were set to equal to the 30-minute values (motion made by Richard Thomas, second by Jim Holler) (AEGL-1: YES, unanimously; AEGL-2: YES: 17; NO: 2; ABSTAIN: 0; AEGL-3: YES: 19; NO: 1; ABSTAIN: 0) (Appendix E).

Furan (CAS Reg. No. 111-00-9)

George Rodgers, chemical manager, presented the 10-minute AEGL values (Attachment 8) as well as AEGLs adjusted by application of default *n* values of 1 and 3 rather than 2. Ten-minute values of 18 ppm and 52 ppm for AEGL-2 and -3, respectively, were proposed based upon the 1-hour exposure data from Terrill et al. (1989) and an *n* of 3. The values were approved unanimously (motion by Mark McClanahan, second by David Belluck) (Appendix F). No AEGL-1 values were developed. It was recommended that the "ID" designation (insufficient data) for missing values be changed to "NR" (Not Recommended).

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

Jim Holler, chemical manager, presented the proposed 10-minute AEGL values (Attachment 9). Due to concerns expressed regarding the use of the empirically-derived n of 0.87, the deliberations were tabled until the next meeting. It was suggested that a cover letter be added to the revised TSD to explain changes.

Tetrachloroethylene (CAS Reg. No. 127-18-4)

Bill Bress, chemical manager, presented the proposed 10-minute AEGL values (Attachment 10).
A motion (George Rodgers, second by David Belluck) was made to accept the proposed 10-minute values and 30-minute values as equal. Some NAC/AEGL members expressed concern that the NAS might send this chemical back because of the use of a chronic animal study for AEGL-2, when human studies were available and felt that the AEGL-3 was too low when you compared the numbers to human data (AEGL-1: YES: 19; NO: 1; ABSTAIN: 0; AEGL-2: YES: 16; NO: 4; ABSTAIN: 0; AEGL-3: YES: 16; NO: 2; ABSTAIN: 2) (Appendix G).

Tetranitromethane (CAS Reg. No. 509-14-8)
Ernest Falke presented the proposed 10-minute values for tetranitromethane (Attachment 11). The proposed values and the altered "n" value used to develop them were accepted (motion by George Rodgers, second by Richard Thomas) (AEGL-1, -2, and -3: YES: 17; NO: 2; ABSTAIN: 0) (Appendix H). It was suggested that the cancer risk values be added as an Appendix in the TSD and that justification be added regarding the 8-hr AEGL-1 reflecting a 1 in 10,000 cancer risk.

Perchloromethyl mercaptan (CAS Reg. No. 594-42-3)
Zarena Post, chemical manager, presented the AEGL adjusted 10-minute values using an *n* value of 1 or 3 according to the SOP (Attachment 12). A motion to accept the values as proposed was made by George Rodgers and seconded by Richard Niemeier. The motion passed (AEGL-1: YES: 17; NO: 1; ABSTAIN: 0; AEGL-2: YES: 17; NO: 1; ABSTAIN: 0; AEGL-3: YES: 18; NO: 0; ABSTAIN: 0) (Appendix I).

REVISIT/RE-ASSESSMENTS OF CHEMICAL-SPECIFIC AEGLS

Hydrogen sulfide
A reassessment of the AEGLs for hydrogen sulfide were necessitated by concerns of the NAS/COT/AEGL (COT/AEGL) Subcommittee regarding the quality of the study used to develop the AEGL-1 values. The COT/AEGL believed that the study of asthmatics would provide for more robust and appropriate AEGL-1 values. Cheryl Bast provided AEGL-1 values developed using this study (Jappinen, 1990). Several members of the NAC/AEGL indicated that the values (Attachment 13) presented by the World Health Organization (WHO) allowed for defensible AEGL-1 values that were in opposition to these values. As a result, no consensus was reached regarding the AEGL-1 values for H_2S.

☞**Action Item**: Following discussion, it was recommended that the COT/AEGL comments and the overall data on H_2S be reviewed by Cheryl Bast, Steve Barbee and George Alexeeff. Furthermore, a specific data analysis will be conducted by Mark Ruijten, Dave Belluck, and Zarena Post regarding the WHO values with attention given to a definitive demarcation of odor and annoyance thresholds. The results of this analysis will be presented at the next NAC/AEGL meeting. Steve Barbee will organize a conference call to discuss general issues of H_2S and to welcome the participation of NAC members.

AEGL PRIORITY CHEMICALS

Uranium hexafluoride, CAS Reg. No. 7783-81-5

Chemical Manager: George Rusch, Chair
Staff Scientist: Cheryl Bast, ORNL Staff Scientist

Cheryl Bast presented an overview of the pertinent data and development of the draft AEGL values (Attachment 14), noting that the toxicity of UF_6 included both a renal toxicity and radiological component. Discussion ensued regarding the most appropriate endpoint for AEGL-1. Additionally, it was decided that an available accident report had notable deficiencies making it unsuitable for development of AEGL values. For AEGL-3, the relevance of the hydrogen fluoride (HF) component (especially for shorter exposure periods) was discussed and the HF and UF_6 AEGL values compared; HF values were lower than those of UF_6 for times >1 hour, equivalent at 1 hour, but greater for 4- and 8-hour periods. A motion was made by George Rodgers (seconded by Ernest Falke) to accept UF_6 values of 550, 100, 36, 4.4, and 1.6 mg/m^3 for the 10-minute, 30-minute, 1-hr, 4-hr, and 8-hr values. It was noted that these values are consistent with the AEGL-3 values proposed for HF. The motion passed YES: 18;

NO: 0; ABSTAIN: 0) (Appendix J). The AEGL-2 values were based upon renal toxicity in dogs and an empirically-derived "*n*" value of 0.66. The AEGL values based on this UF_6 study would also be protective of toxicity due to the HF component of UF_6. The motion made by Ernest Falke, seconded by Steve Barbee) to accept the values of 28, 19, 9.6, 2.4 and 1.2 mg/m^3 for the 10-minute, 30-minute, 1-hr, 4-hr, and 8-hr passed (YES: 19; NO: 1; ABSTAIN: 0) (Appendix I). For AEGL-1, several options were considered; no AEGL values, AEGL values equivalent to HF, and use of the available accident reconstruction report. It was the consensus of the NAC/AEGL that for AEGL-1, HF values would be more appropriate for the shorter time periods (<4 hrs) but that UF_6 would be more relevant at 4 and 8 hours. Therefore, the 10-minute, 30-minute, and 1-hr AEGL values for HF of 3.6 ppm were applied for the same exposure durations for UF_6. For 4- and 8-hrs, no values were recommended for UF_6. A motion was made by Tom Hornshaw (seconded by Richard Thomas) to accept these values; the motion passed unanimously (YES: 19; NO: 0; ABSTAIN: 0) (Appendix J).

SUMMARY OF PROPOSED AEGL VALUES FOR URANIUM HEXAFLUORIDE (mg/m^3)						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint**
AEGL-1	3.6	3.6	3.6	NR	NR	Equivalent to HF
AEGL-2	28	19	9.6	2.4	1.2	Renal toxicity in dogs
AEGL-3	550	100	36	4.4	1.6	Lethality

G Agents (Nerve Agents)
Agent GA, CAS Reg. No. 77-81-6
Agent GB, CAS Reg. No. 107-44-8
Agent GD, CAS Reg. No. 96-64-0
Agent GF, CAS Reg. No. 329-99-7

Chemical Manager: John Hinz, USAF
Staff Scientist: Annetta Watson, ORNL Staff Scientist

The presentation of the agent-specific data and development of the AEGL values for the G-agents was preceded by supporting introductory presentations.

Veronique Hauschild (USACHPPM) presented introductory information from an operational standpoint regarding issues and needs of the U.S. Army relative to AEGLs for chemical warfare agents (Attachment 15). Ms. Hauschild explained the need for expeditiously developed scientifically-based AEGLs, and the U.S. Army's appreciation for the NAC/AEGL role in this effort.

Coleen Weese (USACHPPM) presented a summary of the CDC Public Meeting on airborne exposure limits to nerve agents held in August, 2000, which affirmed that miosis (rather than ChE depression) was the most appropriate endpoint for assessing nerve agent exposure. The August public meeting also identified the most relevant and appropriate data sets, and approved the relative potency approach for developing toxicity values for the data-deficient Agent VX.

Glenn Leach also made a brief presentation noting the critical effects of concern for nerve agents, the most appropriate species for AEGL-3 determinations, and distinguishing derivative values presented in the TSD from those derived experimentally.

An elaboration on issue analyses relevant to nerve agent toxicity and development of AEGL values was presented by Robert Young (Attachment 16). This presentation focused on the toxicology of nerve agents, types of cholinesterases (ChE) and the relevance of ChE in development of AEGLs, and previous peer-reviewed analyses of appropriate endpoints used in developing toxicity values for nerve agents and organophosphate pesticides.

Annetta Watson provided an overview of the available data for the G-agents, noting that a more detailed presentation had been given at the previous NAC/AEGL meeting (NAC/AEGL 18) and that all presentation materials, as well as the TSDs, were previously made available to the NAC membership (Attachment 17). The presentation reflected input from several NAC reviewers and an Air Force review coordinated by John Hinz. Discussion focused on the partitioning of uncertainty factors with NAC consensus that the total uncertainty factor of 30 was appropriate for estimating AEGL-3, but the intraspecies UF should be 10 (greater sensitivity of female rats was not considered justification for a UF of 10) and the interspecies UF should be 3. There was also discussion on the data set selection and derivation of an n of 2 from recent studies of GB vapor exposure to rats (Mioduszewski et al., in press, 2000). A motion to accept the AEGL-3 values for Agent GB was made by Bill Bress and seconded by Loren Koller. The motion passed (AEGL-3: YES: 20; NO: 0; ABSTAIN: 0) (Appendix K).

The AEGL-1 values were based upon data from studies with informed human subjects exposed to GB vapor (0.05 mg/m^3 for 20 min) and experiencing only minimal effects. AEGL-2 effects were based upon a repeat study using informed volunteers (under Helsinki accords and clinical supervision) in which miosis, dyspnea, reduction of RBC-ChE to 60% of baseline, and small changes in single fiber electromyography of the forearm (considered a possible precursor to nondepolarising neuromuscular block) following exposure to 0.5 mg/m^3 GB for 30 minutes. For both AEGL-1 and AEGL-2 values an intraspecies uncertainty factor of 10 was applied, resulting in a composite UF of 10 (interspecies UF of 1 and intraspecies UF of 10; modifying factor not apply). Following discussions of the derivation logic, motions were made to accept the AEGL-2 values (motion made by Koller and seconded by Richard Thomas) (YES: 16; NO: 0; ABSTAIN: 2) (Appendix K) and AEGL-1 values (motion made by Loren Koller and seconded by Steve Barbee). Both motions passed unanimously (AEGL-1 and -2: YES: 20; NO: 0; ABSTAIN: 0) (Appendix K).

Following explanation by Annetta Watson of the process/rationale for the relative potency approach wherein AEGLs for Agents GA, GD and GF were developed relative to GB data, motions were made to accept the AEGLs as presented for these agents. The motion for Agent GA was made by Loren Koller and seconded by Glenn Leach. The motion for Agent GD was made by George Rodgers and seconded by Loren Koller, and the motion for Agent GF was made by Richard Thomas and seconded by Loren Koller. All of the motions passed [**Agent GA**: AEGL-1: YES: 19; NO: 1; ABSTAIN: 0; AEGL-2 and -3: YES: 21; NO: 0; ABSTAIN: 0 (Appendix L). **Agent GD**: AEGL-1: YES: 18; NO: 0; ABSTAIN: 0; AEGL-2 and -3: YES: 21; NO: 0; ABSTAIN: 0 (Appendix M); **Agent GF**: AEGL-2: YES: 18; NO: 0; ABSTAIN: 0; AEGL-2 and -3: YES: 21; NO: 0; ABSTAIN: 0 (Appendix N)].

SUMMARY OF PROPOSED AEGL VALUES (ppm[mg/m^3]) FOR AGENT GA

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

SUMMARY OF PROPOSED AEGL VALUES (ppm[mg/m^3]) FOR AGENT GB						
Classification	**10 min**	**30 min**	**1 hr**	**4 hr**	**8 hr**	**Endpoint**
AEGL 1	0.0012 [0.0069]	0.00068 [0.0040]	0.00048 [0.0028]	0.00024 [0.0014]	0.00017 [0.0010]	Headache, eye pain, rhinorrhea, tightness in chest, cramps, nausea, malaise, miosis in human volunteers exposed to 0.05 mg/m^3 for 20 min. (Harvey, 1952; Johns, 1952)
AEGL 2	0.015 [0.087]	0.0085 [0.050]	0.0060 [0.035]	0.0029 [0.017]	0.0022 [0.013]	Miosis, dyspnea, RBC-ChE depression, electromyographic changes in human volunteers (0.5 mg/m^3 for 30 min; Baker and Sedgwick, 1996)
AEGL 3	0.064 [0.38]	0.032 [0.19]	0.022 [0.13]	0.012 [0.070]	0.0087 [0.051]	Rat lethality (Mioduszewski et al., in press; 2000)

SUMMARY OF PROPOSED AEGL VALUES (ppm[mg/m^3]) FOR AGENT GD						
Classification	**10 min**	**30 min**	**1 hr**	**4 hr**	**8 hr**	**Endpoint**
AEGL 1	0.00046 [0.0035]	0.00026 [0.0020]	0.00018 [0.0014]	0.000091 [0.00070]	0.000065 [0.00050]	Based on relative potency from GB
AEGL 2	0.0057 [0.044]	0.0033 [0.025]	0.0022 [0.018]	0.0012 [0.0085]	0.00085 [0.0065]	Based on relative potency from GB
AEGL 3	0.049 [0.38]	0.025 [0.19]	0.017 [0.13]	0.0091 [0.070]	0.0066 [0.051]	Based on relative potency from GB

SUMMARY OF PROPOSED AEGL VALUES (ppm[mg/m^3]) FOR AGENT GF						
Classification	**10 min**	**30 min**	**1 hr**	**4 hr**	**8 hr**	**Endpoint**
AEGL 1	0.00049 [0.0035]	0.00028 [0.0020]	0.00020 [0.0014]	0.00010 [0.00070]	0.000070 [0.00050]	Based on relative potency from GB

AEGL 2	0.0062 [0.044]	0.0035 [0.025]	0.0024 [0.018]	0.0013 [0.0085]	0.00091 [0.0065]	Based on relative potency from GB
AEGL 3	0.053 [0.38]	0.027 [0.19]	0.018 [0.13]	0.0098 [0.070]	0.0071 [0.051]	Based on relative potency from GB

Agent VX, CAS No. 50782-69-9

Chemical Manager: Glenn Leach, USACHPPM
Staff Scientist: Annetta Watson, ORNL Staff Scientist

Annetta Watson summarized the available data for Agent VX, noting the similarities in signs/symptoms of VX to the G-agents and providing an overview of the gradation of effects with increasing cumulative exposure (Attachment 18). There was considerable discussion regarding the data quality and how this impacted the relative potency approach. The comparative study of Callaway and Dirnhuber (1971) , which evaluated the potency of GB and VX vapor to produce miosis during direct exposure experiments to the eyes of albino rabbits, was interpreted by the NAC to support a relative potency factor of 12 (VX more potent than GB). This determination is different than the relative potency factor of 10 originally proposed in the TSD. In addition, the NAC recommended application of a modifying factor of 3 in the development of all AEGL values for agent VX to account for the incomplete VX data set. For both AEGL-1 and AEGL-2 values, an interspecies UF of 1 and an intraspecies UF of 10 were applied. With addition of the modifying factor of 3, the composite UF for AEGL-1 and AEGL-2 estimates was 30.

A motion to accept the resulting AEGL-1 values was made by Bill Bress and seconded by Ernie Falke. The motion passed (YES: 15; NO: 1; ABSTAIN: 3) (Appendix O). A motion to accept the AEGL-2 values was made by Bob Benson and seconded by Glenn Leach also passed (YES: 11; NO 3; ABSTAIN: 6) (Appendix O).

For AEGL- 3 values, rat lethality data for GB were used with the same relative potency method, but with an added modifying factor of 3 for database inadequacy which was of particular concern to several NAC members. With an interspecies UF of 3 and an intraspecies UF of 10, the composite adjustment was equal to 100. A motion was made by Bill Bress and seconded by Ernie Falke. The motion passed (YES: 16; NO: 1; ABSTAIN: 2) (Appendix O).

A lengthy discussion ensued regarding the adequacy of this adjustment to address the uncertainty associated with the assumption of relative potency and physiological/metabolic similarities between VX and GB. It was the consensus of the NAC/AEGL that the VX database is extremely weak, and was noted by previous National Research Council recommendations (NRC, 1997). To address these significant data gaps and yet provide some guidance for potential current real-world applications, it was the consensus of the NAC/AEGL to propose temporary AEGL values that would expire in 3 years from the date of NAS publication at which time a re-evaluation of any new data would be necessary.

SUMMARY OF PROPOSED TEMPORARY* AEGL VALUES (ppm[mg/m^3]) FOR AGENT VX						
Classification	**10 min**	**30 min**	**60 min**	**4 hr**	**8 hr**	**Endpoint**

Temporary* AEGL 1	0.000018 [0.00020]	0.000010 [0.00011]	0.0000073 [0.000080]	0.0000037 [0.000040]	0.0000026 [0.000028]	Based on relative potency from GB
Temporary* AEGL 2	0.00022 [0.0024]	0.00013 [0.0014]	0.000090 [0.00098]	0.000045 [0.00049]	0.000032 [0.00035]	Based on relative potency from GB
Temporary* AEGL 3	0.00088 [0.0096]	0.00045 [0.0049]	0.00030 [0.0033]	0.00016 [0.0017]	0.00012 [0.0013]	Based on relative potency from GB

*Due to significant data gaps, these values are temporary proposed. They will expire 3 years from the date of NAS publication.

ADMINISTRATIVE ISSUES

Plans for future NAC/AEGL meeting dates were discussed. The following were options:

January 8-10, 2001 (Washington, DC)
March 22-24, 2001 (in conjunction with SOT and the NAS/COT meeting)
June 18-20, 2001 (Oak Ridge, TN)
September 11-13, 2001 (Washington, DC)

Meeting highlights were prepared by Bob Young and Po-Yung Lu, Oak Ridge National Laboratory.

LIST OF ATTACHMENTS

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

1. NAC/AEGL Meeting No. 19 Agenda
2. NAC/AEGL Meeting No. 19 Attendee List
3. NAS/COT/AEGL Subcommittee comments on AEGLs and TSDs
4. Data analysis of 10-minute AEGLs for Allyl alcohol
5. Data analysis of 10-minute AEGLs for Boron trichloride
6. Data analysis of 10-minute AEGLs for Chloromethyl methyl ether
7. Data analysis of 10-minute AEGLs for Diborane
8. Data analysis of 10-minute AEGLs for Furan
9. Data analysis of 10-minute AEGLs for Propylene oxide
10. Data analysis of 10-minute AEGLs for Tetrachloroethylene
11. Data analysis of 10-minute AEGLs for Tetranitromethane
12. Data analysis of 10-minute AEGLs for Perchloromethylmercaptan
13. Data analysis for Hydrogen sulfide
14. Data analysis for Uranium hexachloride
15. An Overview of Development of Nerve agent AEGLs by Veronique Hauschild
16. Issues for NAC/AEGL in Developing AEGLs for Nerve Agents
17. Data analysis for Nerve Agents (GA, GB, GD, and GF)
18. Data analysis for Nerve Agent VX

LIST OF APPENDICES

Approval of Minutes
Jan 8, 2001

NAC/AEGL Meeting 20: 1/8-10/2001 Appendix 8

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

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

Snyder + Strickland ABSTAIN after "yes" ( ) = NOT PRESENT

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

AEGL 1 Motion: M. McClanahan **Second:** G. Rodgers

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

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

Approved by Chair: _____ **DFO:** _____ **Date:** 1/8/01

NAC/AEGL Meeting 20: 1/8-10/2001

Chemical: PHENOL ØOH **CAS Reg. No.:** 108-95-2

NAC Member	AEGL 1	AEGL 2 (A)	AEGL 2 (B)	AEGL 2 (C)	AEGL 3
George Alexeeff	A	A	A	A	A
Steven Barbee	Y	Y/N*	Y	Y	Y
Lynn Beasley	Y	A	A	A	Y
David Belluck	N	N	N	N	N
Robert Benson	Y	Y	P	Y	Y
Jonathan Borak	P	A	P	P	A
William Bress	Y	Y	N	Y	Y
George Cushmac	Y	Y	N	Y	Y
Ernest Falke	Y	Y	Y	Y	Y
Larry Gephart	Y	Y/N*	Y	Y	Y
John Hinz	A	N	P	Y	N
Jim Holler	Y	Y	Y	Y	Y
Thomas C. Hornshaw	Y	Y/N*	Y	Y	P
Nancy Kim	Y	Y	N	Y	Y
Loren Koller	N	N	P	P	P

NAC Member	AEGL 1	AEGL 2 (A)	AEGL 2 (B)	AEGL 2 (C)	AEGL 3
Glenn Leach	Y	Y/N*	Y	Y	Y
Mark A. McClanahan	Y	N	Y	N	N
John S. Morawetz	N	Y	N	Y	P
Richard W. Niemeier	Y	Y	N	Y	Y
Marinelle Payton	A	A	A	A	A
Zarena Post	Absent	Absent		A	Absent
George Rodgers	Y	N	Y	Y	Y
George Rusch, Chair	Y	Y	Y	Y	Y
Robert Snyder	Y	Y	N	Y	Y
Thomas Sobotka	N	Y	N	Y	N
Kenneth Still	A	A	A	A	A
Judy Strickland	Y	Y	N	Y	Y
Richard Thomas	Y	Y	Y	Y	Y
Thomas Tuccinardi/ ~~Doan Hansen~~	P	Y	Y	Y	Y
TALLY	18/22	18/23 *14/23	11/20	19/21	17/21

*= 10 MIN ONLY

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	8.3, ( )	5.7, ( )	4.5, ( )	2.9, ( )	1.9, ( )
AEGL 2	(A) 19 (B) 28 (C) 19, ( )	19, (73)	15, (58)	9.5, (36)	6.3, (24)
AEGL 3	59, (230)	59, (230)	47, (180)	29, (110)	23, (88)

(A) INCLUDES VOTE FOR AEGL-2, 10 MIN, SEPARATELY
(B) VOTE ON AEGL-2, 10 MIN
(C) VOTE ON AEGL-3, 10 MIN

AEGL 1 Motion: T. HORNSHAW **Second:** R. NIEMEIER

AEGL 2 Motion: (A) R. SNYDER (B) M. McCLANAHAN (C) R. BENSON **Second:** R. THOMAS S. BARBEE J. HINZ

AEGL 3 Motion: R. SNYDER **Second:** R. BENSON

Approved by Chair: [signature] **DFO:** [signature] **Date:** 1/8/01

Appendix D

NAC/AEGL Meeting 20: 1/8-10/2001

Chemical: CO (carbon monoxide) **CAS Reg. No.:** 630-08-0

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach	A	A	A
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	Y	Y	Y	John S. Morawetz	Y	N	N
David Belluck	Y	Y	Y	Richard W. Niemeier	Y	Y	Y
Robert Benson	Y	Y	P	Marinelle Payton	A	A	A
Jonathan Borak	Y	Y	Y	Zarena Post	Absent	Absent	Absent
William Bress	Y	Y	Y	George Rodgers	Y	Y	N
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	N	Robert Snyder	Y	Y	Y
Larry Gephart	N	Y	Y	Thomas Sobotka	Y	Y	Y
John Hinz	Y	Y	Y	Kenneth Still	A		A
Jim Holler	Y	Y	Y	Judy Strickland	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Y	A	A
Nancy Kim	Y	Y	Y				
Loren Koller	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	22/23	21/22	18/21

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR ,( )	NR ,( )	NR ,( )	NR ,( )	NR ,( )
AEGL 2	420 ,(480)	150 ,(170)	83 ,(95)	33 ,(38)	27 ,(31)
AEGL 3	1700 ,( )	600 ,( )	330 ,( )	150 ,( )	130 ,( )

AEGL 1 Motion: J. Borak **Second:** M. McClanahan

AEGL 2 Motion: J. Strickland **Second:** J. Koller

AEGL 3 Motion: S. Barbee **Second:** J. Hinz

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 1/8/01 1/9/01

Appendix E

NAC/AEGL Meeting 20: 1/8-10/2001

Chemical: Sulfur Mustard (Agent HD) **CAS Reg. No.:**

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff			A	Glenn Leach			A
Steven Barbee			Y	Mark A. McClanahan			Y
Lynn Beasley			Y	John S. Morawetz			Y
David Belluck			Y	Richard W. Niemeier			Y
Robert Benson			N	Marinelle Payton			A
Jonathan Borak			Y	Zarena Post	Absent	Absent	Absent
William Bress			Y	George Rodgers			Y
George Cushmac			Y	George Rusch, Chair			Y
Ernest Falke			Y	Robert Snyder			Y
Larry Gephart			Y	Thomas Sobotka			Y
John Hinz			Y	Kenneth Still			A
Jim Holler			Y	Judy Strickland			Y
Thomas C. Hornshaw			Y	Richard Thomas			A
Nancy Kim			Y				
Loren Koller			Y	Thomas Tuccinardi/ Doan Hansen			A A
				TALLY			21/22

Vote on NAS proposal to use n of 3 to scale from 1 hr. to 10 min + 30 min (1 HR, 4 HR, 8 HR NOT AFFECTED)

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	0.59 , (3.9)	0.41 , (2.7)	, ( )	, ( )	, ( )

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

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

AEGL 3 Motion: G. Rodgers **Second:** M. M. Hamilton

Approved by Chair: _____ **DFO:** _____ **Date:** 1/9/01

NAC/AEGL Meeting 20: 1/8-10/2001

Chemical: Phosphine 10' 1h 10' 24h **CAS Reg. No.:** 7803-51-2

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff		A	A
Steven Barbee		N	Y
Lynn Beasley		Y	Y
David Belluck		Y	Y
Robert Benson		P	Y
Jonathan Borak		N	Y
William Bress		Y	Y
George Cushmac		Y	Y
Ernest Falke		Y	Y
Larry Gephart		Y	N Y
John Hinz		Y	Y
Jim Holler		Y	Y
Thomas C. Hornshaw		Y	N Y
Nancy Kim		N Y	P Y
Loren Koller		Y	Y

NAC Member	AEGL 1	AEGL 2	AEGL 3
Glenn Leach		P	P P
Mark A. McClanahan		Y	Y
John S. Morawetz		N N	N Y
Richard W. Niemeier		N Y	N Y
Marinelle Payton		A	A
Zarena Post	Absent	Absent	Absent
George Rodgers		P	Y
George Rusch, Chair		Y	Y
Robert Snyder		N	Y
Thomas Sobotka		Y	N Y
Kenneth Still		A	A
Judy Strickland		Y	Y
Richard Thomas		A	A
Thomas Tuccinardi/ Doan Hansen		A A	A A
TALLY		14/20 16/9	16/21 22/22

~~Adopt values, but reconsider in 3 years, when probably could have more info.~~

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	4.0 , (5.6)	4.0 , (5.6)	2.0 , (2.8)	0.50 , (0.71)	0.25 , (0.35)
AEGL 3	7.2 , (10)	7.2 , (10)	3.6 , (5.1)	0.90 , (1.3)	0.45 , (0.63)

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

AEGL 2 Motion: L. Koller **Second:** M. McClanahan

AEGL 3 Motion: L. Koller **Second:** B. Benson

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 1/9/01

Appendix G

NAC/AEGL Meeting 20: 1/8-10/2001

Chemical: Monochloroacetic acid **CAS Reg. No.:** 79-11-8

NAC Member	AEGL 1 **	AEGL 2	AEGL 3 *	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Glenn Leach	Y	Y	Y
Steven Barbee	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
Lynn Beasley	Y	Y	Y	John S. Morawetz	Y	Y	Y
David Belluck	Y	Y	Y	Richard W. Niemeier	Y	Y	Y
Robert Benson	Y	Y	Y	Marinelle Payton	A	A	A
Jonathan Borak	A	A	A	Zarena Post	Absent	Absent	Absent
William Bress	Y	Y	Y	George Rodgers	Y	Y	P
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Robert Snyder	Y	Y	Y
Larry Gephart	Y	Y	A	Thomas Sobotka	Y	Y	Y
John Hinz	Y	P	Y	Kenneth Still	A	A	A
Jim Holler	Y	Y	Y	Judy Strickland	Y	Y	Y
Thomas C. Hornshaw	A	Y	Y	Richard Thomas	A	A	A
Nancy Kim	Y	Y	Y				
Loren Koller	P	Y	A	Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
				TALLY		22/22	20/20

* Motion not to set AEGL-3 values, due to no lethality inhalation data that could be used of oral data can't be used without a biggrs class.

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	ID ,( )	ID ,( )	ID ,( )	ID ,( )	ID ,( )
AEGL 2	12 ,(47)	8.3 ,(33)	6.6 ,(26)	1.7 ,(6.5)	0.83 ,(3.2)
AEGL 3	ID ,( )	ID ,( )	ID ,( )	ID ,( )	ID ,( )

** Motion not to set values due to lack of data
ID = INSUFICIENT DATA

AEGL 1 Motion: R. Benson **Second:** J. Hinz

AEGL 2 Motion: J. Strickland **Second:** S. Barbee

AEGL 3 Motion: R. Benson **Second:** J. Strickland

Approved by Chair: [signature] **DFO:** [signature] **Date:** 1/9/01

Appendix H

NAC/AEGL Meeting 20: 1/8-10/2001

Chemical: XYLENES **CAS Reg. No.:** 1330-20-7

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Robert Benson	Y	Y	Y
Jonathan Borak	A	A	A
William Bress	Y	Y	Y
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
John Hinz	N	N	N
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y
Nancy Kim	Y	Y	~~A~~ N
Loren Koller	A	A	A

NAC Member	AEGL 1	AEGL 2	AEGL 3
Glenn Leach	A	A	A
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	N	N	N
Richard W. Niemeier	N	N	N
Marinelle Payton	A	A	A
Zarena Post	Absent	Absent	Absent
George Rodgers	Y	Y	Y
George Rusch, Chair	A	A	A
Robert Snyder	Y	Y	Y
Thomas Sobotka	N	N	N
Kenneth Still	A	A	A
Judy Strickland	Y	Y	Y
Richard Thomas	A	A	A
Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
TALLY	16/20		

* Motion: To reconsider 10 & 30 min AEGL-2 & -3 at next meeting following PHARMACOKINETICS ASSESSMENT

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	~~130~~ 130, ( )	130, ( )	130, ( )	130, ( )	130, ( )
AEGL 2	~~430~~ *, ( )	~~430~~ *, ( )	430, ( )	430, ( )	430, ( )
AEGL 3	~~930~~ *, ( )	~~930~~ *, ( )	930, ( )	930, ( )	930, ( )

AEGL 1 Motion: E. Falke **Second:** M. McClanahan

AEGL 2 Motion: E. Falke **Second:** M. McClanahan

AEGL 3 Motion: E. Falke **Second:** M. McClanahan

Approved by Chair: Ernest W. Falke **DFO:** Paul S. Tobin **Date:** 1/9/01

OPTIONAL FORM 99 (7-90)

FAX TRANSMITTAL # of pages ▶ 1

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NSN 7540-01-317-7368 5099-101 GENERAL SERVICES ADMINISTRATION

10 MINUTE NUMBERS

Appendix I

ing 20: 1/8-10/2001

Chemical: ETHYLENE OXIDE **CAS Reg. No.:** 75-56-9

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

Vote on 10 min only for AEGL-1,2,3

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	110 ,( )	110 ,( )	60 ,( )	19 ,( )	11 ,( )
AEGL 2	~~540~~ 1300 ,( )	570 ,( )	290 ,( )	91 ,( )	51 ,( )
AEGL 3	~~1100~~ 2700 ,( )	1100 ,( )	610 ,( )	190 ,( )	110 ,( )

AEGL 1 Motion: J. Holler **Second:** B. Bonnar R. Rymer

AEGL 2 Motion: ↓ **Second:** ↓

AEGL 3 Motion: ↓ **Second:** ↓

Approved by Chair: Ernest W. Falke **DFO:** Paul S. Tobin **Date:** 1/9/01