National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-32
April 19-21, 2003

U.S. Department of Labor
Room C5515 1A & 1B
200 Constitution Ave., N.W.
Washington, DC 20210

Metro: Judiciary Square (Red Line)

AGENDA

Monday, April 19, 2003

10:00 a..m.	Introductory remarks, approval of NAC/AEGL-31 Highlights, and COT meeting update (George Rusch, Ernie Falke, and Paul Tobin)
10:30	2,4-Dinitroaniline (Ernest Falke/Sylvia Talmage)
10:45	Revisit of Disulfur dichloride (Ernest Falke/Kowetha Davidson)
11:00	Review of Methacrylic Acid (Bob Benson/Fritz Kalberlah)
12:30 p.m.	Lunch
1:30	Review of Methyl methacrylate (Bob Benson/Fritz Kalberlah)
3:00	Break
3:15	Review of Ethyl acrylate, Butyl acrylate, and Methyl 2-chloroacrylate (George Woodall/Ursula Gundert-Remy /Carol Wood)
5:30	Adjourn for the day

Tuesday, April 20, 2003

8:00 a.m.	Revisit of Methanol (Ernie Falke/Peter Griem)
9:30	Revisit of Phenol (Bob Snyder/Peter Griem)
10:30	Break
10:45	Revisit of Boron trichloride (Tom Hornshaw/Claudia Troxel/Marquea King)
11:45	Travel Procedures
12:15p.m.	Lunch
1:15	Revisit of Chlorine trifluoride (Sylvia Talmage/Bob Benson)
2:15	Review of Methyl Chloride (George Rodgers/Sylvia Talmage)
3:00	Break
3:15	Bromine- Response to Federal Register Comments (Zarena Post/Sylvia Talmage)
3:45	Exposure Modeling (John Morawetz)
4:15	Discussion of Public Comments (If available): Carbon disulfide, 1,4-Dioxane, Acetone, Acrolein, Chloroform, Epichlorohydrin, Methyl mercaptan, n,n-Dimethylformamide, Nitric acid, Nitric oxide, Nitrogen dioxide, peracetic acid, Sulfur dioxide, Trichloroethylene, Trimethylchlorosilane
5:00	Adjourn for the day

Wednesday, April 21, 2003

8:00 a.m.	Discussion of Public Comments (If available) Continued
9:00	Review of Methyl Bromide (George Rodgers/Sylvia Talmage)
10:15	Break
10:30	Review of Methyl Bromide (continued)
11:30	Administrative matters
12:00 noon	Adjourn meeting

ATTACHMENT 2

NAC/AEGL-32 Attendees

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Response to Federal Register Comments on Bromine
National Advisory Committee Meeting - 31, December 10-12, 2003

Two sets of comments were received on September 8, 2003: one from the Toxicology Excellence for Risk Assessment and one from the American Chemistry Council.

Toxicology Excellence for Risk Assessment (TERA)
Comments:

We appreciate the opportunity to express our views on this important Agency action. We congratulate US EPA's thoughtfulness and clarity in the discussion of data, and appreciate the difficulty with which US EPA has addressed controversial issues, such as the use of human data in its risk assessment positions.

As we understand the EPA (2003) position, it is developing bromine AEGLs 1 and 2 based on the human study by Rupp and Henschler (1967). Previously, EPA (1997) developed these AEGLs by analogy to chlorine. Either position is reasonable, of course, as long as the process is transparent and judgments are supportable.

We agree with EPA that the choice of a human study on bromine is the preferred focus of AEGL 1 and 2. The Rupp and Henschler (1967) paper appears to be the best of several in that it tests a fair number of healthy individuals in a well-known laboratory. EPA (2003, page 10) also correctly points out a number of deficiencies in the reporting of this study, such as actual concentrations were less than nominal concentrations, measurements were taken in the vicinity of a wall and not the immediate area of the subjects, the lack of data from the controls, and the fact that more recent studies of irritation and odor threshold report higher concentrations than does the chlorine part of the Rupp and Henschler (1967) study impuning perhaps its bromine part as well.

In addition to EPA's comments, we have several of our own based on a reading of a partially translated version of Rupp and Henschler (1967). For example, the authors state that the actual concentrations in their study are uncertain. Although the nominal concentrations might be lower, as they suggest, however, subjects might actually be inhaling more because the measurements taken by Rupp and Henschler (1967) were not in the vicinity of the subjects. If the concentrations of Rupp and Henschler (1967) were actually higher, their results might be consistent with the more recent studies of chlorine's irritation and odor threshold mentioned above.

Furthermore, Rupp and Henschler (1967) describe a control dose, but do not give control responses. Although several of the irritation effects might not be anticipated with high frequency in controls, one of them, headache, is a common enough symptom without exposure. In short, the omission of the control incidences is a serious problem in the use of this study for the bromine AEGL without further study or data development.

Moreover, we could not understand either the intensity scores of Table 2 of the Rupp and Henschler (1967) at various concentrations, nor the intent of Figure 4. In fact, the results of Figure 4 seem to be in direct contrast with EPA's method of categorical regression, where severe effects are seen at high concentration and short time, with lesser severity effects associated with lower concentrations and longer times. EPA's thoughts on this table and figure would be highly valued.

We believe that the uncertainty factor of 3 is reasonable from a public health perspective to account for sensitive individuals. However, we question EPA's use of the time extrapolation for irritation effects without further investigation. Our experience with such effects may or may not be affected with time extension, that is, a concentration may be a threshold across time. However, it is most certainly the case that the raw data of Rupp and Henschler (1967) study can be used to answer this question definitively and we encourage EPA to obtain these data. Alternatively, new studies on bromine could be done to enhance this meager database.

We suggest four courses for EPA action on the bromine AEGLs. These are, in no particular order, as follows:

1. Explore categorical regression as an alternate way to develop the bromine AEGLs; as you know well, this EPA method has strong theoretical support and multiple examples.

2. Investigate a full translation of the Rupp and Henschler (1967) paper, and discuss these results with the authors, if possible. This study is important in the development of AEGLs for bromine, but the current description and interpretation are insufficiently transparent to support the use this study directly.

3. Reconsider setting the bromine AEGLs on the basis of chlorine. EPA successfully used this approach in its 1997 draft of the bromine AEGL. Moreover, this approach is entirely consistent with Figures 6, 7, and 8 of Rupp and Henschler (1967), where approximately 2 to 3 fold differences are seen between bromine and chlorine responses in nose and throat irritation and headache. Despite problems associated with the reporting of this study, these internal results are likely to be consistent among themselves, and, thus, the 2 to 3 fold differences appear real.

4. Encourage industry colleagues to conduct some simple experimental animal or human experiments with bromine. EPA has an inhalation research facility in RTP where such testing, appropriately reviewed by ethical boards, could be done.

We thank EPA for allowing us the opportunity to comment on this bromine risk assessment. Your willingness to consider scientific peer input adds to the credibility of the risk assessment position that eventually results. We would be willing to work with you on this assessment if needed.

Response to Federal Register Comments on Bromine
National Advisory Committee Meeting - 31, December 10-12, 2003

Additional Comments on EPA's Bromine AEGL

Limited information exists on the dose-response of bromine acute toxicity. The only such data available are from two human experiments: Matt (1889) and Rupp and Henschler (1967). As indicated in the current AEGL document, many secondary references (Henderson and Haggard, 1943; Flury and Zernik, 1931; Lehman, 1887; Withers and Lees, 1986) cited the data of Matt (1889) who exposed three volunteers to bromine vapor. These data indicated that 1-2 ppm could be tolerated by workers indefinitely, 3.5 ppm is tolerable for one-half to 1 hour, and 4 ppm is intolerable for work conditions. These results are limited due to questionable vapor generation methods and unit conversion in data analysis. The other study was conducted by Rupp and Henschler (1967) who exposed healthy volunteers (20/dose group) to bromine at concentrations ranging from 0 to 0.9 ppm, and recorded the subjective response every 5 minutes during 30 minutes of exposure. This study showed that the bromine odor was perceived at 0.01 ppm; however, bromine odor even at concentrations of 0.1 ppm could not be clearly identified. At 0.02-0.05 ppm the exposed subjects clearly experienced nose and throat irritation as well as headache. Between 0.5 and 0.9 ppm, the irritation was so severe that even a 5-minute exposure was perceived as extremely uncomfortable or barely tolerable. The severity of the bromine effects did not increase at or above 0.5 ppm bromine.

These data are the best dose-response information available at this time for conducting a quantitative dose-response analysis for acute exposure to bromine. However it should be noted that these studies were conducted long time ago. Since then, there have been significant improvements in experiment design and analytical technology. Therefore, it is highly recommended to conduct a new human study in order to better define the acute dose response for this chemical.

During reviewing this AEGL document, the biggest challenge to us was to extract correct information from the critical study (Rupp and Henschler 1967) because the paper was published in German. We would recommend that if any of the original paper in foreign language is going to be used as the basis for deriving a risk value, this paper should be translated into English and its translated version should be made available to the public in order to allow other scientists who might have difficulty to understand the foreign language to review the paper. Otherwise, differences in understanding of the original paper due to variations in language skill might lead to different conclusions.

In addition, there are some concerns regarding the experiment design, data presentation and comparability of the results from Rupp and Henschler (1967) study. As discussed in the AEGL document, one of the shortcomings was the lack of control in the study. However, based on our understanding of the paper, the authors stated in the paper that 0-0.9 ppm bromine were used in the experiment, thus, suggesting the presence of a control group. Nevertheless, the control group data were not presented in the paper. Therefore, it is impossible to evaluate the treatment responses in comparison to the control group. The AEGL document also indicated that in the

same study, Rupp and Henschler (1967) reported sensory irritation for chlorine at concentrations that proved to be non-irritating in later well-conducted studies. This finding indicates a possible over estimation of the sensory irritation for bromine because a similar technique was used in the treatment, air sampling, and sample analytical analysis. Since this is only an indirect comparison in nature, and there is no new bromine study available to provide better sensory irritation effective dose, the Rupp and Henschler (1967) study still constitutes the best data source available for bromine dose-response assessment. However, its use for the development of AEGLs must be tempered with the knowledge that the resulting AEGLs might be too low. Additional research in this area is highly desirable.

Based on the data from Rupp and Henschler (1967) study, EPA derived the current AEGL-1 and AEGL-2. The AEGL-1 was based on that eye irritation, but not nose or throat irritation, occurred during a 30-minute exposure to 0.1 ppm, and at concentrations ≥0.5 ppm, there was a stinging and burning sensation of the conjunctiva. Therefore, the 30-minute 0.1 ppm concentration was divided by an intraspecies uncertainty factor of 3 to protect susceptible individuals, which resulted in an AEGL-1 of 0.03 ppm for 30-minute exposure.

The 0.1 ppm concentration judged to cause only eye irritation was contradictory to our understanding of the paper as summarized above and the TOXNET abstract which states: "*subjective nose and throat irritation, and even headache, were evident at 0.1 ppm chlorine; similar manifestations occurred at bromine levels ranging from 0.02 to 0.05ppm*". Again, individual understanding of the original paper plays a significant role in interpretation of the results.

We seek clarity from EPA on its interpretation of whether AEGL-1 is the threshold (e.g., a LOAEL), or a maximal subthreshold dose (e.g., a NOAEL). Depending on this interpretation, this level should cause, or not cause, *notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation exposure."* This definition suggests that the point of departure (0.1 ppm of bromine) for AEGL-1 should cause, or not cause, *notable discomfort, irritation, or certain asymptomatic, non-sensory effects*, which should also include nose and throat irritation as well as headache. It may not be true if the TOXNET abstract and our understanding of the paper are correct. We recommend that EPA double check the results from the original paper which was used as the basis for deriving currently AEGL-1.

The current AEGL-2 was based on the concentration of 1 ppm for 30 minutes, which the volunteers in the study found irritating (stinging and burning sensation of the conjunctiva and nose and throat irritation). The 30-minute 1 ppm value was divided by an intraspecies uncertainty factor of 3 to protect susceptible individuals, which resulted in an AEGL 2 of 0.33 ppm for 30-minute exposure.

We also seek clarity from EPA on its interpretation of whether AEGL-2 is the threshold (e.g., a LOAEL), or a maximal subthreshold dose (e.g., a NOAEL). Depending on this interpretation, this level should cause, or not cause, impaired ability to escape and this should also include severe eye and respiratory irritation, and headache, which may lead to impaired ability to escape. Based on our understanding of the paper, 0.5 to 0.9 ppm of bromine resulted in the irritation that was so severe that even a 5-minute exposure was perceived as extremely uncomfortable or barely tolerable. The severity of the bromine effects did not increase at or above 0.5 ppm bromine. Therefore, the 1 ppm used as the basis for deriving the AEGL-2 can cause severe eye and respiratory irritation, which may impair the ability to escape.

The proposed AEGL-1 and AEGL-2 for 30 minutes were time-scaled to the other AEGL exposure durations using the $C^{2.2} \times t = K$ relationship derived from the mouse lethality study (ten Berge 1986). It should be noted that AEGL-1 and AEGL-2 are based on irritation response while the $C^{2.2} \times t = K$ relationship were derived from the lethality study. As stated by EPA: the *use of lethality data as the basis for determining an extrapolation for milder effects may not be appropriate, especially when extrapolating to a shorter duration. ... The use of the exponent in the above equation derived based on lethality could overpredict the concentrations leading to less time-dependent mild effects when extrapolating to shorter durations. For these reasons, the use of the limiting value of C = K, that is to assume the same concentration is an equivalent effect level when extrapolating to shorter durations, is a reasonable default."* Actually, the dose-response from Rupp and Henschler (1967) already showed that between 0.5 and 0.9 ppm, the irritation was so severe that even a 5-minute exposure was perceived as extremely uncomfortable or barely tolerable indicating that the maximal tolerable response has been reached as early as 5 minutes. Therefore, for extrapolation of AEGL-1 and AEGL-2 which are based on irritation responses, it is recommended to use the $C = K$ instead of the $C^{2.2} \times t = k$ relationship to extrapolate 30-minute exposure AEGLs to 10 minutes of exposure. Alternatively, and perhaps preferably, categorical regression could be used to model this data directly.

For example, since AEGLs are actually the risk values for various severities of responses ranging from mild irritation, severe response and eventually death, the best way to conduct dose-response analysis associated with exposure duration is through categorical regression. The categorical regression is a type of meta analysis that allows combining all the dose-response information from different experiments using different animals species or humans tested at various exposure concentration and durations. Based on the available dose- and time-response information, it can provide estimated concentrations for certain exposure duration in specific species; therefore, it directly estimates AEGLs for each exposure duration. Since the default approach of $C^n \times t = K$ relationship has many limitations, and categorical regression methodology is readily available at EPA, it is recommended to use categorical regression approach to conduct exposure duration extrapolation for AEGLs. At least, this method can serve as a reference value for default calculation.

Response to Federal Register Comments on Bromine
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Summary
Because a critical paper was published in foreign language, differences in understanding the results from the paper may lead to different conclusions among risk assessors. We highly recommend an official translation of the paper, made available for public review. We can work with EPA, industry and others to develop this translation if needed. Furthermore, we think that the Rupp and Henschler (1967) study is currently the best dose-response data available for conducting a quantitative dose-response analysis, but additional clarity is needed in its results before a final interpretation can be made for the bromine AEGLs. In terms of duration extrapolation, we recommend the use of $C = K$ instead of $C^n \times t = K$ to extrapolate across durations for AEGLs 1 and 2, as a default. Our preferred method is to use categorical regression to directly estimate duration specific effective concentration. Finally, we encourage EPA, industry and others to conduct additional human testing for this chemical to further refine levels appropriate for the protection of public health.

Response:
The National Advisory Committee thanks TERA for the full translation of the Rupp and Henschler 1967 paper.

The NAC agrees that the Rupp and Henschler 1967 paper has several shortcomings including lack of a reported control group, uncertain analytical measurements, and unclear explanations of some of the reported data. Our explanations of the table and figure are as follows. Table 2 refers to odor alone, and shows that, as expected, the intensity of odor increases with increasing concentrations from 0.01 to 1.0 ppm. The "intensity" of odor became "strong" to "very strong" above 0.2 ppm. Unfortunately, the scoring system was not explained. In Figure 4, concentrations increased from 0.1 to 0.9 ppm over a period of 60 minutes. Eye irritation appears to start at ≤0.1 ppm. As stated by Rupp and Henschler, concentrations of 0.5 to 0.9 ppm (experienced over a 5-minute period) were uncomfortable.

Because of the difficulty in interpreting the Rupp and Henschler (1967) paper, the NAC contacted Dr. Henschler for his interpretation of the paper. We specifically asked his opinion on what concentrations of bromine would correspond to our AEGL levels. His reply (letter from Dr. Henschler to Sylvia Talmage, dated December 21, 1999) states that a level of discomfort in accord with the AEGL-1 would be 0.5 ppm. He further states that none of the tested concentrations meet the definitions of the AEGL-2 and AEGL-3 when applied to healthy subjects.

The NAC agrees that additional toxicity data would be helpful. To that end, the NAC asked the producers of bromine to undertake additional toxicology tests to support development of realistic AEGL values (personal communication from Larry Gephart, chemical reviewer for bromine, NAC, to Dr. John Biesemeier, Great Lakes Chemical Company, dated April 2, 1998). Specifically, we asked for an "Alarie" irritancy test with

mice and 1- and 4-hour LC_{50} studies in rats. Our letter was forwarded to the Chemical Manufactures' Association Brominated Flame Retardant Industry Panel. That panel declined to perform the studies based on (1) lack of scientific basis for performing the studies, and (2) animal use issues, due to bromine's corrosiveness (response letter from Wendy Sherman, Brominated Flame Retardant Industry Panel, dated March 19, 1999). Without additional data, and in light of some of the uncertainties associated with the Rupp and Henschler study, the NAC felt it necessary to apply protective uncertainty factors to the sparse data.

Based on insufficient data and questionable data quality, the NAC does not think that development of AEGL values via categorical regression is appropriate. However, the NAC will reconsider some of the AEGL values based on the following factors. (1) The bromine TSD was written in 1997. Since that time the NAC has adopted the policy of "flatlining" AEGL-1 values for irritants. Using the same value across all AEGL-1 exposure durations is based on the premise that adaptation occurs to the slight irritancy that defines the AEGL-1. "Flatlining" will also be considered for the AEGL-2.
(2) Based on relative irritancy to other halogens, the AEGL-1 and AEGL-2 values do not appear in line with those of chlorine and fluorine. The NAC will discuss the relative potency of the halogens at its December 2003 meeting.

As noted by TERA, there are differences in the interpretation of the definitions of the AEGLs. The NAC has followed the guidance in the Standard Operating Procedures that the basis for each AEGL is an effect level, and that meeting the definition of the AEGL would be a NOAEL for that AEGL level. That is, mild sensory irritation is a NOAEL for the AEGL-1. Notable discomfort would be a LOAEL for the AEGL-1.

American Chemistry Council
Comments:

The American Chemistry Council's Bromine Transportation Security Task Group (the "Task Group") appreciates the opportunity to submit the following comments on the proposed Acute Exposure Guideline Levels (AEGLs) for bromine (68 Federal Register 42710; July 18, 2003). Also, the Task Group appreciates EPA granting an extension for filing comments on the Bromine AEGLs until September 8, 2003. The Task Group represents the major U.S. manufacturers and importers of bromine (CAS #7726-95-6).

The Panel has reviewed the proposed AEGL values presented in the July 18, 2003, Federal Register notice and the supporting document - the "Public Draft: of the Proposed Acute Guideline Levels (AEGLs) for Bromine - that provide the detailed toxicology review and derivation of these proposed AEGLs. The applied uncertainty factors and extrapolation for the time periods appear to be consistent with the established guidelines published in "Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous

Chemicals (NRC, 2001).

The Task Group recognizes that the National Advisory Committee/AEGL Committee wishes to produce meaningful and useful guidance in the event that bromine is spilled and the potential for general population exposures to bromine vapors becomes eminent. This document is an excellent review of the available data and we appreciate the time and effort that were expended on behalf of the USEPA in preparing it. Dr. Talmage has certainly reviewed the data carefully and concisely and the AEGL Committee has used these documents according to its own SOP for developing guidance. The Task Force offers the following comments on the proposed AEGL values.

The AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort. "Hypersusceptible" individuals are not considered in these predictions. Below the AEGL-1 concentration, irritation, mild odor, taste, or certain asymptomatic, non-sensory effects are expected. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

The Task Group does not feel that the proposed AEGL-1 values are accurate and useful numbers that meet the definition and needs of an AEGL-1 for the following reasons:

1. There are concerns about the selection of the study by Rupp and Henschler (1967) as the key study because of obvious design flaws (see p. 10 of the May 2002 version of the Bromine AEGL Technical Support Document (TSD)). There is no control population, which is appropriate for any subjective human observations. Also, as described by the authors themselves, is the questionable nature of the atmospheric concentration of bromine to which the human volunteers were exposed due to the sampling technique. This issue is validated by the results obtained for chlorine by Rupp and Henschler (1967) compared to the results obtained in a more recently conducted, well-controlled study by Rotman et al. (1983) (see p. 10 of the Bromine TSD). The previous study reported irritation after 15 minutes exposure to 0.5 ppm chlorine and the latter reported no serious symptoms of irritation at 1 ppm chlorine for 8 hours. Previous AEGL Committee reviewers concluded that "The lack of controls in the Rupp and Henschler (1967) study call into question the results of this study (OSHA 1989). The more recent studies of odor threshold also call into question the results of the Rupp and Henschler study" (pp. 4 and 7, October 1997 version of the Bromine AEGL TSD).

2. The application of an intraspecies uncertainty factor of 3 appears unwarranted in this case because the eye irritation threshold value of 0.1 ppm for 30 min is not expected to vary between individuals. As stated in the draft TSD, 1997, bromine is a direct-acting irritant; effects are not expected to differ among individuals. This irritation is most likely to

trigger tearing and would not have a variable threshold like respiratory effects in sensitive subpopulations.

3. The time-scaling formula derived from the ten Berge et al. (1986) analysis of the work of Bitron and Aharonson (1978) was based on an analysis of exposure concentration (C), exposure time (t) and mortality (LC_{50}) in male albino mice exposed to bromine. In this case, mortality is a systemic toxic effect of exposure to bromine. The ten Berge et al. formula derived from the work of Bitron and Aharonson could justifiably be applied to predicting C, t or LC_{50} for a similar acting chemical. However the ten Berge et al. formula should not be used to derive C, t or EC_{50} when the effect is irritation or other direct toxicity effect and not the effect upon which the correlation was derived. We have been advised that it is now the policy of the Committee not to apply time scaling for irritant vapor concentrations for AEGL-1 time points. Since the measured bromine value for irritation from the Rupp and Henschler 1967 study was 0.1 ppm, the unscaled level for all AEGL-1 time points will likely be set at 0.03 ppm due to the application of an additional safety factor to protect sensitive subpopulations. The Task Group believes the AEGL- 1 time points should be unscaled, similar to the treatment for chlorine.

4. The Task Group has concerns about the usefulness of such low AEGL-1 values in an emergency response situation. To the best of our knowledge, there is no convenient way to detect bromine at the proposed AEGL-2 levels; the most sensitive hand-held halogen or photoionization detectors typically have limits of detection at 0.1 to 0.05 ppm.

Therefore, the Task Group requests that the AEGL Committee consider adoption of an AEGL- 1 value of 0.1 ppm across all time points. This value more accurately reflects the AEGL-1 definition as described above. This value is further supported by evidence from an OSHA (1997) reference in the document (see p. 13 of Bromine TSD) that reports current worker exposures to be in the vicinity of 0.00 to 0.18 ppm - no adverse effects are associated with these levels.

The AEGL-2 value is the airborne concentration (expressed as pprn or mg/m3) of a substance above. which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape. Again, "hypersusceptible" individuals are not included in the estimates.

The Task Group does not feel that the proposed AEGL-2 values are accurate and useful numbers that meet the definition and needs of an AEGL-2 value as described above for the reasons stated in items 1,2 and 3 for the AEGL-I.

Additionally, the Task Group has concerns that the proposed AEGL-2 values do not meet the above definition for an AEGL-2, because the toxicity endpoint chosen (eye, nose and throat irritation in humans) is not an irreversible or other serious, long-lasting adverse health effect, nor

impairs ability to escape. There is also some concern about the usefulness of such low proposed AEGL-2 values in emergency planning and response situations.

While the Task Group realizes that reliable human data with higher exposure concentrations is unavailable, we would like to propose two possible alternative approaches to addressing the issue. We would suggest that the Committee consider using the basis for the derivation of AEGL-2 values for chlorine (Rotman et al. (1983) and D'Alessandro et al. (1996)) and adapt it to bromine using the regression analysis developed for time scaling of bromine ($C^{2.2} \times t = k$) from the data of Bitron and Aharonson (1978). This would incorporate the characterization of a dose-response relationship for bromine using chlorine data, which would be conservative since chlorine is known to be more toxic than bromine (Bitron and Aharonson (1978)).

Alternatively, one could calculate the difference observed between the threshold for sensory irritation from the older vs. the newer chlorine studies, Le., Rupp and Henschler (1967) vs, Rotman at al. (1983) and D'Alessandro et al. (1996) and use this same factor to "normalize" the bromine data from Rupp and Henschler (1967). Although the latter method is less scientific, these calculations could be carried out and compared to determine if there is a way to use the available data to arrive at more realistic levels considered safe for susceptible populations. This is a reasonable approach since we do know the primary mechanism of toxicity for bromine and chlorine is respiratory irritation and there is considerable monitoring data to support informed judgments about potential effects of exposures.

AEGL-3 is the airborne concentration (expressed as ppm or mgm^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

The Task Group does not feel that the proposed AEGL-3 values are accurate and useful numbers that meet the definition and needs of an AEGL-3 value as described above for the following reasons:

1. The data of Schlagbauer and Henschler (1967) have some of the same detractors as the Rupp and Henschler (1967) study. Withers and Lee (1986) noted that in reviewing the data for chlorine and bromine, the chlorine 30-minute LC_{50} value of Schlagbauer and Henschler (1967) was lower than the values of other researchers.

2. No justification is given in the document for using the mouse lethality data of Bitron and Aharonson (1978) to derive the concentration-exposure duration relationship while the data of Schlagbauer and Henschler (1967) were used as the actual basis for the AEGL-3. Since the data of Schlagbauer and Henschler (1967) did report a reliable concentration-effect relationship, these data should be used for consistency.

3. Presumably the mouse data of Bitron and Aharonson (1978) were considered inappropriate to use since there were many delayed deaths due to bronchopneumonia.. Therefore, it may be inappropriate to use the existing lethality data for bromine to derive AEGL-3 levels. In order to arrive at more useful, reliable numbers, we feel it is appropriate to use the chlorine lethality data to derive acceptable bromine AEGL-3 levels (using the regression analysis developed for bromine). Again, this would be conservative because chlorine was shown to be more toxic than bromine in the comparative LC_{50} studies. Alternatively, all existing bromine and chlorine data might be used in a regression model(s) where each data set reinforces the other data sets.

Response:

AEGL-1. Questions concerning the quality of the Rupp and Henschler (1967) paper were addressed in the previous response.

It has been a general principal of the NAC to apply an intraspecies uncertainty factor of 3 to irritants at the AEGL-1 level. This uncertainty factor is considered sufficient to protect asthmatics should the gas reach the bronchi. Both eye and throat irritation were mentioned at 0.1 ppm.

The NAC will consider "flatlining" the AEGL-1 value as they have done for other irritants. The value would be that on which the present values are based.

The NAC does not derive values based on chemical detectability, although this may be a consideration. For many emergency situation scenarios, there will be no actual measurements. Predicted atmospheric concentrations will be based on modeling results. The NAC will reconsider the AEGL-1 value at the December 10-12, 2003 meeting.

AEGL-2: The originally-proposed bromine AEGL-2 values were based on chemical similarity to chlorine. The NAC chose instead to use the empirical data from the Rupp and Henschler (1967) paper. Given the problems with interpretation of the Rupp and Henschler paper, the NAC will reconsider the AEGL-2 values at the December 10-12, 2003 meeting. The proposed bromine values are not in line with the final chlorine values. The chlorine AEGL-2 values protect against an asthmatic attack in a sensitive individual. Given that bromine is more water soluble than chlorine, and thus better scrubbed in the upper respiratory passages, and that bromine is less toxic than chlorine, as evidenced by LC_{50} values, the bromine values should reasonably be as high as or higher than the chlorine values.

AEGL-3. Both the Bitron and Aharonson (1978) and Schlagbauer and Henschler (1967) papers have shortcomings. However, as noted by the commenter, the Schlagbauer and Henschler mouse LC_{50} is below that of more recent researchers.

As noted, the data of Schlagbauer and Henschler (1967) did report a reliable concentration-effect relationship. Unfortunately, their data do not provide a concentration-exposure duration relationship for a single endpoint (they looked at only 30 minutes). At least two, preferably three, concentration-exposure duration relationships for the same endpoint are needed to calculate the "n" value in the $C^n \times t = k$ relationship. Therefore, the only data available for time scaling, the data of Bitron and Aharonson (1978) were used.

The NAC may reconsider the data of Bitron and Aharonson (1978) as the basis for the AEGL-3. Bitron and Aharonson's chlorine data for the mouse is more in line with that of several other researchers than that of Schlagbauer and Henschler. In addition, based on the predicted greater scrubbing of bromine compared to chlorine in the upper respiratory tract and the greater toxicity of chlorine relative to bromine [mouse LC_{50} values for bromine and chlorine in both the Bitron and Aharonson (1978) and Schlagbauer and Henschler (1967) papers], the AEGL-3 values for bromine should not be lower than those for chlorine.

Comments to the Federal Register: Bromine

1. Toxicology Excellence for Risk Assessment (TERA)
2. American Chemistry Council (ACC)

TERA

1. Explore categorical regression
2. Full translation of Rupp and Henschler (1967) key study
3. Reconsider setting bromine AEGLs on the basis of chlorine
4. Encourage industry to conduct simple experimental animal or human experiments with bromine

ACC

Numbers are not accurate and useful

AEGL-1

1. Design flaws in Rupp and Henschler 1967 paper
2. Uncertainty factor of 3 unwarranted
3. Time scaling not warranted
4. Bromine undetectable at the AEGL-1

AEGL-2

1. Design flaws in Rupp and Henschler 1967 paper
2. Uncertainty factor of 3 unwarranted
3. Time scaling not warranted
4. Endpoint does not meet the definition of an AEGL-2

AEGL-3

1. Data of Schlagbauer and Henschler (1967) are flawed
2. Time scaling used from another study
3. Suggest using the chlorine data for bromine

ACUTE EXPOSURE GUIDELINE LEVELS
for
BROMINE:
Re-evaluation of AEGL Values

National Advisory Committee for AEGLs Meeting 31
December 10-12, 2003

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Reviewer:
Larry Gephart

BROMINE

Relative Irritancy and Toxicity of Bromine and Chlorine

At low concentrations, bromine may be more irritating to the upper respiratory passages because it is more water soluble than chlorine and thus more readily scrubbed.

At concentrations causing mortality, chlorine is more toxic than bromine, probably because it more readily penetrates to the lungs than bromine.

LC_{50} values differ by a factor of 1.4 to 2:

Relative Toxicities of Chlorine and Bromine to the Mouse		
Chemical	30-Minute LC_{50}	Reference
Chlorine	203 127	Bitron and Aharonson 1978 Schlagbauer and Henschler 1967
Bromine	424 174	Bitron and Aharonson 1978 Schlagbauer and Henschler 1967

BROMINE

WHY Revisit the Bromine AEGL Values??

1. They are not in line with the values derived for other halogens.
2. The studies on which the bromine AEGL values are based have serious shortcomings. For example, for chlorine in the Rupp and Henschler (1967) paper, subjects reported discomfort at 0.5 ppm. In more recent, well-conducted studies, no discomfort was experienced at 0.5 ppm; discomfort was reported at 1.0 ppm.
3. The study author (Dr. Henschler) does not agree with the NAC's interpretation of his data.
4. The AEGL values are not in line with workplace standards (0.1 ppm). The 10-minute AEGL-1 value is half of the 8-hour ACGIH TLV. The 8-hour AEGL-2 is less than the 8-hour ACGIH TLV.
5. The AEGL-1 value, if based on slight irritation, should be "flatlined."

BROMINE
Comparison of AEGL Values with Other Halogens

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1					
fluorine	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm
chlorine	0.5 ppm	0.5 ppm	0.5 ppm	0.5 ppm	0.5 ppm
bromine	0.055 ppm	0.033 ppm	0.024 ppm	0.013 ppm	0.0095 ppm
AEGL-2					
fluorine	20 ppm	11 ppm	5.0 ppm	2.3 ppm	2.3 ppm
chlorine	2.8 ppm	2.8 ppm	2.0 ppm	1.0 ppm	0.71 ppm
bromine	0.55 ppm	0.33 ppm	0.24 ppm	0.13 ppm	0.095 ppm
AEGL-3					
fluorine	36 ppm	19 ppm	13 ppm	5.7 ppm	5.7 ppm
chlorine	50 ppm	28 ppm	20 ppm	10 ppm	7.1 ppm
bromine	19 ppm	12 ppm	8.5 ppm	4.5 ppm	3.2 ppm

BROMINE

"A threshold for uncomfortable (subjective) effects can be set, on the basis of our findings, at 0.5 ppm, which is in line with your AEGL-1."

"A threshold for irreversible effects, in the sense of irrepairable tissue damage, can not be derived from our studies and those of others; what can be said is that it should be expected to be higher then 2 ppm."

Re: AEGLs for Bromine and Chlorine
Prof. Dr. D. Henschler
Institute für Toxikologie
Versbacherstrasse 9, Würzburg
December 21, 1999

BROMINE

Suggestion: Consider making the bromine AEGL-1 values half of the chlorine AEGL-1 values:

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1					
fluorine	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm
chlorine	0.5 ppm	0.5 ppm	0.5 ppm	0.5 ppm	0.5 ppm
bromine	0.25 ppm	0.25 ppm	0.25 ppm	0.25 ppm	0.25 ppm

Bromine is thought to be more irritating than chlorine, based on its greater water solubility and thus greater scrubbing in the upper respiratory passages.

BROMINE

Suggestion: Consider making the bromine AEGL-2 values equal to, or half of, the chlorine AEGL-2 values (the reasoning for the same values is that bromine is better scrubbed in the upper respiratory tract and will not induce the asthmatic-like attack that occurred with chlorine at 1.0 ppm):

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2					
fluorine	20 ppm	11 ppm	5.0 ppm	2.3 ppm	2.3 ppm
chlorine	2.8 ppm	2.8 ppm	2.0 ppm	1.0 ppm	0.71 ppm
bromine	2.8 ppm	2.8 ppm	2.0 ppm	1.0 ppm	0.71 ppm

Support: Monkeys exposed to 2.3 ppm chlorine for 6 hours/day, 5 days/week for 1 year had ocular irritation and minimal lesions of the upper respiratory tract.

BROMINE

Suggestion: Consider making the bromine AEGL-3 values equal to the chlorine AEGL-3 values. This is a conservative approach as bromine is less toxic than chlorine.

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3					
fluorine	36 ppm	19 ppm	13 ppm	5.7 ppm	5.7 ppm
chlorine	50 ppm	28 ppm	20 ppm	10 ppm	7.1 ppm
bromine	50 ppm	28 ppm	20 ppm	10 ppm	7.1 ppm

BROMINE

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	0.25 ppm	0.25 ppm	0.25 ppm	0.25 ppm	0.25 ppm
AEGL-2	2.8 ppm	2.8 ppm	2.0 ppm	1.0 ppm	0.71 ppm
AEGL-3	50 ppm	28 ppm	20 ppm	10 ppm	7.1 ppm

Methanol

(CAS No. 67-56-1)

Discussion of NAS-COT Comments

NAC/AEGL Meeting 32, April 19-21, 2004

The AEGL document on methanol was reviewed by the Subcommittee on Acute Exposure Guideline Levels of the National Academy of Sciences Committee on Toxicology on January 27-29, 2003.

The subcommittee had many recommendations (including many editorial comments). Major concerns were

(1) COT suggested to use a weight-of-evidence discussion of clinical information rather than a single key study to set a blood methanol concentration as a starting point for derivation of AEGL-1, -2 and -3 values;

(2) for calculation of methanol concentrations in air not the PBPK model by Perkins, but another validated model should be used;

(3) a pharmacokinetic study should not be used as key study for AEGL-1;

(4) the developmental toxic effects in rodents should not be used to derive AEGL-2 due to the fundamental differences in metabolism between rodents and primates;

(5) instead of using a questionable pharmacokinetic model to extrapolate back to a maximum blood concentration for derivation of AEGL-3, a blood level should be selected that is associated with clinically significant but reversible symptoms.

The COT subcommittee will reevaluate a revised methanol AEGL document after the NAC/AEGL committee responds to the concerns.

Comments on AEGL-1

COT: The pharmacokinetic study of Batterman et al. (1998) should not be adopted as key study unless factual documentation was obtained to support the claim that inhalation of methanol at 800 ppm for 8 hours produced no adverse effects. Such documentation might include the protocol indicating that subjects were to report symptoms, the informed consent forms encouraging reporting of adverse symptoms etc. Recollection by the second author does not suffice. The study was not single or double-blinded. Secondhand information from a study designed for other purposes cannot be considered reliable.

A threshold exposure for mucus membrane irritation and inebriation appears to be an 8-hour 1000-ppm inhalation exposure. The blood methanol level should be 35-40 mg/l at the end of such an exposure. A validated PBPK model should be used for time scaling.

The proposed AEGL-1 values are too conservative. An 8-hour AEGL-1 of 500-750 ppm would be more reasonable.

Reply: Batterman reported no effects at methanol blood levels of 30.6 mg/l. However, due to insufficient reporting, interindividual variability and limited sample size, a somewhat lower methanol blood level would be considered more adequate.

In addition, 30.6 mg/l resulted in calculated air concentrations (by use of the models from Perkins or Bouchard) well above 1000 ppm after 10 minutes, 30 minutes and 1 hour. These concentrations are associated with irritation, headache, dizziness, blurred vision and nausea/upset stomach after short term occupational exposure and therefore above AEGL-1 level.

In consequence, the derivation of AEGL-1 based on blood concentrations does not provide AEGL-1 estimates with less uncertainties than the usual approach using UFs on air concentrations.

Comments on AEGL-2

COT: The mouse developmental studies should not be used as a basis for AEGL-2. The toxicokinetics and metabolism of methanol are too different in mice and humans to extrapolate findings from one species to the other. Even though a part of the UF can be used to account for pharmacodynamic differences, application of the total factor of 10 on the internal concentration is inappropriate.

The NAC is to be commended for its use of a PBPK model for species and time extrapolations. However, it should be rectified or justified why in the model equations used there is no input based on the oral or intravenous routes. NAC questions the derivation of Michaelis-Menten parameters from single subjects receiving single doses.

From clinical experience, it is known that blood methanol levels <100 mg/l do not lead to acute or chronic toxicity. It is widely accepted that CNS symptoms may begin to appear at >200 mg/l. Ethanol therapy is recommended for patients with blood levels >200 mg/l.

A logical means of deriving AEGL-2 would be selection of a blood methanol level, e.g. 150-200 mg/l, associated with modest, reversible CNS depression. A PBPK model should be used for time scaling.

Comments on AEGL-2

Reply: The NAC/AEGL committee should confirm the relevance of developmental toxic effects for humans.

This relevance has been questioned by Clary (RTPh 2003): he argued that the NOEL for teratogenic effects in mice (2000 ppm x 7 h) would correspond to a total dose of 1638 mg/kg. This dose level would correspond to a lethal dose in humans (at bolus ingestion) and therefore the methanol-induced developmental effect would be irrelevant in humans.

However, US-EPA (2001) and NTP-CERHR (2002) determined developmental toxic effects as a relevant endpoint for humans and considered a blood concentration of 10 mg/l as a safe level. Starr and Festa (2003) proposed a RfC based on the developmental toxicity data by Rodgers in mice (BMC_{10} 97mg/l, UF 3x10; 3.2 mg/l, corresponding to 135 mg/m³ using the Bouchard model).

The practice guidelines on the treatment of methanol poisoning of the American Academy of Clinical Toxicology (2002) could be used to select blood levels. At methanol levels of >200 mg/l ethanol therapy is recommended, while peak concentrations below 200 mg/l are usually associated with asymptomatic individuals. Visual dysfunction occurs when formate concentrations exceed 200-300 mg/l. However, it should be considered that >90% of all underlying intoxications involve adult males and that possible teratogenic effects are not discussed. Therefore, using a MF or UF of 2 a starting level of 100 mg/l methanol would have to be chosen.

In order to use the PBPK model of Bouchard et al. (2001), Prof. Michele Bouchard, University of Montreal, did the necessary calculations. The results are in very good agreement with those from the Perkins model.

Comments on AEGL-3

COT: The NAC used a reasonable approach to calculate AEGL-3s. The NAC should clarify that it used a MF of 2 to conservatively estimate a peak blood methanol concentration from a calculated peak blood level in a fatal case of methanol ingestion.

It is logical to try to discern what the lethal blood levels were. It does not seem prudent, however, to use a questionable pharmacokinetic model to do this extrapolation. A better approach might be to select blood levels that are associated with clinically significant but reversible symptoms. A starting point of 300-400 mg/l is suggested with the steepness of dose-response relationship and the extent of intersubject variability in mind. A PBPK model should be used for time scaling.

It would be preferable to use blood formate instead of methanol levels.

Reply: The NAC/AEGL committee should discuss if a methanol level could be selected on a weight-of-evidence discussion, AEGL-3 values would not be based on a key study.

The practice guidelines on the treatment of methanol poisoning of the American Academy of Clinical Toxicology (2002) could be used to select blood levels. Peak blood methanol levels of >500 mg/l indicate serious poisoning and a blood concentration of >500 mg/l formate indicates a poor prognosis. In clinical experience the formate levels corresponded well with blood pH (acidosis). Using a MF or UF of 2 a starting level of 250 mg/l methanol or formate could be chosen, because clinical experiences is mostly based on intoxications on adult males.

This would make the calculations of peak blood methanol levels in poisoning cases, criticized by NAS, unnecessary.

The PBPK model of Prof. Bouchard was used to do calculations on the basis of methanol and/or formate levels. The results are in very good agreement with those from the Perkins model.

Methanol - AEGL-1

Keystudy: Batterman et al. (1998); Franzblau, pers. commun. (1999)

Endpoint: No odor, irritation, headache, alteration of vision or other non-specific symptoms in humans after exposure to 800 ppm for 8 hours

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

10 min = 30 min, because no studies were available that investigated effects after short exposure durations and because also for longer exposure periods characterization of the dose-response relationship for slight effects on the central nervous system is lacking.

Total uncertainty factor: 3

Interspecies: not applicable

Intraspecies: 3

because exposure level was considered below effect threshold and thus the effect level was less severe than AEGL-1 definition. However, interindividual variability for slight neurotoxic effects (e.g. headache) is likely to exist (but cannot be quantified) and, thus, slight effects in general population at 800 ppm cannot to be excluded.

AEGL-1 Values for Methanol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
670 ppm 880 mg/m^3	670 ppm 880 mg/m^3	530 ppm 690 mg/m^3	340 ppm 450 mg/m^3	270 ppm 350 mg/m^3

Support: occupational exposure studies indicate effect threshold of 1000 ppm: eye irritation in one duplicating machine operator after 25 min at 1025 ppm (NIOSH 1980), higher frequencies of headaches, dizziness, blurred vision and nausea/upset stomach in duplicating machine operators after mean exposure to 1060 ppm (variable exposure time) (Frederick et al. 1984), no more severe effects after higher exposure levels, 3000-5500 ppm for 8 h (Kawai et al. 1991).

Discussion of NAS-COT proposal for AEGL-1

Batterman et al. (1998) reported a blood methanol concentration of 30.6 mg/l after exposure to 800 ppm for 8 hours under resting conditions.

The lack of clinical effects associated with this exposure is only based on a personal communication. However, this statement is supported by estimating the blood methanol level after occupational exposure to about 1000 ppm that was reported to result in increased frequencies of headaches, dizziness, blurred vision and nausea/upset stomach (Frederick et al. 1984). Using a ventilation rate of 10 m^3/ 8-hours, a methanol concentration of about 105 mg/l is predicted by the Perkins model.

This approach would imply a UF of 1.

A level of 30 mg/l is achieved after :

Model	10 min	30 min	1 hour	4 hours	8 hours
Perkins	7000 ppm	2500 ppm	1300 ppm	460 ppm	340 ppm
Bouchard	7450 ppm	2620 ppm	1430 ppm	560 ppm	445 ppm

While this level will be protective of CNS symptoms, irritation is likely to occur at concentrations above 1000 ppm in sensitive individuals. Therefore, the AEGL-1 value would have to be flat lined for 1 hour and 30 and 10 minutes at 1000 ppm.

Alternative AEGL-1 Values for Methanol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1000 ppm	1000 ppm	1000 ppm	460 ppm	340 ppm

Methanol - AEGL-2

Keystudy: Rogers et al. (1993; 1995, ab; 1997); Rogers (1999, p comm)

Endpoint: Mice were exposed on gd 7 to different C-T combinations. Cervical rib induction occurred at CxT products ≥15000 ppm h, but not below 15000 ppm h. The highest NOEL CxT product was 2000 ppm for 7 hours.

Support: In repeated 7-h/d exposure studies during gd 6-15, an increase in cervical ribs was observed at >= 2000 ppm; other malformations, such as exencephaly and cleft palate, occurred at >= 5000 ppm (Rogers et al., 1993). The same type of malformations occurred after a single 7-hour exposure to 10000 ppm (Rogers et al., 1997).

The end-of-exposure blood concentration in mice after exposure was measured as 487 mg/l (Rogers et al., 1993). The UF was applied to the blood methanol concentration resulting in a concentration of 48.7 mg/l, on which calculations of AEGL-2 exposure concentrations were based.

Scaling: A pharmacokinetic model was used to calculate exposure concentrations that would lead to blood methanol concentrations at the end of periods of 8 hours, 4 hours, 1 hour and 30 minutes. The 10-minute value was set at the 30-minute value.

Interspecies UF: 1

because sensitive species was used (blood levels at LOEL was 5fold lower and at NOEL 16fold lower in mice vs. rats) and because toxicokinetic species differences were accounted for by using a pharmacokinetic model

Intraspecies UF: 10

because no information on developmental toxic effects of methanol on humans is available and because also for other chemicals the variability in susceptibility of humans for developmental toxic effects is not well known

AEGL-2 Values for Methanol					
Model	**10 min**	**30 min**	**1 hour**	**4 hours**	**8 hours**
Perkins	11000 ppm	4000 ppm	2100 ppm	740 ppm	530 ppm
Bouchard	12000 ppm	4200 ppm	2300 ppm	870 ppm	680 ppm

Discussion of NAS-COT proposal - AEGL-2

The practice guidelines on the treatment of methanol poisoning of the American Academy of Clinical Toxicology (2002) could be used to select blood levels. At methanol levels of >200 mg/l ethanol therapy is recommended, while peak concentrations below 200 mg/l are usually associated with asymptomatic individuals. Visual dysfunction occurs when formate concentrations exceed 200-300 mg/l. However, it should be considered that >90% of all underlying intoxications involve adult males. Therefore, using a MF or UF of 2 a starting level of 100 mg/l methanol could be chosen.

Using the modified Perkins model for a blood methanol level of 100 mg/l, the following results are obtained.

AEGL-2 Values for Methanol					
Model	**10 min**	**30 min**	**1 hour**	**4 hours**	**8 hours**
Perkins	24000ppm*	8300 ppm	4400 ppm	1500 ppm	1000 ppm
Bouchard	25000 ppm *	8600 ppm	4600 ppm	1700 ppm	1200 ppm

* value could eventually by higher than the AEGL-3 value

Methanol - AEGL-3

Keystudy: Naraqi et al. (1979) Erlanson et al. (1965), Bennett et al. (1953), Gonda et al. (1978)

Endpoint: Lethality in humans after oral intoxication. Lowest calculated peak blood methanol concentration of lethal cases without significant blood ethanol concentrations

peak blood methanol concentration: 1109 mg/l

LOEL-NOEL extrapolation factor: 2

because of the very steep dose-response relationship reported by Gilger and Potts (1955) for rhesus monkeys (no signs of toxicity after 2 g/kg or lower, but death at 3 g/kg or higher) and because conservative assumptions were made in the calculation of peak blood concentrations from the Naraqi et al. (1979) study.

peak blood methanol concentration: 1109 mg/l / 2 = 555 mg/l

Total uncertainty factor: 3 Interspecies: na Intraspecies: 3

because of the very steep dose response-relationship for lethality after oral exposure seen in rhesus monkeys and because a factor 10 would have resulted in blood methanol concentrations of about 55 mg/l which would be far below a level of 130 - 200 mg/l, at which ethanol therapy is recommended.

peak blood methanol concentration: 555 mg/l / 3 = 185 mg/l

Scaling: Exposure concentrations were calculated using a pharmacokinetic model

10 min = 30 min because additional toxic effects, such as respiratory shock, cannot be excluded at the calculated concentration of 44000 ppm and because the value is close to the lower explosive limit in air

AEGL-3 Values for Methanol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
15000 ppm 20000 mg/m^3	15000 ppm 20000 mg/m^3	7900 ppm 10000 mg/m^3	2500 ppm 3300 mg/m^3	1600 ppm 2100 mg/m^3

Alternative Methanol - AEGL-3

The practice guidelines on the treatment of methanol poisoning of the American Academy of Clinical Toxicology (2002) could be used to select blood levels. Peak blood methanol levels of >500 mg/l indicate serious poisoning and a blood concentration of >500 mg/l formate indicates a poor prognosis. In clinical experience the formate levels corresponded well with blood pH (acidosis). Using a MF or UF of 2 a starting level of 250 mg/l methanol or formate could be chosen, because clinical experiences is mostly based on intoxications on adult males.

Using the modified Perkins model for a blood methanol level of 250 mg/l, the following results are obtained.

AEGL-3 Values for Methanol					
Model	**10 min**	**30 min**	**1 hour**	**4 hours**	**8 hours**
Perkins	21000* ppm	21000 ppm	11000 ppm	3600 ppm	2400 ppm
Bouchard	21000* ppm	21000 ppm	11000 ppm	3500 ppm	2300 ppm

Flat line at 21000 ppm because calculated value of 61000 ppm would be above the lower explosive limit.

The Bouchard model calculates maximum blood formate levels between 2.26 and 2.75 mg/l for the different time periods.

Methanol - DERIVATION OF LOA

Study: Hellman and Small (1974)

Odor detection threshold for methanol: 4.26 ppm

Odor detection threshold for n-butanol: 0.3 ppm

OT_{50}: OT(MeOH) * 0.04 ppm /OT(n-butanol): 0.057 ppm

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

$$I = kw * \log (C / OT50) + 0.5$$

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

$3 = 2.33 * \log (C / 0.11) + 0.5$ which can be rearranged to

$\log (C / 0.11) = (3 - 0.5) / 2.33$

$= 1.07$ and results in

$C = (10^{1.07}) * 0.057$

$= 11.8 * 0.057$

$= 6.7$ ppm

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

LOA = 6.7 ppm * 1.33

= 8.9 ppm

The LOA for methanol is 8.9 ppm.

Peter Griem discussed the COT/AEGL's comments, noting that comments on methanol and phenol were conflicting. The COT/AEGL considered the interim AEGL-1 for methanol too conservative and recommended against using the Batterman et al. (1998) study as the key study. Ernie Falke moved and Richard Thomas seconded using a "weight-of-evidence" approach for the AEGL-1 and keeping the values the same. Documentation from the Batterman et al. authors regarding informed consent would be requested. The motion carried (YES:18; NO: 2; ABSTAIN: 0) (Appendix X). For the AEGL-2, the COT/AEGL rejected use of the mouse developmental toxicity studies of Rogers et al. (1993; 1997) because the toxicokinetics and metabolism of methanol are different in mice and humans.

The AEGL-2

The AEGL-3

The LOA

Phenol (CAS No. 108-95-2)

Staff Scientist: Peter Griem, FoBiG, GmbH
Chemical Manager: Bob Snyder, Rutgers

Peter Griem addressed the major COT/AEGL comments which were as follows: (1) the phenol values are too conservative and the ERPG values are more consistent with the toxicologic profile, (2) the use of a NOAEL from a two-week study for the AEGL-1 is too conservative, (3) the NAC needs to reconsider the basis for the AEGL-2 (a fraction of the AEGL-3 values), and (4) the validity of the AEGL-3 key study was questioned.

The NAC decided to retain the AEGL-1 key study (CMA 1998; Hoffman et al. 1999), but add support from a 90-day study with monkeys (5 ppm NOAEL for lung histopathology; Sandage 1961). The interspecies uncertainty factor of 3 was reduced to 1 and the intraspecies uncertainty factor of 3 was retained. Although irritation was the endpoint, the values were time-scaled rather than flatlined as usually done for irritants. It was moved by Marc Ruijten and seconded by John Hinz to accept the revised values. The motion passed (YES: 13; NO: 6; ABSTAIN: 1) (Appendix X).

The basis for the AEGL-2, originally derived by dividing the AEGL-3 by 3, was changed to a combination of the two studies originally used for the AEGL-3 (Flickinger 1976; Brondeau et al. 1990). Although both studies had shortcomings, i.e., aerosol exposures, nominal concentrations, and no description of toxic signs in one study, taken together, they had consistent results. The 8-hour exposure (based on Flickinger [1976]) of rats to 211 ppm (based on vapor concentration in Brondeau et al. [1990]) was used as the point of departure. Based on the small data base and study shortcomings, a modifying factor of 2 was applied. The resulting value was adjusted by

PHENOL

(CAS Reg. No. 108-95-2)

Discussion of NAS-COT Comments

NAC/AEGL Meeting 32, April 19-21, 2004

The AEGL document on phenol was reviewed by the Subcommittee on Acute Exposure Guideline Levels of the National Academy of Sciences Committee on Toxicology on January 27-29, 2003.

The subcommittee had about one hundred recommendations (many of which were of an editorial nature).

Major concerns were

(1) that COT felt that the all AEGL values were too conservative and that the ERPG values were far more consistent with the phenol toxicologic profile;

(2) the use of a NOAEL from a two-week animal study for derivation of AEGL-1;

(3) that AEGL-2 values were derived as a fraction of the AEGL-3 values;

(4) that COT questioned the validity of the AEGL-3 key study.

The COT subcommittee will reevaluate a revised phenol AEGL document after the NAC/AEGL committee responds to the concerns.

Comments on AEGL-1

COT: The AEGL-1 at 10 min to 1 hour is virtually identically with the occupational experience reported by Shamy et al (1994). What "notable discomfort" is associated with the 8-hour AEGL-1, which is less than half the current occupational limits?

Reply: AEGL-1 values are set in order to prevent notable discomfort in susceptible individuals. Thus, for derivation of AEGL-1 values the highest concentration is selected that does not elicit the symptoms or effects defined by the AEGL tier in question.

Comments on AEGL-1

COT: Data indicating the absence of histopathological effects in a 2-week animal study have been used to derive AEGL-1. It is important to look for data on the irritation/discomfort relating to phenol exposures and to use them for AEGL-1 derivation. The NAC should reconsider human data and review the basis for the occupational exposure values.

It would be more reasonable to use the apparent maximum no-effect vapor concentrations of Piotrowski (1971) and Ogata et al. (1986) as an AEGL-1. Humans were exposed to 5-6.5 ppm for as long as 8 hours without apparent ill effects. These exposures would very likely have been discontinued had the subjects experienced notable discomfort. Monkeys inhaling 5 ppm continuously for 90 days exhibited no adverse effects (Sandage, 1961).

Reply: The pharmacokinetic study of Piotrowski (1971) was not used because it did not report health effects, which was the reason for the COT to reject a similar study as keystudy for methanol AEGL-1 values (cf. COT methanol comments). No more relevant human data could be located in the literature.

The Sandage (1961) study was not used because, apparently, exposure chambers did not allow observation of monkeys during the exposure and histopathology was performed on the lungs, but not on the upper respiratory tract.

The CMA (1998) (Hoffman et al. 2001) study is the only one fulfilling the SOP requirements for a key study and should therefore be retained.

The NAC/AEGL committee should discuss if the total UF can be reduced to 3. Due to the lack of data on irritation in humans and the lack of experimental human or monkey data at >5 ppm, a MF=2 should be considered.

The values should be flat-lined as irritation is probably the most relevant effect.

Comments on AEGL-2

COT: The phenol AEGL-2 at 8 hours (7.7 ppm) said by NAC to be disabling and to impair one's ability to escape it not toxicologically different from the current occupational limits.

The proposed derivation of AEGL-2 based on reduction of the AEGL-3 is arbitrary. The approach could be acceptable only if relevant data are not available.

COT requests that NAC/AEGL committee to provide a proper justification for dividing AEGL-3 by a factor of 3 to derive an AEGL-2.

The AEGL-2 rationale does not mention the RD50 of 166 ppm. Generally, a 1-hour AEGL-2 can be about 1/5 of the RD50. Since the proposed value is about 1/10 of the RD50, the AEGL-2 could be higher.

Reply: The relevance of the RD50 for humans is unclear and is not considered an adequate basis for the derivation of AEGLs.

The NAC/AEGL committee should discuss use of a chemical-specific basis (studies of Flickinger et al., 1978, Brondeau et al., 1994) as basis for deriving AEGL-2 values.

Comments on AEGL-3

COT: The use of the study of Flickinger (1976) as the basis for AEGL-3 is questionable, primarily due to the determination of the exposure concentration. The use of nominal concentrations of phenol should be avoided if other data exist that can be better relied upon.

In a liquid aerosol exposure, the rats would have been soaking wet with phenol. Thus, the exposure was the equivalent to a combined inhalation, dermal and oral study. Yet, there were no deaths. Therefore, the maximum non-lethal concentration for this study would have been significantly higher, probably at least a factor of two. It appears that the AEGL-3 levels could be increased substantially.

If it cannot be demonstrated that there is no statistically significant difference between vapor and aerosol inhalation toxicity, a clear explanation for why the particular aerosol concentration is both physically and biologically equivalent to the vapor concentration should be given.

The magnitude of the total uncertainty factor is not properly justified.

Reply: No other relevant studies with analytically determined exposure concentration were located for the derivation of AEGL-3.

The NOEL for lethal effects cannot be estimated with certainty from the Flickinger study because of the likely dermal and oral exposure.

There are no acceptable vapor or aerosol LC50 studies and no reports about lethality after inhalation exposure in humans.

Due to the moderate vapor pressure, even in case of accidental release of phenol, high concentrations in air are considered unlikely.

The NAC/AEGL committee should discuss not to derive AEGL-3 values for the lack of a sufficient data basis.

Phenol - 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

Phenol - Proposal for alternative 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: use same concentration at all time periods, because slight irritation effect depend primarily on exposure concentration

Total uncertainty factor: 3

Interspecies: 1

The toxicokinetic component of the uncertainty factor was reduced to 1 because toxic effects are mostly caused by phenol itself without requirement for metabolism, moreover, possible local irritation effects depend primarily on the phenol concentration in inhaled air with little influence of toxicokinetic differences between species. The starting point for AEGL derivation was a NOAEL of a repeated exposure study and, thus, the effect level was below that defined for AEGL-1. The human experimental and workplace studies support the derived values. Therefore, the interspecies factor was reduced to 1.

Intraspecies: 3

For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic effects. Therefore the toxicokinetic component of the uncertainty factor was reduced to 1 while the factor of 3 for the toxicodynamic component, reflecting a possible variability of the target-tissue response in the human population was retained.

Modifying factor: 2 due to lack of human irritation data

Alternative AEGL-1 Values for Phenol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
4.2 ppm (16 mg/m^3)	4.2 ppm (16 mg/m^3)	4.2 ppm (16 mg/m^3)	4.2 ppm (16 mg/m^3)	4.2 ppm (16 mg/m^3)

Supporting data: No reported human health effects at 6.5 ppm for 8 hours (Piotrowski, 1971) and 5.4 ppm at the workplace (Shamy et al., 1994)

Phenol - AEGL-2

Keystudy: not applicable

Endpoint: derived as fraction of AEGL-3

Scaling: not applicable

Divisor: 3

because a larger divisor would have resulted in an 8-hour concentration to which subjects have been exposed in a pharmacokinetic study and which was reported for 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)

Phenol - Proposal for alternative AEGL-2

- Brondeau et al. (1989): inhalation study in 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, concentrations analytically determined

- Flickinger (1976): inhalation study in 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

  only nominal concentrations reported; possible dermal (and oral) exposure in addition to inhalation

Phenol - Proposal for alternative AEGL-2

Keystudy: Flickinger (1976); Brondeau et al. (1989)

Endpoint: In rats, exposure to 900 mg/m³ aerosol (≈ 234 ppm) for 4 hours caused irritation and slight CNS effects. Exposure of rats to 211 ppm vapor for 4 hours caused no severe effects. 211 ppm for 4 hours were used as point of departure.

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

Total uncertainty factor: 10

Interspecies: 3

The toxicokinetic component of the uncertainty factor was reduced to 1 because the irritation and CNS effects are caused primarily by phenol itself and not be a metabolite.

Intraspecies: 3

because the study of Baker et al. (1978) that investigated health effects in members of 45 families (including children and elderly), that were exposed to phenol through contaminated drinking water for several weeks, did not indicate that symptom incidence or symptom severity was higher in any specific subpopulation. Moreover, newborns and infants were not considered more susceptible than adults because of their smaller metabolic capacity to form toxic phenol metabolites (cf. Section 4.4.2.).

Alternative AEGL-2 Values for Phenol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
42 ppm (160 mg/m³)	42 ppm (160 mg/m³)	33 ppm (130 mg/m³)	21 ppm (81 mg/m³)	11 ppm (41 mg/m³)

Supportive evidence: Baker et al. (1978): only gastrointestinal symptoms in 17/39 persons after uptake of doses of 10 - 240 mg/day via drinking water.

8-hour AEGL-2: 41 mg/m³ x 10 m³ x 1/70 kg = 5.9 mg/kg

Phenol - 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 pharmacokinetic studies no effects were mentioned. The total uncertainty factor of 10 was formally split up into an interspecies factor of 3 and an intraspecies factor of 3

Interspecies: 3

Intraspecies: 3

AEGL-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
- AEGL-3 for 30 min, 1, 4 and 8 h correspond to 2.1, 3.2, 7.9 and 13 mg/kg, respectively, which is 8-48fold lower than the estimated dose (106-874 mg/kg) for lethal cases after oral and dermal exposure [*COT: comparison with bolus dose not adequate*].

Phenol - DERIVATION OF LOA

A Level 1 odor studies is available:

Odor detection threshold for phenol: 0.016 ppm (TNO, 1988)

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

$I = kw * \log (C / OT50) + 0.5$

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

$3 = 2.33 * \log (C / 0.11) + 0.5$ which can be rearranged to

$\log (C / 0.11) = (3 - 0.5) / 2.33$

$= 1.07$ and results in

$C = (10^{1.07}) * 0.016$

$= 11.8 * 0.016$

$= 0.19$ ppm

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

$LOA = 0.19 \text{ ppm} * 1.33$

$= 0.25$ ppm

The LOA for phenol is 0.25 ppm.

BORON TRICHLORIDE

- Very limited database:
  - 1 hr-LC_{50} values in male and female rats from Vernot et al., 1977
  - pilot studies by Stokinger and Spiegl (1953) which provide only a description of what typical effects might follow from exposure

- stoichiometric equation for the hydrolysis reaction

$$BCl_3 + 3H_20 \rightarrow H_3BO_3 + 3HCl$$

Because HCl produced, the toxicity of BCl_3 was compared to HCl:

Comparison of BCl_3 and HCl LC_{50} Values in Male Rats			
Time (min)	**HCl (vapor) (ppm)**	**BCl_3 (ppm)**	**References**
5	40,989	-	Higgens et al., 1972
30	4700	-	Darmer et al., 1974
60	3124 -	2541 4418 (females)	Vernot et al., 1977

Because 3 moles of HCl produced from hydrolysis of BCl_3, it was decided that the AEGL-1 and AEGL-2 values be recommended guidance levels based on ⅓ of the NAS approved values for HCl (*note: no consideration was given to the boric acid produced during hydrolysis*). The AEGL-3 values based on an estimated no-effect-level for death in male rats following BCl_3 exposure (Vernot et al., 1977).

Summary of Current Proposed AEGL Values for BCl_3 (ppm)						
Level	**10-m**	**30-m**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	~~1.8~~ 0.6	~~1.8~~ 0.6	~~1.8~~ 0.6	~~1.8~~ 0.6	~~1.8~~ 0.6	Recommended as guidance levels: ⅓ the NAC-approved HCl values [No-adverse-effect-level of HCl in exercising human asthmatics]
AEGL-2	~~100~~ 33	~~43~~ 14	~~22~~ 7.3	~~11~~ 3.7	~~11~~ 3.7	Recommended as guidance levels: ⅓ the NAC-approved HCl values [Mouse RD_{50}; Histopathology in rats]
AEGL-3	170	57	28	7.1	7.1	⅓ the 1-hour BCl_3 LC_{50} value of 2541 ppm in male rats

AEGL-3 VALUES				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
170 ppm	**57 ppm**	**28 ppm**	**7.1 ppm**	**7.1 ppm**

Reference: Vernot, E.H., MacEwen, J.D., Haun, C.C., Kinkead, E.R. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42: 417-423.

Test Species/Strain/Sex/Number: 5 Male or 5 female Sprague-Dawley derived rats/exposure group

Exposure Route/Concentrations/Durations: Inhalation to various concentrations of BCl_3 for 1 hour (exact exposure concentrations not stated) for determination of LC_{50}

Effects: 1 hour LC_{50}:
males: 2541 ppm
females: 4418 ppm

Endpoint/Concentration/Rationale: The endpoint chosen was ⅓ of the male 1-hour LC_{50} value, or 847 ppm. One-third of the LC_{50} value is a conservative estimate of the threshold for lethality, a defined endpoint for the AEGL-3.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 10 - not much is known about interspecies differences
Intraspecies: 3 - based on the HCl data (HCl interspecies UF of 3 supported by the steep concentration-response curve which implies little individual variability)

Modifying Factor: Not applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: No BCl_3 data were available from which to derive an n value for the scaling of the derived AEGL-3 value across time. Because BCl_3 hydrolyzes in moist air to form hydrogen chloride, the value of $n = 1$ for hydrogen chloride as calculated by ten Berge (1986) was used for the scaling to the 10- and 30-minute, 1-, and 4-hour exposures using the relationship $C^n \times t = k$. **The 8-hour AEGL-3 value was set equal to the 4-hour to be consistent with the AEGL-2 values.**

Comments: The derived AEGL-3 values were consistent with the application of the Stokinger and Spiegl (1953) data where exposure to 50 ppm for 2 x 7 hours in rats, mice, and guinea pigs did not result in mortality when clean cages were substituted every 2 hours of the exposure (to reduce contact with the hydrolysis products formed in the cage).

COT COMMENTS:

MAIN COMMENTS:

- The SOP manual should be updated to define the minimum data set necessary for AEGL development. **The subcommittee recommends that AEGL values not be derived for BCl_3.** However, if the NAC is able to get additional data on this compound, AEGL values can be developed with greater confidence and validity. The comments below are offered by the subcommittee should the NAC reconsider the database and continue to pursue development of AEGLs.

- If proceed with AEGL development for BCl_3:

  - AEGL-3: While concerned about the paucity of data, the subcommittee agreed with the approach

  - AEGL-2: It is suggested that AEGL-2 could be derived by dividing the AEGL-3 value by 3, as

outlined in the SOPs

- AEGL-1: The paucity of data on BCl_3 precludes derivation of AEGL-1

If decide to proceed with derivations and use COT's suggestions for derivations, need to decide if anything should be based on HCl - currently use n=1 based on HCl, and intraspecies UF of 3 based on steepness of dose-response curve for HCl.

- if keep the value of n based on HCl and total UF of 30, then the 8-hour AEGL-3 needs to be scaled across time to 3.5 ppm

- if no longer base anything on HCl, then the default values of n and UF should be used.

Summary of Proposed AEGL Values for BCl_3 (ppm)						
Level	**10-m**	**30-m**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	NR	NR	NR	NR	NR	
If keep n=1 based on HCl and UF = 30						
AEGL-2	57	19	9.3	2.4	1.2	⅓ the AEGL-3 values
AEGL-3	170	57	28	7.1	3.5	⅓ the 1-h BCl_3 LC_{50} value in male rats
If use default values of n = 3, 1 and UF = 100						
AEGL-2	5.0	3.7	2.8	0.70	0.37	⅓ the AEGL-3 values;
AEGL-3	15	11	8.5	2.1	1.1	⅓ the 1-h BCl_3 LC_{50} value in male rats

National Research Council/National Academy of Sciences Comments on Chlorine Trifluoride (following Meeting-12, July 21-23, 2003)

Organization of this document is redundant. There are relatively few publications available from which to derive AEGLs, but descriptions of the same studies are repeated over and over. For example, at page 15 lines 12 and 21the paragraphs begin, "As reported in Section 3.1.2..."; page 12, lines 20-26 repeat page 10, lines 3-14 and page 16, line 12 begins, "As reported in Section 3.1.3...

Derivation of the AEGL-3 is problematic. The authors elected to utilize the mouse data based on a calculated LC_{01} primarily because "more mice than monkeys were tested" (page 21, line 30) and the "data for the mouse resulted in a clearer dose-response relationship." Previous AEGL discussions of irritants stressed the differential nature of irritant deposition in rodent upper nasal airways as contrasted to primates and the differences in delivered dose of these materials to the deep lung in obligate nose-breathers compared to other species. Rather than rely on a more convenient data set that seemed more amenable to statistical manipulation, the differences in primate and rodent response were neglected in the AEGL-3 derivations. While the mouse is the "most sensitive species as determined by the 1-hour LC_{50}", the mouse is not necessarily the most appropriate species upon which to base the AEGL-3 given the availability of controlled inhalation studies in Rhesus monkeys of appropriate duration and outcomes (page 10, lines 1-29). Rather than rote conclusion about the "most sensitive" species, a discussion of high scholarship citing reviews of differential deposition and response between rodents and primates should be included at Section 7.3.

Given the fact that none of the four monkeys exposed to 127 ppm for 1 hour died - a value similar to the 135 ppm LC_{01} from the mice (page 21, line 34) - and that the resulting AEGL-3 values based on the primate data do not vary substantially from those proposed based on mice (page 22, lines 8-11; page 22, line 38), it is wise that the NAC revisit the AEGL-3. Given that the primate 1-hour LC_{50} (230 ppm) was associated with a lower confidence limit of 167 ppm (page 10, line 14), the selection of uncertainty factors and calculation of an LC_{01} should include detailed discussion of the slope of the concentration-response. Generally, probit analyses programs (e.g., G.M. Schoofs and C.C. Wilhite. 1984. A probit analysis program for the personal computer. J. Appl. Toxicol. 4:141-144.) calculate the slope of the dose-response along with the LC_{50} or other dose metric along with the confidence limits. At Section 3, it would be helpful to include a table showing the LC_{50}, LC_{01}, their confidence limits and the slope of the primate, mouse, and rat lethality curves. Most programs also allow the user to test for parallelism between the curves and it would be of interest to determine if the slopes of the curves are significantly different or are actually quite similar between species. It appears in light of the 123 ppm LC_{01} (page 22, line 38) and the 95% lower confidence limit on the LC_{50} (page 10) for Rhesus monkeys that the concentration-response relationship is very steep - such that relatively small changes in concentration result in marked changes in response.

No indication is given whether it is the duration of exposure (area under the concentration: time curve) or whether it is the maximum concentration (C_{max}) that most closely determines outcome following acute chlorine trifluoride inhalation.

During verbal discussions following the presentation to the COT, it was further suggested that by using the monkey data and adding discussions of (1) the differences in relative respiratory rate between rodents and primates and (2) the similar morphology of the respiratory tract among primates, the interspecies uncertainty factor can be reduced. It was also stated that in light of the data, the 1-hour AEGL-3 value of 14 ppm is too low.

Response - Recalculated Values

The basis for the revised AEGL-3 is the highest 1-hour non-lethal value in monkeys, 127 ppm (an LC_{01} of 123 ppm was calculated in the original TSD, but could not be replicated with current probit analysis programs). The recalculated AEGL-3 values, using the monkey data and an interspecies uncertainty factor of 1 or 2 and keeping the intraspecies uncertainty factor of 3 are in bold in the table below (n=1). The NAC might also consider setting the 8-hour AEGL-3 value equal to the 4-hour value because dogs exposed to approximately 21 ppm for two days did not die during the following month of observation, and dogs tolerated 5.15 ppm for 6 hours/day, 5 days/week for >2 weeks before succumbing (Horn and Weir 1955).

The amended discussion will include the following.
The nasal passages vary considerably in size and shape among species. The nasal passages of rodents and primates differ in gross anatomy, the amount and distribution of types of respiratory epithelium, and airflow patterns. The nose of primates (humans and monkeys) show great similarity in these three factors (Schreider 1986), and the monkey is a more appropriate model for extrapolation of inhalation effects to humans than is the rodent.

The respiratory rate of primates is lower than that of rodents. Therefore, uptake to the target tissue (the lung) in primates is lower than that of rodents. Furthermore, based on relative body size, the respiratory rate of humans is lower that of monkeys, with resulting lesser uptake to the target tissue, and there is no need for an interspecies uncertainty factor (or an interspecies uncertainty factor of 2 will suffice). An intraspecies uncertainty factor of 3 is applied because the mechanism of action - destruction of the lung tissue - should not differ greatly among humans.

Summary of AEGL Values for Chlorine Trifluoride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling) UF = 3,3	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	Slight irritation - dog (Horn and Weir 1956)
AEGL-2 (Disabling) UF = 3,3	6.2 ppm (24 mg/m^3)	6.2 ppm (24 mg/m^3)	3.1ppm (12 mg/m^3)	0.77 ppm (2.9 mg/m^3)	0.39 ppm (1.5 mg/m^3)	Threshold, impaired ability to escape - dog (Horn and Weir 1955)
AEGL-3 (Lethal) **UF = 1,3** **UF = 2,3**	81 ppm (308 mg/m^3) **254 ppm** **127 ppm**	27 ppm (103 mg/m^3) **85 ppm** **42 ppm**	14 ppm (53 mg/m^3) **42 ppm** **21 ppm**	3.4 ppm (13 mg/m^3) **11 ppm** **5.3 ppm**	1.7 ppm (6.5 mg/m^3) **5.3 ppm** **2.6 ppm**	Lethality (LC_{01}) - mouse (MacEwen and Vernot 1970) **No deaths - monkey (MacEwen and Vernot 1970)**

Raw Data (MacEwen and Vernot 1970)

Species	LC_{50} (ppm)	95% Confidence Limits (ppm)	no deaths	LC_{01} (ppm)
monkey	230	167-317	127	---
rat	299	260-344	200	156
mouse	178	169-187	125	135

Schreider, J.P. 1986. Chapter 1: Comparative anatomy and function of the nasal passages. In: C.S. Barrow, ed., Toxicology of the Nasal Passages. New York: Hemisphere Publishing Corp.

Two Additional Points to Consider:

1. We flatlined the 10-minute AEGL-2 because the key study was a 6-hour study (5.15 ppm for 6 hours). But, we have LC_{50} data for exposure durations of 13.5 minutes to 3.7 hours. Therefore, there is no need to set the 10-minute AEGL-2 equal to the 30-minute AEGL-2. The revised value would be 19 ppm.

2. I recently graphed the LC_{50} data (see graph below; check TSD for original data). The n value, previously estimated at 1 is actually 1.3 (using all of the data). The NAC might consider adjusting the AEGL-2 and AEGL-3 values by applying the n value of 1.3 (see revised values below).

Summary of AEGL Values for Chlorine Trifluoride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	0.12 ppm (0.46 mg/m^3)	Slight irritation - dog (Horn and Weir 1956)
AEGL-2 (Disabling)	6.2 ppm (24 mg/m^3) **8.1 ppm**	6.2 ppm (24 mg/m^3) **3.5 ppm**	3.1ppm (12 mg/m^3) **2.0 ppm**	0.77 ppm (2.9 mg/m^3) **0.70 ppm**	0.39 ppm (1.5 mg/m^3) **0.41 ppm**	Threshold, impaired ability to escape - dog (Horn and Weir 1955)
AEGL-3 (Lethal) **UF = 1,3** **UF = 2,3**	81 ppm (308 mg/m^3) **168 ppm** **84 ppm**	27 ppm (103 mg/m^3) **72 ppm** **36 ppm**	14 ppm (53 mg/m^3) **42 ppm** **21 ppm**	3.4 ppm (13 mg/m^3) **15 ppm** **7.3 ppm**	1.7 ppm (6.5 mg/m^3) **8.6 ppm** **4.3 ppm**	Lethality (LC_{01}) - mouse (MacEwen and Vernot 1970) **No deaths - monkey (MacEwen and Vernot 1970)**

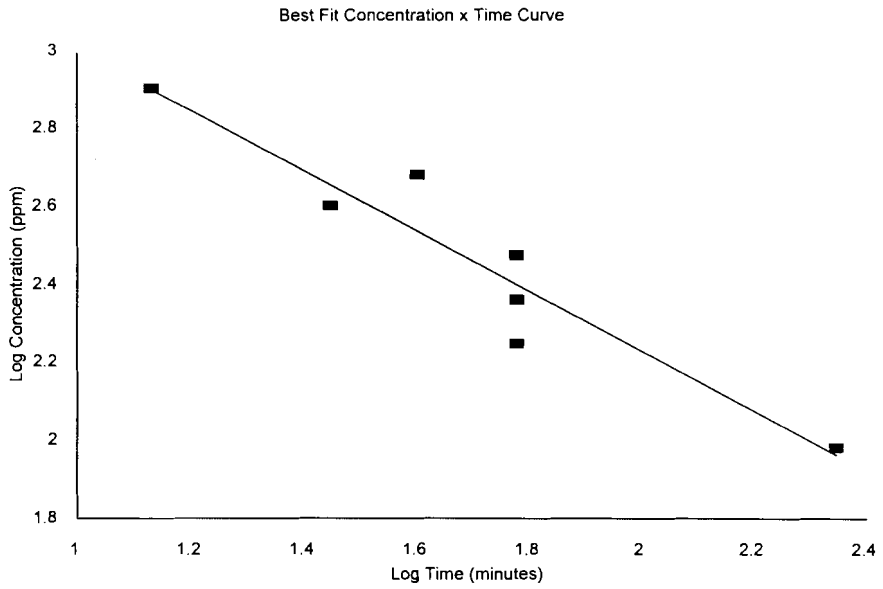


Figure 1. Chlorine trifluoride - LC_{50} values

Time	Conc.	Log Time	Log Conc.
60	230	1.7782	2.3617
13.5	800	1.1303	2.9031
40	480	1.6021	2.6812
28	400	1.4472	2.6021
60	299	1.7782	2.4757
222	96	2.3464	1.9823
60	178	1.7782	2.2504

Regression Output:	
Intercept	3.7684
Slope	-0.7692
R Squared	0.9014
Correlation	-0.9494
Degrees of Freedom	5
Observations	7

n = 1.3
k = 79325.99

Category Graph of Animal Data and "Old" AEGL Values

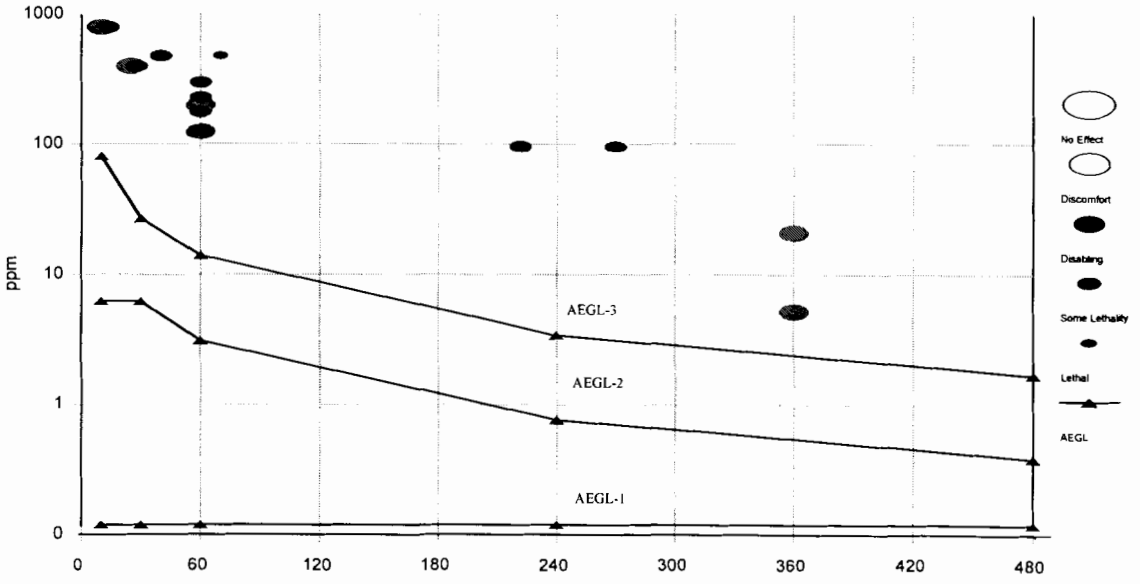


Figure 2. Toxicity Data and AEGL Values for Chlorine Trifluoride.

ACUTE EXPOSURE GUIDELINE LEVELS for CHLORINE TRIFLUORIDE Modification of AEGL-3

National Advisory Committee for AEGLs Meeting 32
April 19-21, 2004

ORNL Staff Scientist:
Sylvia S. Talmage

Suggested revisions to Chlorine Trifluoride

1. Change time-scaling from n = 1 (estimated) to n = 1.3, based on all of the data.
Adjust AEGL-2 values
Time-scale the 10-minute AEGL-2 because the time-scaling data exposure durations range from 13.5 to 222 minutes.

2. Base AEGL-3 on primate data
Use highest 1-hour nonlethal value of 127 ppm
Change interspecies uncertainty factor to 1 or 2
Time scale using an n value of 1.3

MODIFICATION OF AEGL-2,3

Classification	Exposure Duration (Values in ppm)				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 **n = 3,3**	0.12	0.12	0.12	0.12	0.12
AEGL-2 **n=3,3**	6.2 **8.1**	6.2 **3.5**	3.1 **2.0**	0.77 **0.70**	0.39 **0.41**
AEGL-3 **n=1,3** **n = 2,3**	81 **168** **84**	27 **72** **36**	14 **42** **21**	3.4 **15** **7.3**	1.7 **8.6** **4.3**

AEGL-1: Based on nasal discharge in dogs during first 3 hours of a 6-hour exposure to 1.7 ppm.
No signs in rats inhaling 1.17 ppm for 6 hours (exposures were repeated).
Combined interspecies and intraspecies UF of 10; no time scaling... adaptation.

AEGL-2: Strong irritation in dogs exposed to 5.15 ppm for 6 hours; signs reversible.
Rats exposed to this concentration appeared unaffected.
Combined interspecies and intraspecies UF of 10; Time scaled using $C^1 \times t = k$.
Change time-scaling to $C^{1.3} \times t = k$.

AEGL-3: Based on 1-hour LC_{01} of 135 ppm in mouse, most sensitive species.
Combined interspecies and intraspecies UF or 10; $C^1 \times t = k$.
Use primate data; no deaths following 1-hour exposure to 127 ppm
Use smaller interspecies uncertainty factor; time scale using $C^{1.3} \times t = k$.

2,4-Dinitroaniline
(CAS No. 97-02-9)

The chemical 2,4-dinitroaniline is a water insoluble solid with a vapor pressure of 5.9×10^{-7} mm Hg at standard conditions (O'Neill et al. 2001; HSDB 2003). It is used in the manufacture of azo dyes. Workers may be exposed through dermal contact or inhalation of the dust. The fire hazard is slight.

Data are available on skin irritation; oral toxicity in rats, mice and guinea pigs; intravenous toxicity in rats; developmental effects in rats (inhalation), and mutagenicity (HSDB 2003; RTECs 2004). The only inhalation study is a poorly described developmental study in rats (Khipo et al. 1982). The method of generation of the atmospheres is not described. It is not clear if a vapor, aerosol, or dust was generated. No data relevant to development of AEGL values can be taken from this article.

Based on the fact that this chemical is practically nonvolatile and data relevant to development of AEGL values are not available, no AEGL values should be developed.

HSDB (Hazardous Substances Databank). 2003. MEDLARS Online Information Retrieval System, National Library of Medicine, retrieved 12/19/03.

Khipko, S.e., N.M. Vasilenko, M.Y. Kudrya, and F.A. Kolodub. 1982. Experimental study of the effect of 2,4-dinitroaniline on embryogenesis. Gig. Tr. Prof. Zabol. 6:47-49. (Russian).

O'Neil, M.J., A. Smith, and P.E. Heckelman, eds. 2001. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 13th ed. Whitehouse Station, NJ: Merck & Co., Inc.

RTECs (Registry of Toxic Effects of Chemicals). 2004. 2,4-Dinitroaniline. On-line data base retrieved 01/23/04.

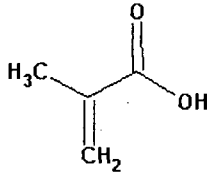
ATTACHMENT 9

Acute Exposure Guideline Levels (AEGLs)

for

Methacrylic acid

(CAS No. 79-41-4)



NAC/AEGL Meeting 32, 19-21 April 2004, Washington, D.C.

FoBiG Scientist:
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Robert Benson, U.S.EPA, Denver, CO

Methacrylic Acid

PROPERTIES

- clear, colorless liquid
- acrid, repulsive odor, odor threshold 0.032-0.17 ppm (not validated sour
- soluble in water
- vapor pressure 0.9 hPa (68 °F), aerosol/vapor mixtures at high exposure concentrations (saturated vapor concentration: ≈1300-2000 ppm)

PRODUCTION and USE

- production of methacrylic esters; co-monmer in different kinds of polyme
- mainly production of ethylmethacrylate (direct esterification) and aquous based polymers, coatings
- Production of 34,800 t in Europe (1993, ECETOC 1996)

TOXICITY MECHANISM AND CONCERNS

- irritative and corrosive acting substance (mainly local effects),
- direct acting
- animals more sensitive than humans to URT effects
- no relevant concern as to reproductive and/or carcinogenic properties

DATA RELEVANT TO AEGL-1

IUMAN

Dow Chemicals, 1997

acute workplace exposures to ≤113 ppm resulted in skin toxicity and severe corneal burn. No information on exposure duration provided

no human data available to derive AEGL-1

NIMAL

CIIT, 1984

Repeated whole-body exposure of 2 strains of rat and mice for 6 hours/d, 4 exposures

20 ppm: Rhinitis, minimal to mild degeneration of olfactory epithelium (see table)

100 ppm: as 20 ppm, slightly increasing severity

CITT, 1983

Range-finding study: Repeated whole-body exposure of 2 strains of rat and 1 strain of mice for 6 hours/d, 5 animals/sex/ strain/ exposure level; 10 exposures, 0,100, 500, 1000 ppm

100, 500 ppm: no effects reported after first exposure in this range finding study, no histopathological examination , relevant effects after 10 exposures in both concentrations

1000 ppm: nasal discharge, lacrimation, activity changes **in some animals after first exposure**, relevant effects after 10 exposures

CIIT 1984, effects seen after 4 exposures, possibly occurring earlier

ppm	0		20		100		300		species/
effects, respiratory	m	f	m	f	m	f	m	f	strain
rhinitis	0	0	4	2	2	4	9	7	F344 rats
hyperplasia, goblet	0	0	0	0	0	0	3	6	10/sex/concentration examined
ulceration	0	0	0	0	0	0	3	1	
necrosis	0	0	0	0	0	0	1	0	
hyperkeratosis	0	0	0	0	0	0	1	3	
exudate	0	0	0	0	0	0	3*	4	
rhinitis	2	0	3	2	4	4	6	6	S-D rats
exudate	0	0	1	0	0	0	3	3	10/sex/concentration examined
ulceration	0	0	0	0	0	0	1	1	
hyperkeratosis	0	0	0	1	2	3	2	7	
lung lymphocytes	3	4	7	3	8	6	7	6	
larynx lymphocytic infiltrate	0	0	1	1	1	2	1	2	
rhinitis	0	0	0	0	0	0	5	6*	B6C3F1 -mice
necrosis	0	0	0	0	0	0	7*	6	10/sex/concentration examined
exudate	0	0	0	0	0	0	2*	1*	
ulceration	0	0	0	0	0	0	0	1	
larynx inflamm	0	0	0	0	0	0	0	1	
no. of effects /animals	9/60		25/60		36/60		115/60		
*) effects not restricted to turbinates, level A (observed also at level B,C, or D)									

DISCUSSION: RELATIVE SENSITIVITY HUMAN/ ANIMALS

for AEGL-1 and AEGL-2 effects

- high deposition efficiency of MAA in the URT
- higher sensitivity of rodents compared to humans shown for effects in the URT from acrylic acid and for methyl methacrylate (Frederick et al., 1998; Andersen et al., 1999), assumed also for MAA
- not to be assumed for very high concentrations (effects in the pulmonary region)

▸▸ interspecies uncertainty factor AEGL-1 and AEGL-2 = 1 (covering toxicokinetics and -dynamics)

AEGL-1

Keystudy: CIIT (1984)

Endpoint: irritation (observed: slight degeneration olfactorial epitheliu rhinitis) , rat, repeated 6 hour/d - exposure (4 exposures) , 2 ppm

Total uncertainty factor: 3

Interspecies: 1

For MAA it is assumed that humans are less or equally susceptible as rodents for effects in the upper respiratory tract (as derived from data related to acrylic acid, Frederick et al., 1998, and methyl methacrylate, Andersen et al., 1999). The interspecies uncertainty factor of 1 is used t compensate for both, toxicokinetic and toxicodynamic differences betw species.

Intraspecies: 3

The intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between individuals. For local effects limited toxicodynamic differences exist between individua MAA is a directly acting agent leading to limited differences in toxicokinetics.

Modifying factor: 1

effect size is above AEGL-1 level. However, because of repeated expos in the key study no modifying factor >1 is afforded.

Time Scaling: **no increase of effect severity with time expect**

for slight local irriating effects no relevant increase of effect size with exposu duration is expected as evidenced with acrylic acid.

AEGL-1 DERIVATION (con'd)

AEGL-1 Values for Methacrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
6.7 ppm	6.7 ppm	6.7 ppm	6.7 ppm	6.7 ppm
24 mg/m^3	24 mg/m^3	24 mg/m^3	24 mg/m^3	24 mg/m^3

Supporting data:

AEGL- 1 as proposed integrates well between methyl methacrylate and acrylic cid

DERIVATION OF LOA

0.032 ppm odor threshold cit. ECETOC 1996

0.17 ppm odor threshold cit. ECETOC 1996

0.56 ppm „point of impingement standard" Ontario, Ministry of Environment 2001

- data insufficient for the derivation of a LOA (level of odor awareness)

DATA RELEVANT TO AEGL-2

HUMAN

- Dow Chemicals, 1997 — acute workplace exposures to ≤113 ppm resulted in skin toxicity and severe corneal burn. No information on exposure duration provided
- no human data available to derive AEGL-2

ANIMAL

- **no adequate studies with only slight or minimal local effects after single exposure**
- CIIT, 1984 — Repeated whole-body exposure of rats and mice for 6 hours/d, 4 exposures

  100 ppm: Rhinitis, discharge, inflammation, light to minimal degeneration of olfactory epithelium (see table)

  300 ppm: Rhinitis, discharge, inflammation, ulceration of olfactory epithelium, increasing severity
- CITT, 1983 — Range-finding study: Repeated whole-body exposure of 2 strains of rat and 1 strain of mice for 6 hours/d, 5 animals/sex/ strain/ exposure level; 10 exposures, 0,100, 500, 1000 ppm

ANIMAL (con'd):

100, 500 ppm: no effects reported after fi exposure in this range finding study, no histopathological examination ; relevant effects after 10 exposures in both concentrations

1000 ppm: nasal discharge, lacrimation, activity changes **in some animals after fi exposure** , relevant effects after 10 exposures

AEGL-2

Keystudy: CIIT (1984)

Endpoint: ulceration, degeneration of olfactory epithelium, rat/mice, repeated 6 hour/d - exposure (4 exposures) , 100 ppm

Total uncertainty factor: 3

Interspecies: 1

For MAA it is assumed that humans are less or equally susceptible as rodents for effects in the upper respiratory tract (as derived from data related to acrylic acid, Frederick et al., 1998, and methyl methacrylate, Andersen et al., 1999). The interspecies uncertainty factor of 1 is used to compensate for both, toxicokinetic and toxicodynamic differences between species.

Intraspecies: 3

The intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between individuals. For local effects limited toxicodynamic differences exist between individuals. MAA is a directly acting agent leading to limited differences in toxicokinetics.

Modifying factor: 1

effect size is slightly above AEGL-2 level. However, because of repeated exposure in the key study no modifying factor >1 is afforded.

AEGL-2 DERIVATION (con'd)

Time Scaling: **default**

Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-minute, 1-hour- and 4-hour- time points and n = 1 for the 8-hour time point. The 10-min AEGL-2 was set at the same concentration as the 30 min. AEGL-2 due to the overall uncertainty of this extrapolation.

AEGL-2 Values for Methacrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
76 ppm 270 mg/m^3	76 ppm 270 mg/m^3	61 ppm 220 mg/m^3	38 ppm 140 mg/m^3	25 ppm 90 mg/m^3

Supporting data:

- AEGL- 2 as proposed integrates well between methyl methacrylate and acrylic acid

DATA RELEVANT TO AEGL-3

HUMAN:

no studies with human exposure to lifethreatening effects to MAA are available

ANIMALS:

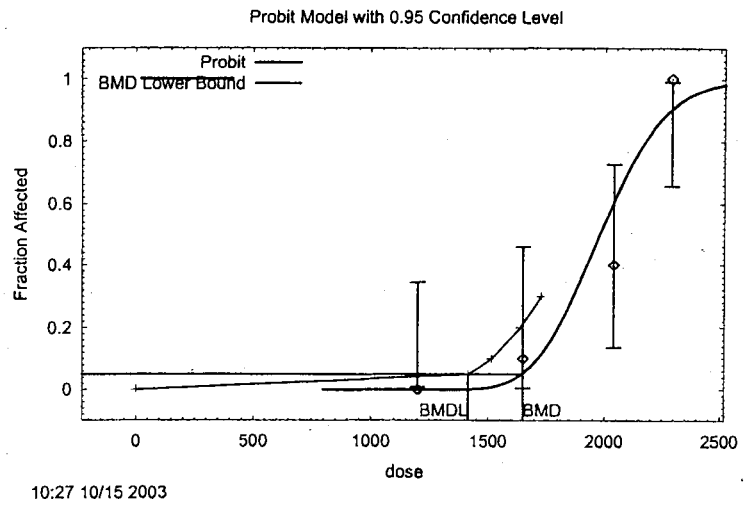
- Dupont (1993a) rat, LC_{50}-study, nose-only, mixed vapor/aerosol; effects of respiration

concentration [ppm] (4 hours exposure)	mortality / exposed animals
1200 (21% aero/79% vap)	0/10
1650 (37% aero/63% vap)	1/10
2040 (50% aero/50% vap)	4/10
2290 (57% aero/43% vap)	10/10

Calculated : LC_{50} 1980 ppm

At AEGL-3 level not only effects in the upper respiratory effects may be expected, but also pulmonary effects

BENCHMARK CALCULATION - lethality data Dupont (1993a)



BMDS-ware 1.3.2, EPA 2003

log-probit model was selected,

p=0.1983

BMCL 05 = 1414.4 ppm

BMC 01 = ~~1650.65~~ ppm 1528

==> only minor differences between the two values: the more conservati BMDL $_{05}$ was chosen as point of departure for AEGL3 derivation

AEGL-3

Keystudy: Dupont ,1993a

Endpoint: lethality in rats, 4 hours exposure, $BMCL_{05}$ 1414 ppm

Total uncertainty factor: **10**

Interspecies: **3**

Published interspecies comparisons are focused on the upper respiratory tract at lower doses. No definitive data for the involvement of the lung at higher doses are available. MAA causes lethal effects by local tissue destruction in the lung with limited influence of systemic distribution, metabolism and elimination. Therefore, the toxicokinetic differences are considered smaller than for other chemicals that require systemic distribution and metabolism. Also the toxicodynamic variability is considered to be limited because MAA causes cell necrosis presumably in a similar way as acrylic acid (by reducing the pH and destroying mitochondria), which are unlikely to be influenced by species-specific differences. Overall these arguments support a reduced interspecies uncertainty factor of 3

Intraspecies: **3**

The toxicokinetic differences are considered smaller than for other chemicals that require systemic distribution and metabolism because MAA causes lethal effects by local tissue destruction in the lung with limited influence of systemic distribution, metabolism and elimination although there might be some difference between babies and adults based upon projections from breathing rates, lung capacity, etc. The toxicodynamic variability is considered to be limited because MAA causes cell necrosis in a presumably similar way as acrylic acid (by reducing the pH and destroying mitochondria), which are unlikely to be influenced by interindividual differences. Taken together, these arguments support a reduced intraspecies uncertainty factor of 3.

AEGL 3 (con'd):

Time Scaling: **default**

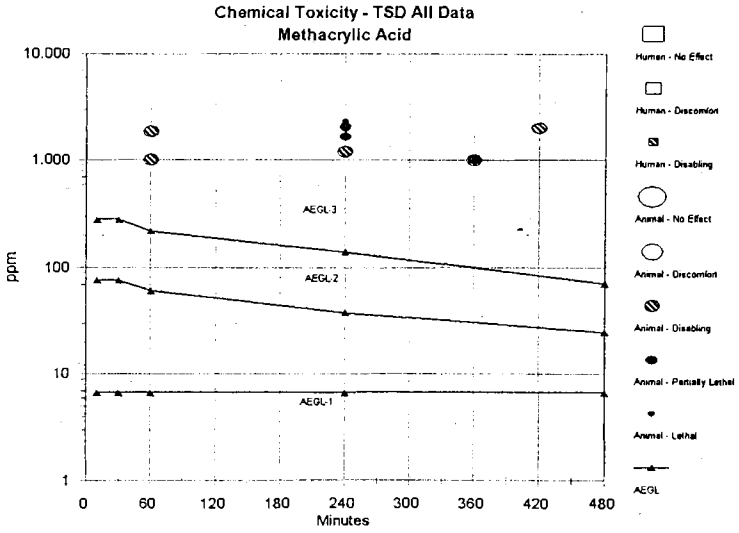
Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-minute-, and the 1-hour- time points and n = 1 for the 8-hour time point. For 10 minutes the same value was used as for 30 minutes due to high uncertainties of extrapolating to this very short exposure time.

AEGL-3 Values for Methacrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
280 ppm 1000 mg/m^3	280 ppm 1000 mg/m^3	220 ppm 790 mg/m^3	140 ppm 500 mg/m^3	71 ppm 250 mg/m^3

Support:

The derived AEGL-3 is consistent with the AEGL-3 for acrylic acid and methyl methacrylate

Category Plot of Toxicity Data compared to AEGL Values



CONSISTENCY WITH RELATED SUBSTANCES

[ppm]

AEGL-1	UF (Inter; Intra; Modify) **Total)**	10 min	30 min	60 min	4 h	8h
MMA	1;3;2;**6**	18	18	18	18	18
MAA	1;3;1;**3**	6,7	6,7	6,7	6,7	6,7
Acrylic acid	1;3;1;**3**	1,5	1,5	1,5	1,5	1,5

AEGL-2						
MMA	1;3;1;**3**	150	150	120	76	50
MAA	1;3;1;**3**	76	76	61	38	25
Acrylic acid	1;3;1;**3**	68	68	46	21	14

AEGL-3						
MMA	3;3;1;**10**	630	630	500	310	160
MAA	3;3;1;**10**	280	280	220	140	71
Acrylic acid	3;3;1;**10**	480	260	180	85	58

Fritz's handout #1

AEGL Values for MAA [ppm]					
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	6.7	6.7	6.7	6.7	6.7
AEGL-2	76	76	61	38	25
AEGL-3	280	280	220	140	71

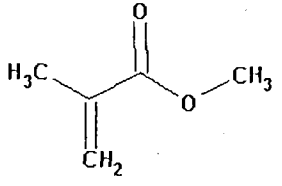
ATTACHMENT 10

Acute Exposure Guideline Levels (AEGLs)

for

Methyl Methacrylate

(CAS No. 80-62-6)



NAC/AEGL Meeting 32, 19-21 April 2004, Washington, D.C.

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Chemical Manager in German Expert Group:

Hans-Uwe Wolf, University of Ulm

Industry Reviewer for German Expert Group:

Harald Müllerschön, Roehm GmbH & Co KG, Darmstadt

Chemical Manager:

Robert Benson, U.S.EPA, Denver, CO

Methyl Methacrylate

PROPERTIES

- colorless liquid
- acrid, fruity odor, derived LOA 0,11 ppm
- soluble in water
- vapor pressure 36-47 hPa (68 °F)

PRODUCTION and USE

- production of polymers/ co-polymers and reactive resins
- forwarded to external processing sites (production of emulsions, dispersic solvent polymers, acrylic sheet like polymers)
- relevant human exposure: use as bone cement
- 610,000 t/a (production capacity, EU, 1996 - ref. OECD,SIDS 2001)

TOXICITY MECHANISM AND CONCERNS

- irritative and corrosive acting substance (mainly local effects), lower concentrations: URT, higher: also pulmonary region
- toxicity mainly determined by active metabolite: methacrylic acid
- animals more sensitive than humans to URT effects
- concern of asthma caused by MMA (?)
- as liquid, penetrates skin to a relevant amount; some indications of skin sensitization
- no relevant concern as to reproductive and/or carcinogenic properties

DATA RELEVANT TO AEGL-1

HUMAN

- Roehm 1994: medical examination of workers poly-MMA-cast sheet production (4 areas)

  Personal air sampling, questionnaire, rhinoscopy nasal cavity, detailed anamnesis

  n=211, 1-6h/d exposure, current exposure 3-40 ppm; highest: 4-5h/d current at 30-40 ppm, n=56; peaks/ spills: 100-300 ppm (one occasion 680 ppm), 5-15 minutes

self reported symptoms at 10-40 ppm: lacrimation, impaired nose breathing, dry nose, reduced sense of smell - only single cases, confounders (hey fever, sinusitis, smoking, antibiotics, peak exposures), therefore questionable

>100 ppm „short term" peak exposures (5-15 min.): transient eye- and URT-irritation, lacrimation, reversible after end of exposure

≤40 ppm for 6 hours: no irritation (rhinoscopy)

<40 ppm: no asthma despite 12.8% atopics within exposed workers

- Cromer and Kronoveter 1976: NIOSH-study

  Medical examination of workers 5 poly-MMA-sheet production plants, occup.history, pre-/postshift examinations for acute effects (symptomatology, blood pressure, pulse rate) and chronic effects

HUMAN (con'd)

Personal air sampling, exposure: 4-49 ppm, occasional spills,

n=91 exposed/ 43 non-exposed screening questionaire n=350, highest exposed: 25-50 ppm n=24

High: eye- and URT-irritation, headache, lightheadedness ,attributed to spills

≤50 ppm for 8 hours: no significant effects incl. no cardiovascular, no change in lung function after acute exposure, some unconfirmed indications of chronic respiratory effects (URT) and neurotoxicity

- Lindberg et al. 1991: occupational exposure, floor layers, exposu 0.7-12 years,

  Medical examination, psychophysiological tests, neurophysiological tests, lung functio blood and urine tests

  room air sampling, 62-601 ppm (median: 17 ppm), for ca. 20 minutes, then: 30-60 minut break, plus possible extended skin contact liquids, personal exposure not measured

  n=10

62-601 ppm (median: 175 ppm), repeatedly 20 minutes: irritation UR 3/10 workers irritation, 6/10 reddened tonsiles and palates, no change in lung function

HUMAN (con'd)

- Coleman 1963: 170-240 ppm occupational exposure „very definite irritation" , no details and no precise data on exposure duration provided

  100 ppm „it was their impression, that 100 ppm could be tolerated without discomfort"

- Pickering et al. 1993: cross sectional occupational questionnaire study, MMA „direct or indirect exposure"

  n=384

  no or only rare cases of URT-effects (no exposure data)

  no evidence of occupational asthma (Pickering et al., 1986 obversed 1 case of asthma in a nurse after MMA exposure)

- Muttray et al. 1997 Loss of olfactory epithelium in chronically exposed workers was assessed by testing the sense of smell

  n=175 male, exposed for >1 year, TWA ≤ 50 ppm for last 6 years, some excursions with higher exposure for short periods of time due to spills

  ≤ 50 ppm: no indication of reduced sense of smell

- other (contradictory) studies not sufficiently documented to be used for risk assessment, i.e.: Mizunuma et al., 1993; Korczynski 1998; Karpov 1954a,b; 1955a,b; Dobrinskij 1970

DATA RELEVANT TO AEGL-1

ANIMAL

- **no adequate animal studies with only slight or minimal local effects**

- Pinto 1997: 5 female rats/group, single whole body exposure

  110 ppm, 400 ppm (6h)

  110 ppm: -degeneration and necrosis of the olfac epithelium of minimal severity, subsequently „repaired"

  400 ppm: -degeneration and necrosis of the olfactory epithelium (moderate severity, up to 50 of epithelium affected), bowman glands, inflammatory exudate

- Jones 2002: 5 male rats, single exposure, whole body

  200 ppm, (6h), degeneration and necrosis of the olfactory epithelium (3/5 animals)

- Mainwaring et al. 2001: 5 female rats(group, single exposure, whole bod

  200 ppm, 3 and 6 hours

  200 ppm (3h): -no morphological abnormalities, immediately after exposure, no later examination

  200 ppm (6h): degeneration/atrophie olfactory epithelium, increased 18 hours after cessation of exposure

ANIMAL (cont'd)

- Raje et al. 1985: 4 male rats, single exposure, nose-only

  95 ppm, 2,3,4 hours

  Lung effects: interalveolar congestion, hemorrhage, edema

  (Contradicted by other studies, e.g., Pinto et al., 1997)

for AEGL-1 and AEGL-2 effects

Animals: **110 ppm (6 hours)** single exposure : degenerative changes URT

Humans: **170-240 ppm** (8 hours?, repeated exposure?) Very definitive irritation -Coleman, 1963

62-601 ppm (median: 175 ppm), repeatedly 20 minutes: irritati URT, 3/10 workers irritation (Lindberg et al., 1971)

- irritation effects at lower concentrations in rodents and humans restricte to URT
- irritation mainly due to methacrylic acid (metabolite via carboxylesterase (effects reduced by -partial- enzyme inhibition; Mainwaring et al., 2001)
- enzyme activity (carboxylesterase) higher or equal in nasal tissues of ra than in humans (Mainwaring et al., 2001; Bogdanffy et al.,1987,1998), enzyme activity in humans in the URT not restricted to the olfactory epithelium (Jones, 2002).
- olfactory epithelium rats (large surface): located in primary air flow, humans (small surface): located in secondary air flow
- dosimetric adjustment factor nasal tissue from Andersen et al., 1999 (PBPK-modelling): 2.4-4.76 rat/human (To assume equal enzyme activit may already largely account for sensitive subpopulations with high enzyr activity)

▸▸ **interspecies uncertainty factor AEGL-1 and AEGL-2 = 1 (covering toxicokinetics and -dynamics)**

AEGL-1

Keystudy: Pinto (1997)

Endpoint: irritation (observed: slight degeneration olfactorial epithelium), single 6 hour exposure, rats, 110 ppm

Total uncertainty factor: Incl. modifying factor: 6 (UF: 3x2)

Interspecies: **1**

For MMA it is shown that humans are less or equally susceptible as rodents for effects in the upper respiratory tract (Andersen et al.,1999,2002; Bogdanffy et al., 1987,1998) . The interspecies uncertainty factor of 1 is used to compensate for both, toxicokinetic and toxicodynamic differences between species.

Intraspecies: **3**

The intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between individuals. For local effects limited toxicodynamic differences exist between individuals. For the relevant variability between individuals regarding carboxylesterase activity (Mainwaring et al., 2001) is already largely accounted for by use of the interspecies factor of 1.

Modifying factor: **2**

The observed effect is more pronounced compared to AEGL-1 definition

Time Scaling: **no increase of effect severity with time expected**

Slight irritational effects are not expected to increase relevantly with time as evidenced by comparable data with acrylic acid.

AEGL-1 DERIVATION (con'd)

AEGL-1 Values for Methyl Methacrylate				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
18 ppm	18 ppm	18 ppm	18 ppm	18 ppm
75 mg/m^3	75 mg/m^3	75 mg/m^3	75 mg/m^3	75 mg/m

Supporting data:

No irritational effects were seen in human studies after 6 or 8 hours occupatic exposure to 40-50 ppm (Cromer and Kronoveter, 1976; Roehm, 1994), which the current TLV (ACGIH) for MMA. Applying an intraspecies factor of 3 to account for sensitive subpopulations, human data lead to very similar AEGL-values

DERIVATION OF LOA for MMA

0.21 ppm	odor threshold	Leonardos et al., 1969
0.05 ppm	odor detection	Hellman and Small 1974, as accepted by AIHA, 1997
0.083 ppm	odor threshold	Amoore and Hautala, 1983

Hellman and Small (1974)

odor detection threshold for MMA:	0.05 ppm
odor detection threshold for n-butanol:	0.3 ppm
OT_{50}: OT(MMA) * 0.04 ppm /OT(n-butanol)	0.067 ppm

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

$3 = 2.33 * \log (C / 0.067) + 0.5 \qquad C = 0.08$ ppm

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

LOA for MMA = 4.4 ppm * 1.33 = 0,11 ppm

Procedure according to van Doorn et al., 2002

DATA RELEVANT TO AEGL-2

HUMAN

- Lindberg et al. 1991: occupational exposure, floor layers, exposu 0.7-12 years, (see AEGL-1)

  n=10

  62-601 ppm (median: 175 ppm), repeatedly 20 minutes: irritation URT, 3/10 workers irritation, 6/10 reddened tonsiles and palates, no change in lung function

- Coleman 1963: **170-240 ppm** occupational exposure „very definite irritation" , no details and no preci data on exposure duration provided

- Pickering et al. 1986: asthma attac after **45 seconds** exposure to **374 ppm MMA** (single case, chronic exposure to MMA)

  No effects after exposure to **76 ppm**

no other qualified human inhalation studies with irreversible or disabling effects after short term MMA exposure available

ANIMAL:

- Pinto 1997: 5 female rats/group, single whole body exposure,

  110 ppm, 400 ppm (6h)

  110 ppm (6h): -degeneration and necrosis of the olfactory epithelium of minimal severity, subsequently „repaired"

  400 ppm (6h): -degeneration and necrosis of the olfactory epithelium (moderate severity, up to 50% of epithelium affected), bowman glands, inflammatory exudate

- Jones 2002: 5 male rats, single exposure, whole body

  200 ppm, (6h), degeneration and necrosis of the olfactory epithelium (3/5 animals)

- Mainwaring et al. 2001: 5 female rats(group, single exposure, whole

  body, 200 ppm, 3 and 6 hours

  200 ppm (3h): -no morphological abnormalities, immediately after exposure, no later examination

  200 ppm (6h): degeneration/atrophie olfactory epithelium, increased 18 hours after cessation of exposure

AEGL-2

Keystudy: Mainwaring et al. 2001, Jones 2002

Endpoint: severe irritation (observed: atrophie, degeneration olfactori epithelium) , rat, single 6 hour exposure, rats, 200 ppm

Total uncertainty factor: 3

Interspecies: 1

For MMA it is shown that humans are less or equally susceptible as rodents effects in the upper respiratory tract (Mainwaring et al., 2001; Andersen et al.,1999,2002; Bogdanffy et al., 1987,1998) . The interspecies uncertainty fac of 1 is used to compensate for both, toxicokinetic and toxicodynamic differen between species.

Intraspecies: 3

The intraspecies uncertainty factor is used to compensate for both, toxicokine and toxicodynamic differences between individuals. For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic effects. Therefore, a reduced uncertainty factor was retained to account for toxicodynamic differences between individuals. The relevant variability between individuals regarding carboxylesterase activity (Mainwaring et al., 2001) is already largely accounted for by use of the interspecies factor of 1.

Modifying factor: 1

The observed effect is above AEGL-2 threshold. Therefore a modifying facto 2 should be appropriate. However, as evidenced by human data (see supportir data) this would result in an AEGL-2 level below concentrations which are tolerated without relevant effects after chronic occupational exposure. Thus, a modifying factor >1 would lead to overly conservative values.

Time scaling: **default**

As shown by the study from Mainwaring et al. (2001) effect size increases with time. However, no qualified data exist to specify the effect-duration relationship. Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an qualified empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-minute, 1-hour- and 4-hour- time points and n = 1 for the 8-hour time point. The 10-min AEGL-2 was set at the same concentration as the 30 min. AEGL-2 due to the overall uncertainty of this extrapolation.

AEGL-2 Values for Methyl Methacrylate				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
150 ppm	150 ppm	120 ppm	76 ppm	50 ppm
620 mg/m^3	620 mg/m^3	500 mg/m^3	320 mg/m^3	100 mg/m^3

Supporting data:

- Human occupational data show no effects after single or repeated exposure to 50 ppm (Cromer and Kronoveter, 1976; Roehm, 1998). In consequence, no disabling effects are expected for sensitive subpopulations at single exposures to this concentration of MMA (8 hours).
- Human occupational data show relevant irritation at about 170-240 ppm (Lindberg et al., 1991; Coleman, 1963), which may be regarded as a threshold for AEGL-2. Inclusion of an uncertainty factor of 3 for intraspecies variability supports an AEGL-2 of 50 ppm (8 hours)
- An asthma attac was observed in a case study at exposures to MMA to 374 ppm with no effects at 76 ppm. Because asthma is linked to sensitiv subpopulations and appears to be a rare event in case of MMA-exposure and is not definitely verified no additional uncertainty factor is afforded. The NOEL of 76 ppm is close to AEGL-2, supporting the chosen value.
- In case of relevant problems of the existing data base for AEGL-2 effects the SOP provides the method to set AEGL-2 levels at AEGL-3 /3. Using this procedure the proposed values are supported.
- The derived AEGL-2 is consistent with the AEGL-2 for acrylic acid and methacrylic acid

DISCUSSION of POTENTIAL SENSITIZING PROPERTIES of MMA after INHALATION

- EU-Risk Assessment MMA, 2001: „...isolated cases of asthma in the context of methyl methacrylate exposure. Substance-specific bronchioconstriction or delayed asthmatic responses respectively were confirmed only in very few cases. Asthmatic reactions seem to be restricted to exposure levels which primarily result in respiratory tract irritation."
- OECD 2001, Health Canada 2002, similar assessment results, not classified as respiratory sensory irritant
- CEFIC: **aggravation** of asthma is considered reasonable
- No cases of asthma also in groups with occupational exposure including a high percentage of atopics (Roehm 1994; n=211)
- Pickering- case: asthma confirmed for the exposed nurse, but could be unspecific, and MMA not necessarily the primary cause, quite high concentrations

→Consequence: If MMA is an respiratory sensitizer, it is assumed to have very low potency. Derived AEGL-2 is below effect concentration (Pickering et al. 1986) for all durations, below NOAEL for longer durations. To use the 30-minutes AEGL-2 also for 10-minutes is justified to minimize risk for asthmatic responses due to relevant irritancy or by other mechanisms of action

DATA RELEVANT TO AEGL-3

HUMAN:

no studies with human exposure to lifethreatening effects to MMA are availab

ANIMALS:

- NTP (1986) no lethality was observed in 10 rats exposed to **4632 ppm** for 4 hours; after 6 hours exposure to 5000 ppm males and 2/5 females died after the first exposure in repeated exposure study
- Tansy et al. (1980a) rat, LC_{50}-study

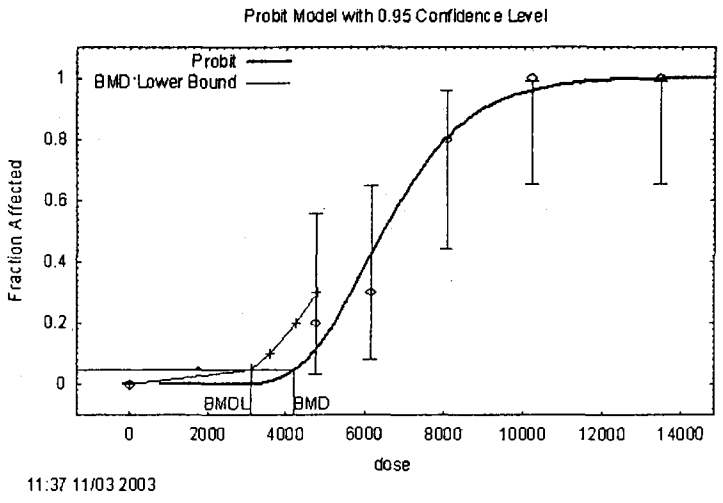
concentration [ppm] (4 hours exposure)	mortality / exposed animals
4750	2/10
6146	3/10
8044	8/10
10209	10/10
13479	10/10

Calculated : LC_{50} 7093 ppm

- other studies were less qualified or support the data from above; mice, guinea pigs and rabbits have a similar sensitivity

At AEGL-3 level not only effects in the upper respiratory effects may be expected, but also pulmonary effects and neurotoxicity

BENCHMARK CALCULATION - lethality data Tansy et al. 1980a



BMDS-software 1.3.2, EPA 2003

log-probit model was selected, zero incidence of lethality was assumed for no exposure (artificial control group),

p=0.7874

BMCL 05 = 3124.67 ppm

BMC 01 = 3537.83 ppm

==> only minor differences between the two values: the more conservative $BMDL_{05}$ was chosen as point of departure for AEGL3 derivation

Keystudy: Tansy et al. 1980a

Endpoint: lethality in rats, 4 hours exposure, $BMCL_{05}$ 3125 ppm

Total uncertainty factor: **10**

Interspecies: **3**

Lethality concentrations (LC_{50}, 4 hours) differed only marginally between rats, mice, rabbits and guinea pigs. Consequently, no large interspecies differences a expected.

Intraspecies: **3**

MMA causes lethal effects by local tissue destruction in the lung with limited influence of systemic distribution. The toxicodynamic variability is considered be limited because MMA causes death by unspecific mechanism. These arguments support a reduced intraspecies uncertainty factor of 3.

Time Scaling: **default**

Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.: (ten Berge et al. 1986). In the absence of a qualified empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolatin to the 30-minute-, 1 hour- time points and n = 1 for the 8-hour time point. For minutes the same value was used as for 30 minutes due to high uncertainties of extrapolating to this very short exposure time.

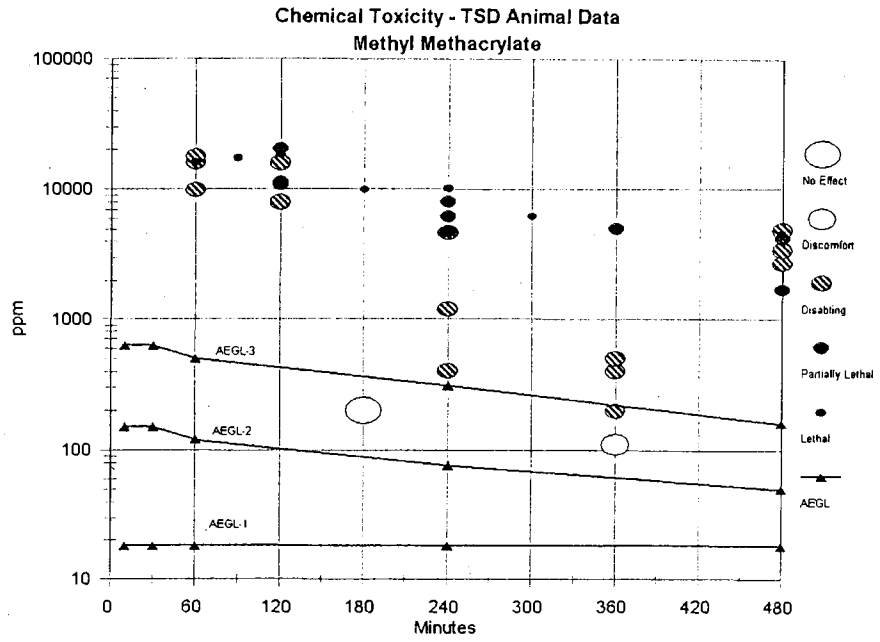
(AEGL-3, con'd:)

AEGL-3 Values for Methyl Methacrylate				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
630 ppm 2600 mg/m^3	630 ppm 2600 mg/m^3	500 ppm 2100 mg/m^3	310 ppm 1300 mg/m^3	160 ppm 670 mg/m^3

Support:

The derived AEGL-3 is consistent with the AEGL-3 for acrylic acid and methacrylic acid

Category Plot of Toxicity Data compared to AEGL Values



Proposed AEGL - animal studies [ppm]						
	10 min	30 min	1 hour	4 hours	8 hours	
AEGL-1 UF=6 (mod=2)	18	18	18	18	18	Pinto, 1997
AEGL-2 UF=3	150	150	120	76	50	Mainwaring et al., 2001
AEGL-3	630	630	500	310	160	Tansy et al., 1980

pro's:

- animal studies with controlled exposure conditions
- no qualified human study with specified duration for AEGL-2 endpoint

con's:

- uncertainties in interspecies extrapolation
- Mainwaring et al., 2001, effect > AEGL2
- Pinto, 1997 effect at concentration too close to AEGL-1

Alternatives:

- use human data for AEGL-1 (Cromer and Kronoveter, 1976): identical values (17 vs. 18 ppm). UF=3
- use human data for AEGL-2 (Cromer and Kronoveter, 1976): 50 ppm (8hours, identical) use standard time scaling from 8hours to short durations?!, UF=1
- use AEGL-3/3: 53/76/170/210/210 ppm

[ppm]

AEGL-1	UF (Inter; Intra; Modify) **Total)**	10 min	30 min	60 min	4 h	8h
MMA	1;3;2;**6**	18	18	18	18	18
MAA	1;3;1;**3**	6,7	6,7	6,7	6,7	6,7
Acrylic acid	1;3;1;**3**	1,5	1,5	1,5	1,5	1,5

AEGL-2						
MMA	1;3;1;**3**	150	150	120	76	50
MAA	1;3;1;**3**	76	76	61	38	25
Acrylic acid	1;3;1;**3**	68	68	46	21	14

AEGL-3						
MMA	3;3;1;**10**	630	630	500	310	160
MAA	3;3;1;**10**	280	280	220	140	71
Acrylic acid	3;3;1;**10**	480	260	180	85	58

AEGL Values for MMA *) [ppm]					
	10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1	18	18	18	18	18
AEGL-2	150	150	120	76	50
AEGL-3	630	630	500	310	160
	*) sensitizing properties and skin penetration may not be excluded after dermal contact				

Fritz handout #2

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

ETHYL ACRYLATE
(CAS Reg. No. 140-88-5)

SUMMARY OF HUMAN DATA

- No reports of fatalities
- No reports of respiratory sensitization
- No epidemiologic studies found
- Occupational monitoring:
  - <0.1-30 ppm
  - <1-27 ppb

SUMMARY OF ANIMAL DATA
LETHAL

Conc.	Duration	Species	Effect	Ref.
1204 ppm	7 hr/d, 3 days	monkey	death; irritation, spasmodic respiration, convulsions	Treon et al. 1949
1204 ppm 501 ppm 272 ppm	7 hr 7 hr/d, 4/13 d 7 hr/d, 8-17/28 d	rabbit/ guinea pig	death; irritation, spasmodic respiration, convulsions	Treon et al. 1949
1204 ppm 501 ppm	7 hr, 2 d 7 hr/d, 13 d	rat	death; irritation, spasmodic respiration, convulsions	Treon et al. 1949
6493 ppm	1 hr	rat	LC_{50}	Nachreimer and Dodd 1989
2180 ppm	4 hr	rat	LC_{50}	Oberly and Tansy 1985

SUMMARY OF ANIMAL DATA E7
NON-LETHAL

Conc.	Duration	Species	Effect	Ref.
75 ppm	3 or 6 hr	monkey	nasal lesions; incr with duration	Harkema et al. 1997; Rohm and Haas 1994
25 ppm	2-4 hr/d, 12 w	dog	irritation	DuPont 1946
272 ppm	7 hr/d, 28 exp	monkey, rat	irritation	Treon et al. 1949
24.5-26.2 ppm	7 hr/d, 130 exp	monkey, rat	none	Treon et al. 1949
74.8 ppm 24.5 ppm	7 hr/d, 50 exp 7 hr/d, 130 exp	rabbit, guinea pig	none	Treon et al. 1949
≥75 ppm ≥25 ppm	6 hr/d, 30 d 6 hr/d, 6 month	rat and mouse	nasal lesions; incr with concentration	BASF 1989

PROPOSED AEGL-1 VALUES

AEGL-1 Values for Ethyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	2.5	2.5	2.5	2.5	2.5

Key study: Treon et al. 1949, ~~DuPont 1946~~

Exposure: monkey; 25 ppm, 7 hr/d, 130 exp

Effect: NOAEL

UF: 10: 3 - interspecies
3 - intraspecies

Scaling: none

www. Sceence Direct

PROPOSED AEGL-2 VALUES

AEGL-2 Values for Ethyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	66	45	36	19	9.4

Key study: Harkema et al. 1997, Rohm and Haas 1994

Exposure: monkey; 75 ppm, 3 hr

Effect: lesions on ~15% of the olfactory epithelium

UF: ~~10~~ 3: 1 - interspecies
3 - intraspecies

Scaling: $C^n \times t = k$, where n = 1 or 3

PROPOSED AEGL-3 VALUES

AEGL-3 Values for Ethyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	701	486	386	97	49

Key studies: Nachreiner and Dodd 1989, Oberly and Tansy 1985

Exposure: rats; 6493 ppm, 1 hr
2730 ppm, 4 hr

Effect: LC_{50}

Calculations: log-probit analysis to estimate threshold for lethality
LC_{01} = 3855 ppm, 1 hr
LC_{01} = 1775 ppm, 4 hr

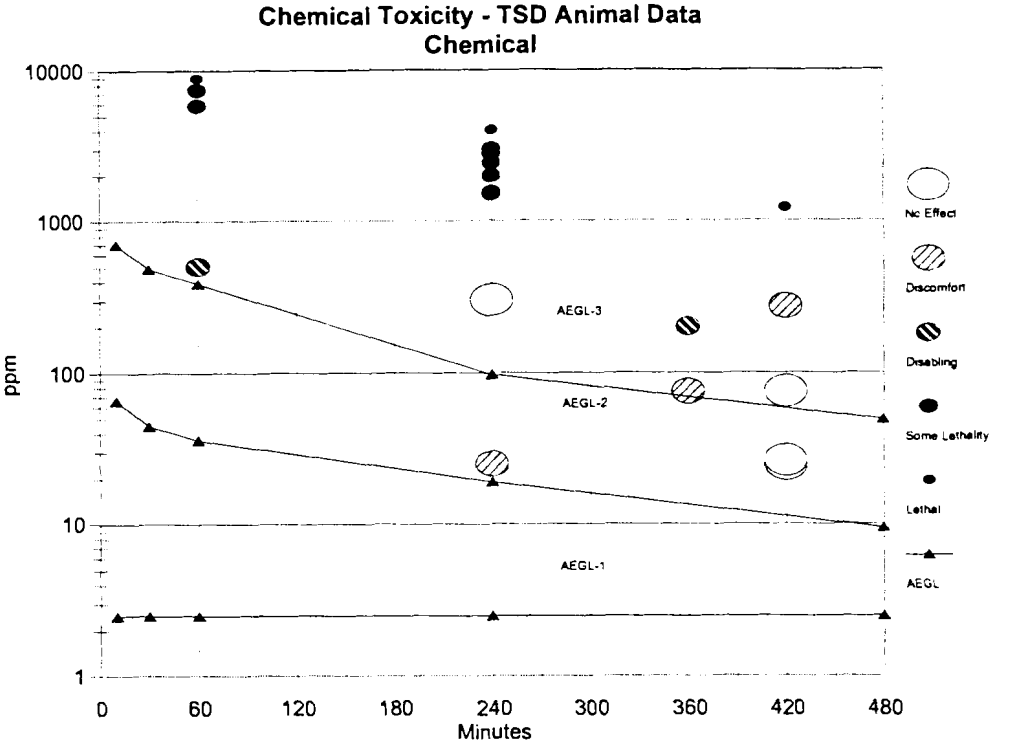
UF: 10 - 3: interspecies
3: intraspecies

Scaling: $C^n \times t = k$ where n = 1 or 3

SUMMARY OF PROPOSED AEGL VALUES FOR ETHYL ACRYLATE (ppm)

AEGL level	10-min	30-min	1-hr	4-hr	8-hr
1	2.5	2.5	2.5	2.5	2.5
2	66	45	36	19	9.4
3	701	486	386	97	49

PROPOSED VALUES



ALTERNATE AEGL VALUES

- Interspecies UF = 1 as with other acrylates and acrylic acid
- Time scaling n = 1.8 from acrylic acid
- $BMCL_{05}$ as basis for AEGL-3

ALTERNATE AEGL-1 VALUES

AEGL-1 Values for Ethyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	8.3	8.3	8.3	8.3	8.3

Key study: Treon et al. 1949, ~~DuPont 1946~~

Exposure: monkey; 25 ppm, 7 hr/d, 130 exp

Effect: NOAEL

UF: ~~10~~ 3: 1 - interspecies (humans less susceptible)
3 - intraspecies

Scaling: none

Frederick

5 ppm — 1, 3, ~~6~~ 5 hours no effects

25 ppm — no effects at 1 hr
3-hr: 2/5 - lesions on dorsal meatus
6-hr: 3/5 - " "

75 ppm — more lesions all times, 1 & 5 times
nothing at 1 hour

5 recovery

ALTERNATE AEGL-2 VALUES

AEGL-2 Values for Ethyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	68	68	46	21	14

Key study: Harkema et al. 1997, Rohm and Haas 1994

Exposure: monkey; 75 ppm, 3 hr

Effect: lesions on ~15% of the olfactory epithelium

UF: ~~10~~ 3: 1 - interspecies
3 - intraspecies

Scaling: $C^n \times t = k$, where n = 1.8 (from acrylic acid)

ALTERNATE AEGL-3 VALUES

AEGL-3 Values for Ethyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	434	301	239	71	35
	430	300	240	71	35

Key studies: Nachreiner and Dodd 1989, Oberly and Tansy 1985

Exposure: rats; 6493 ppm, 1 hr
2730 ppm, 4 hr

Effect: LC_{50}

Calculations: log-probit analysis to estimate
$BMCL_{05}$ = 2387 ppm, 1 hr
$BMCL_{05}$ = 706 ppm, 4 hr

UF: 10 - 3: interspecies
3: intraspecies

Time scaling: $C^n \times t = k$ where n = 1 or 3

ALTERNATE AEGL-3 VALUES FOR ETHYL ACRYLATE

Scaling: $C^n \times t = k$, where n = 1.8 (from acrylic acid)

AEGL-3 Values based on 1- and 4-hr LC_{01}					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	1043	566	386	97	66

AEGL-3 Values based on 1- and 4-hr $BMCL_{05}$					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	646	351	239	71	48

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

n-BUTYL ACRYLATE
(CAS Reg. No. 141-32-2)

SUMMARY OF HUMAN DATA

- No reports of fatalities
- No reports of respiratory sensitization
- No epidemiologic studies found
- Occupational monitoring:
  - 0.4-10.5 ppm
  - 12-93 ppb

SUMMARY OF ANIMAL DATA
LETHAL

Conc.	Duration	Species	Effect	Ref.
817 ppm	6 hr/d, 4 days	hamster	partial lethality; dyspnea, eye and nasal discharge	Engelhardt andKlimisch 1983
2730 ppm	4 hr	rat	LC_{50}; signs of irritation	Oberly and Tansy 1985
≥1278 ppm	4 hr	rat	death	BASF 1979
546 ppm	6 hr/d, 5 d/w, 13 weeks	rat	partial lethality; decr wt gain; irritation	Klimisch et al. 1978

SUMMARY OF ANIMAL DATA: NON-LETHAL

Conc.	Duration	Species	Effect	Ref.
≥677 ppm	4 hr	rat	irritation	BASF 1979, 1980
820 ppm	6 hr/d, 4 days	rat	dyspnea, eye discharge	Engelhardt andKlimisch 1983
340 ppm	30 minutes	mouse	RD_{50}	Kirkpatrick 2003
25 ppm	6 hr/d, GD 6-15	rat	none	Rohm and Haas Co. 1992
135 or 250 ppm	6 hr/d, GD 6-15	rat	irritation; decr wt gain; decr live fetuses; incr resorp	Rohm and Haas Co. 1992
108 ppm	6 hr/d, 5 d/w, 13 weeks	rat	decr weight gain; NOAEL for nasal lesions	Klimisch et al. 1978
211 ppm	6 hr/d, 5 d/w, 13 weeks	rat	decr weight gain; nasal lesions	Klimisch et al. 1978

PROPOSED AEGL-1 VALUES

AEGL-1 Values for Butyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	2.5	2.5	2.5	2.5	2.5

Key study: Rohm and Haas Co. 1992, Merkle and Klimisch 1983, Kirkpatrick 2003

Exposure: rats; 25 ppm, 6 hr/d, 10 d
mice; 30 ppm, 30 min

Effect: NOAEL for irritation and respiratory depression

UF: 10: 3 - interspecies
3 - intraspecies

Scaling: none

PROPOSED AEGL-2 VALUES

AEGL-2 Values for Butyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	~~118~~ 120	~~118~~ 120	94	59	30

Key study: none

Derivation: one-third AEGL-3

PROPOSED AEGL-3 VALUES

AEGL-3 Values for Butyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	355	355	282	178	89

Key study: Oberly and Tansy 1985

Exposure: rats; 2730 ppm, 4 hr

Effect: LC_{50}

Calculations: log-probit analysis to estimate threshold for lethality
LC_{01} = 1775 ppm

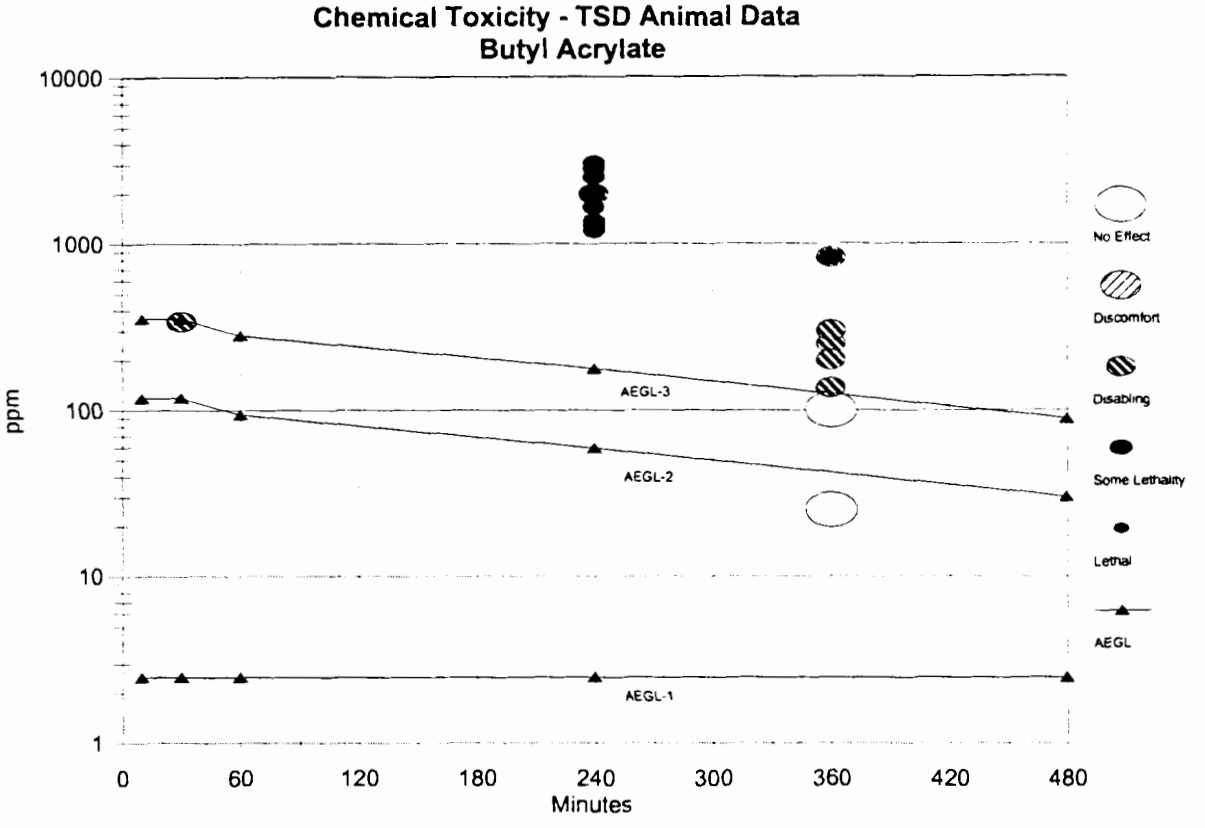
UF: 10 - 3: interspecies
3: intraspecies

Time scaling: $C^n \times t = k$ where n = 1 or 3

SUMMARY OF PROPOSED AEGL VALUES FOR BUTYL ACRYLATE (ppm)

AEGL level	10-min	30-min	1-hr	4-hr	8-hr
1	2.5	2.5	2.5	2.5	2.5
2	118	118	94	59	30
3	355	355	282	178	89

PROPOSED VALUES



ALTERNATE AEGL VALUES

- Interspecies UF = 1 as with other acrylates and acrylic acid
- Time scaling n = 1.8 from acrylic acid
- $BMCL_{05}$ as basis for AEGL-3

ALTERNATE AEGL-1 VALUES

AEGL-1 Values for Butyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	8.3	8.3	8.3	8.3	8.3

Key study: Rohm and Haas Co. 1992, Merkle and Klimisch 1983, Kirkpatrick 2003

Exposure: rats; 25 ppm, 6 hr/d, 10 d
mice; 30 ppm, 30 min

Effect: NOAEL for irritation and respiratory depression

UF: ~~10~~ 3: 1 - interspecies (humans less susceptible)
3 - intraspecies

Scaling: none

ALTERNATE AEGL-2 VALUES

AEGL-2 Values for Butyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	82	82	65	41	27

Key study: Klimisch et al. 1978

Exposure: rats; 108 ppm, 6 hr/d, 5 d/w, 13 weeks

Effect: NOAEL for histopathology of the nasal mucosa

UF: ~~10~~ 3: 1 - interspecies
3 - intraspecies

Scaling: $C^n \times t = k$, where n = 1 or 3

ALTERNATE AEGL-2 VALUES

AEGL-2 Values for Butyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	143	143	97	45	31

Key study: Klimisch et al. 1978

Exposure: rats; 108 ppm, 6 hr/d, 5 d/w, 13 weeks

Effect: NOAEL for histopathology of the nasal mucosa

UF: ~~10~~ 3: 1 - interspecies
3 - intraspecies

Scaling: $C^n \times t = k$, where n = 1.8 (from acrylic acid)

ALTERNATE AEGL-3 VALUES

AEGL-3 Values for Butyl Acrylate (ppm)					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	330	330	262	165	83

Key study: Oberly and Tansy 1985

Exposure: rats; 2730 ppm, 4 hr

Effect: LC_{50}

Calculations: log-probit analysis to estimate
$BMCL_{05}$ = 1652 ppm

UF: 10 - 3: interspecies
3: intraspecies

Time scaling: $C^n \times t = k$ where n = 1 or 3

ALTERNATE AEGL-3 VALUES FOR BUTYL ACRYLATE (ppm)

Scaling: $C^n \times t = k$, where n = 1.8 (from acrylic acid)

AEGL-3 Values based on 4-hr LC_{01}					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	564	564	383	178	121

AEGL-3 Values based on 4-hr $BMCL_{05}$					
AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	524	524	357	165	112

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

METHYL-2-CHLOROACRYLATE
(CAS Reg. No. 80-63-7)

Chemical and Physical Properties

- Cl replaces CH_3 in MMA
- water insoluble
- strong vesicant
- rapidly polymerizes

Available Data

- no production data
- Harris 1953
- Karpov 1956
- Texas Instruments 1992

Harris, DK 1953 Br. J. Ind. Med. 10:255-268

Case Reports:

- introduction statement that 5-10 ppm markedly irritating to eyes; effects may be latent

- liquid on skin causes blistering
- liquid in eye causes edema and conjunctivitis

Karpov BD 1956 Farmakologiya i Toksikologiya. 19:60 (Russian)

Exposures:

200-10,000 mg/m^3 (40.6-2028.4 ppm)
static chambers; calculated concentrations
cats, rabbits, guinea pigs, rats, mice

Results:

<u>Single 2-hr exposure</u>

500 mg/m^3 death of approximately 50% of animals
1000 mg/m^3 lethal to all animals
400 mg/m^3 minimum lethal to mice (most sensitive?)
severe irritation during exposure; survivors developed conjunctivitis, bronchitis

<u>Repeated exposure 2 hr/day</u>

cats, rabbits, gp
400 mg/m^3 animals died after 7-28 days
developed cough and lost weight

<u>Pathology</u>

epithelium lacking in some areas of trachea and bronchi
hemorrhagic edema in lungs

Karpov 1956 continued:

Comments

vapor effect threshold in cats: 500-1500 mg/m^3 for 15 minutes resulted in drooling and lacrimation

Humans:

20 mg/m^3 no effects (4.1 ppm)

100-200 mg/m^3 eye and respiratory irritation

Texas Instruments 1992
Ph.D. thesis by FL McClure in 1984

Exposures:

1 hour
dynamic chambers; analytical concentrations
male and female rats

Results:

	Unsexed	Male	Female
LC_{50}	105 ppm	119 ppm	120 ppm
LC_{16}	73 ppm	58 ppm	56 ppm
LC_{84}	152 ppm	245 ppm	260 ppm

signs of irritation, lacrimation, nasal discharge
pulmonary edema

CONCLUSIONS:

DATA ARE INSUFFICIENT FOR DERIVATION OF AEGL VALUES

- case reports lack concentration-duration
- calculated vs analytical concentrations
- no concentration-response data
- lack of supporting information
- lethality data inconsistent

ACUTE EXPOSURE GUIDELINE LEVELS
for
METHYL CHLORIDE

National Advisory Committee for AEGLs Meeting 31
December 10-12, 2003

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
George Rodgers

Chemical Reviewer:
Jim Holler

ATTACHMENT 14

METHYL CHLORIDE

Data for AEGL-1:

Stewart et al. 1985

100 ppm... 9 exercising male and 9 female subjects
both "fast" and "slow" methyl chloride metabolizers
1, 3, or 7.5 hours/day for 5 consecutive days
no eye, nose, or throat irritation
no physiological effects
no neurological symptoms

100 ppm (50-150 ppm)... 9 male subjects (exercise)
1, 3, or 7.5 hours/day for 5 consecutive days
no eye, nose, or throat irritation
no physiological effects; no neurological symptoms

150 ppm...4 male subjects (exercise)
1, 3, or 7.5 hours/day for 2 consecutive days
no eye, nose, or throat irritation
no physiological effects; no neurological symptoms

METHYL CHLORIDE

Putz-Anderson et al. 1981a

0, 100, or 200 ppm for 3 hours...

8-12 male and female subjects

no noticeable odor

"little or no effect on three tests of alertness"

Putz-Anderson et al. 1981b

0 or 200 ppm for 3.5 hours...

12 male and female subjects

no significant impairment on tests of alertness

co-exposures to other chemicals: effects not greater than sum of effects

METHYL CHLORIDE

Suggestion: Basis for AEGL-1 is 100 ppm based on repeated exposures in well-conducted study of Stewart et al. (1981), supported by well-conducted studies of Putz-Anderson et al. (1981a;b). The 100 and 150 ppm concentrations with repeated exposures were NOAELs for any effect in the Stewart et al. study. The 100 ppm value is half of the NOAEL for any effect (200 ppm) in the Putz-Anderson et al. studies. Intraspecies uncertainty factor of 1 was applied based on use of male and female subjects, exercise incorporated in one protocol, testing of "fast" and "slow" metabolizers, and fact that higher exposures were also NOAELs.

No time scaling applied because steady state is rapidly attained and metabolism is rapid.

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	100 ppm	100 ppm	100 ppm	100 ppm	100 ppm

METHYL CHLORIDE

Data for AEGL-2:

Human data:
MacDonald (1967) (concentrations were monitored, but not given as TWA)
up to 1600 ppm, 1000-2000 ppm, and repeated exposure to 2000-4000 ppm
symptoms of dizziness, blurring of vision, headache, nausea

Animal data:
Mouse is not a good model - metabolic pathway different from rats and humans

Dodd et al. (1982)
rat - 1500 ppm for 6 hours - no clinical signs

Mitchell et al. (1981b)
rat - 1500 ppm for 90 days - no clinical signs, no organ lesions

METHYL CHLORIDE

Suggestion: Basis for AEGL-2 is a combination of human and animal studies. Transient symptoms of blurring of vision, dizziness, nausea, etc. were described following a single human exposure to 1000-2000 ppm and following a repeated exposure to 2000-4000 ppm (MacDonald 1964). No clinical signs were observed in rats exposed to 1500 ppm for 6 hours (Dodd et al. 1982) or 90 days (Mitchell et al. 1981b). Applying a single intraspecies uncertainty factor of 3 to the lower mean concentration (1500 ppm) in the MacDonald study or to the 1500 ppm concentration in the Dodd et al. or Mitchell et al. studies results in a value of 500 ppm. An interspecies uncertainty factor of 1 is sufficient as (1) uptake is greater in rodents than in humans (Landry et al. 1983; Nolan et al. 1985), and (2) one of the rodent studies was subchronic.

No time scaling was applied because steady state is rapidly attained; metabolism is rapid.

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	500 ppm	500 ppm	500 ppm	500 ppm	500 ppm

METHYL CHLORIDE

Data for AEGL-3:

Conflicting/insufficient

Suggestion: Data that address effects at the AEGL-3 level are conflicting/insufficient. Mice are particularly sensitive to methyl chloride and are not good surrogates for humans. Rat data from repeat exposures show that a 6-hour exposure to 5000 ppm (Chellman et al. 1986b; Morgan et al. 1982) and a 10-minute exposure to 20,000 ppm (Kolkmann and Volk 1975) are non-lethal. Humans have survived exposures to 2000-4000 ppm and short excursion to 10,000 ppm (MacDonald 1967). In order to give guidance to emergency responders, scientific judgement indicates that exposures would have to be higher than 2000 ppm in order to be lethal to humans.

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	>2000 ppm	>2000 ppm	>2000 ppm	>2000 ppm	>2000 ppm

METHYL CHLORIDE

Classification	Exposure Duration				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	100 ppm	100 ppm	100 ppm	100 ppm	100 ppm
AEGL-2	500 ppm 1650 ppm	500 ppm 1100 ppm	500 ppm 900 ppm	500 ppm 570 ppm	500 ppm 450 ppm
AEGL-3	>2000 ppm	>2000 ppm	>2000 ppm	>2000 ppm	>2000 ppm

ACUTE EXPOSURE GUIDELINE LEVELS
for
METHYL CHLORIDE

National Advisory Committee for AEGLs Meeting 31
December 10-12, 2003

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
George Rodgers

Chemical Reviewer:
Jim Holler

METHYL CHLORIDE

Data for AEGL-1:

Stewart et al. 1985

100 ppm... 9 exercising male and 9 female subjects
both "fast" and "slow" methyl chloride metabolizers
1, 3, or 7.5 hours/day for 5 consecutive days
no eye, nose, or throat irritation
no physiological effects
no neurological symptoms

100 ppm (50-150 ppm)... 9 male subjects (exercise)
1, 3, or 7.5 hours/day for 5 consecutive days
no eye, nose, or throat irritation
no physiological effects; no neurological symptoms

150 ppm...4 male subjects (exercise)
1, 3, or 7.5 hours/day for 2 consecutive days
no eye, nose, or throat irritation
no physiological effects; no neurological symptoms

METHYL CHLORIDE

Putz-Anderson et al. 1981a

- 0, 100, or 200 ppm for 3 hours...
  - 8-12 male and female subjects
  - no noticeable odor
  - "little or no effect on three tests of alertness"

Putz-Anderson et al. 1981b

- 0 or 200 ppm for 3.5 hours...
  - 12 male and female subjects
  - no significant impairment on tests of alertness
  - co-exposures to other chemicals: effects not greater than sum of effects

METHYL CHLORIDE

Suggestion: Basis for AEGL-1 is 100 ppm based on repeated exposures in well-conducted study of Stewart et al. (1981), supported by well-conducted studies of Putz-Anderson et al. (1981a;b). The 100 and 150 ppm concentrations with repeated exposures were NOAELs for any effect in the Stewart et al. study. The 100 ppm value is half of the NOAEL for any effect (200 ppm) in the Putz-Anderson et al. studies. Intraspecies uncertainty factor of 1 was applied based on use of male and female subjects, exercise incorporated in one protocol, testing of "fast" and "slow" metabolizers, and fact that higher exposures were also NOAELs.

No time scaling applied because steady state is rapidly attained and metabolism is rapid.

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	100 ppm	100 ppm	100 ppm	100 ppm	100 ppm

METHYL CHLORIDE

Data for AEGL-2:

Human data:
MacDonald (1967) (concentrations were monitored, but not given as TWA)
up to 1600 ppm, 1000-2000 ppm, and repeated exposure to 2000-4000 ppm
symptoms of dizziness, blurring of vision, headache, nausea

Animal data:
Mouse is not a good model - metabolic pathway different from rats and humans

Dodd et al. (1982)
rat - 1500 ppm for 6 hours - no clinical signs

Mitchell et al. (1981b)
rat - 1500 ppm for 90 days - no clinical signs, no organ lesions

METHYL CHLORIDE

Suggestion: Basis for AEGL-2 is a combination of human and animal studies. Transient symptoms of blurring of vision, dizziness, nausea, etc. were described following a single human exposure to 1000-2000 ppm and following a repeated exposure to 2000-4000 ppm (MacDonald 1964). No clinical signs were observed in rats exposed to 1500 ppm for 6 hours (Dodd et al. 1982) or 90 days (Mitchell et al. 1981b). Applying a single intraspecies uncertainty factor of 3 to the lower mean concentration (1500 ppm) in the MacDonald study or to the 1500 ppm concentration in the Dodd et al. or Mitchell et al. studies results in a value of 500 ppm. An interspecies uncertainty factor of 1 is sufficient as (1) uptake is greater in rodents than in humans (Landry et al. 1983; Nolan et al. 1985), and (2) one of the rodent studies was subchronic.

No time scaling was applied because steady state is rapidly attained; metabolism is rapid.

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	500 ppm	500 ppm	500 ppm	500 ppm	500 ppm

METHYL CHLORIDE

Data for AEGL-3:

Conflicting/insufficient

Suggestion: Data that address effects at the AEGL-3 level are conflicting/insufficient. Mice are particularly sensitive to methyl chloride and are not good surrogates for humans. Rat data from repeat exposures show that a 6-hour exposure to 5000 ppm (Chellman et al. 1986b; Morgan et al. 1982) and a 10-minute exposure to 20,000 ppm (Kolkmann and Volk 1975) are non-lethal. Humans have survived exposures to 2000-4000 ppm and short excursion to 10,000 ppm (MacDonald 1967). In order to give guidance to emergency responders, scientific judgement indicates that exposures would have to be higher than 2000 ppm in order to be lethal to humans.

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	>2000 ppm	>2000 ppm	>2000 ppm	>2000 ppm	>2000 ppm

METHYL CHLORIDE

Classification	Exposure Duration				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	100 ppm	100 ppm	100 ppm	100 ppm	100 ppm
AEGL-2	500 ppm 1650 ppm	500 ppm 1100 ppm	500 ppm 900 ppm	500 ppm 570 ppm	500 ppm 450 ppm
AEGL-3	>2000 ppm	>2000 ppm	>2000 ppm	>2000 ppm	>2000 ppm

ACUTE EXPOSURE GUIDELINE LEVELS
for
METHYL BROMIDE

National Advisory Committee for AEGLs Meeting 32
April 19-21, 2004

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
George Rodgers

Chemical Reviewer:
Jim Holler

ATTACHMENT 15

METHYL BROMIDE

Data for AEGL-1: No acute data that meets definition of AEGL-1

Options: 1. Do not set an AEGL-1

2. Set a safe level from a repeat-dose or chronic study; for example,

20 ppm for 6 weeks, NOAEL in dogs (Schaefer 2002)

20 ppm for all days of gestation, NOAEL for maternal toxicity and developmental effects in rabbit (Breslin et al. 1990)

27 ppm for 8 months, NOAEL for neurotoxicity in rabbit (Russo et al. 1984)

33 ppm for 2 years, NOAEL for any effect in mice (NTP 1992)

Suggestion: Basis for AEGL-1 is NR or 20 ppm (the old ACGIH TWA was 20 ppm). No time scaling was applied because steady state is rapidly attained and metabolism is rapid. Also, study is long term.

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	NR 20 ppm	NR 20 ppm	NR 20 ppm	NR 20 ppm	NR 20 ppm

METHYL BROMIDE

Data for AEGL-2:

Human data: No relevant, reliable human data

Animal data: Weight of evidence approach; endpoint is neurotoxicity

213 ppm for 5 hours, NOAEL for neurotoxicity in dogs (Newton 1993a)
200 ppm for 4 hours no clinical signs in rats (Hastings 1990)
225 ppm for 4 hours no clinical signs in rat, mouse (JML 1992)
transient impairment of olfactory function
200 ppm for 6 hours, no clinical signs in rat (Hurtt et al. 1988)
reversible olfactory epithelium degeneration

Suggestion: Start with lowest value (200 ppm) for shortest time (4 hours)

METHYL BROMIDE

Uncertainty Factors:

Interspecies: Rodents have higher levels of glutathione-*S*-transferase than humans (Griem et al. 2002), resulting in faster metabolism and potentially, faster production of toxic metabolites (alkylation of vital proteins). Additionally, uptake is greater in rodents due to their higher respiratory rate.

Adjust with interspecies UF of 1

Intraspecies: Humans differ in number of copies of GST gene, i.e., they are slow or fast metabolizers of the methyl halides difference of questionable toxicological significance (<3-fold) (Nolan et al. 1985).

Adjust with intraspecies UF of 3

Time-scaling: n = 1.2, based on rodent lethality studies.

Classification	Exposure Duration				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-2	940 ppm	380 ppm	210 ppm	67 ppm	67 ppm

METHYL BROMIDE

Data for AEGL-3:

Use highest non-lethal value in rodents

rat, 4 hours, 700 ppm (Kato et al. 1986)
rat, 4 hours, 506 ppm (Japanese Ministry of Labour 1992)
rat, 8 hours, 268 ppm (Honma et al. 1985)
mouse, 1 hour, 900 ppm (Alexeeff et al. 1985)
mouse, 4 hours, 338 ppm (Japanese Journal of Labour 1992)
mouse, 4 hours, 312 ppm (Yamano 1991)

Choose most sensitive species.... mouse

Uncertainty Factors:

Interspecies: Rodents have higher levels of glutathione-*S*-transferase than humans (Griem et al. 2002), resulting in faster metabolism and potentially, faster production of toxic metabolites (alkylation of vital proteins). Additionally, uptake is greater in rodents due to their higher respiratory rate.

Adjust with interspecies UF of 1

METHYL BROMIDE

Intraspecies: Humans differ in number of copies of GST gene,
i.e., they are slow or fast metabolizers of the methyl halides
difference of questionable toxicological significance
(Nolan et al. 1985).
Adjust with intraspecies UF of 3

Time-scaling: n = 1.2, based on rodent lethality studies.

Classification	Exposure Duration				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-3					
mouse, 900-1	1300 ppm	530 ppm	300 ppm	95 ppm	95 ppm
mouse, 338-4	1600 ppm	640 ppm	360 ppm	110 ppm	63 ppm
rat, 700-4	3300 ppm	1300 ppm	740 ppm	230 ppm	130 ppm
rat, 268-8	2200 ppm	900 ppm	500 ppm	160 ppm	89 ppm

METHYL BROMIDE

Classification	Exposure Duration				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	NR 20 ppm	NR 20 ppm	NR 20 ppm	NR 20 ppm	NR 20 ppm
AEGL-2	940 ppm	380 ppm	210 ppm	67 ppm	67 ppm
AEGL-3	1300 ppm	530 ppm	300 ppm	95 ppm	95 ppm

Methyl Bromide

California Department of Pesticide Regulations
- responsible for establishing permit conditions that govern the application of methyl bromide for pest control
- regulates agricultural use of methyl bromide

Risk Characterization
- Acute RfC: 210 ppb
- Subchronic (1-week): 120 ppb, adults; 70 ppb, children
  6-week: 2 ppb, adults, 1 ppb for children
- Chronic: 2 ppb, adults, 1 ppb, children

Environmental Levels (ATSDR 1992)
- Over oceans: <0.025 ppb (natural source)
- Rural areas: <0.025 ppb
- Suburban/urban U.S.: up to 1.2 ppb
- Near fumigated areas: 25 ppm

Accidental Exposures

1. Ingram 1951
   50 cases methyl bromide symptoms in date processing plants
   measurements with halide torch and colorimetrically
   concentrations up to 100 ppm in workroom air
      up to 500 ppm near walls of fumigation chamber
         (located next to workroom)
      1000 ppm in breathing zone of workers entering
         fumigation chamber

2. Hustinx et al. 1993
   greenhouse fumigation
   severe neurological symptoms
   five hours later: 150-200 ppm, suggesting the original
      concentration was >200 ppm
   detection by Drager tubes

3. Deschamps and Turpin 1996
   two fumigation workers
   entered building at measured concentration (GC) of 4370 ppm
   charcoal cartridge respirators saturated in a few minutes
   remained in the building for 1 hour
   severe symptoms, permanent neurological damage in one worker

Current main AEGL web page
http://www.epa.gov/oppt/aegl/

The Development of
Acute Exposure Guideline Levels (AEGLs)
A collaborative effort of the public and private sectors worldwide

Acute Exposure Guideline Levels, or AEGLs, describe the dangers to humans resulting from short-term exposure to airborne chemicals. The National Advisory Committee for AEGLs is developing these guidelines to help both federal and local authorities, as well as private companies, deal with emergencies involving spills, or other accidental exposures.

SOP

The AEGL Standard Operating Procedures section "Purpose and Objectives of the AEGL Program and the NAC/AEGL Committee" (page 21) states:

> "The primary purpose of the AEGL program and the NAC/AEGL Committee is to develop guideline levels for once-in-a-lifetime, short-term exposures to airborne concentrations of acutely toxic, high-priority chemicals."

In order to accurately reflect this statement two suggestions have been made and one alternative suggestion.

Suggested additional phrases

Add "once-in-a-life-time"

1) Acute Exposure Guideline Levels, or AEGLs, describe the dangers to humans resulting from **ONCE-IN-A-LIFETIME**, short-term exposure to airborne chemicals. The National Advisory Committee for AEGLs is developing these guidelines to help both federal and local authorities, as well as private companies, deal with emergencies involving spills, or other accidental exposures.

Add "are intended to" and once-in-a-life-time"

2) Acute Exposure Guideline Levels, or AEGLs, **ARE INTENDED TO** describe the dangers to humans resulting from **ONCE-IN-A-LIFETIME**, short-term exposure to airborne chemicals. The National Advisory Committee for AEGLs is developing these guidelines to help both federal and local authorities, as well as private companies, deal with emergencies involving spills, or other accidental exposures.

Add "rare or infrequent"

3) I strongly object to the term "once in a life-time" because I have had the most unpleasant experience of people who will take that term and apply it to mean that AEGL's do not apply to two accidental releases 20 years apart in the same community etc. I can support a term "rare or infrequent" with a definition of less than once in 6 months or 1 year etc. But the proposed changes are so rigid that it all but spells the end of the usefulness of the AEGL committee.

FMC

Acute Exposure Guideline Levels (AEGLs) for Peracetic Acid

April 20, 2004

Dr. Myra Weiner

Research Fellow in Toxicology

FMC Corporation

Princeton, NJ

ATTACHMENT 17

FMC

What is peracetic acid (PAA)?

- An equilibrium mixture

$$\mathbf{CH_3COOOH + H_2O \Leftrightarrow CH_3COOH + H_2O_2}$$

peracetic acid + water acetic acid + hydrogen peroxide

- Concentration of PAA in air will be a function of the concentration of each component in the formulation.
- PAA decomposes rapidly in air ($T_{1/2}$ =22 min). The decomposition products are acetic acid and hydrogen peroxide.

Reference: ECETOC JACC Report No. 40, Peracetic Acid, 2001.

FMC

Proposed AEGLs for PAA

AEGL-1	30 min: 0.17 ppm	1 hr: 0.17 ppm	4 hr: 0.17 ppm	8 hr: 0.17 ppm
AEGL-2	30 min: 0.5 ppm	1 hr: 0.5 ppm	4 hr: 0.5 ppm	8 hr: 0.5 ppm
AEGL-3	30 min: 9.6 ppm	1 hr: 4.8 ppm	4 hr: 2.6 ppm	8 hr: 1.9 ppm

FMC

FMC Comments

- AEGL-1: No objection to the EPA proposal
- AEGL-2: Level is too conservative
- AEGL-3: Available data support a higher level for longer time periods

FMC

Comments on AEGL-2

- Humans have extreme discomfort after 5 minutes at 3 ppm.

  Reference: Fraser, JAL and Thorbinson, A. 1986. Fogging Trials with Tenneco Organics Limited (30th June, 1986) at Collards Farm.

- AEGL-2 (0.5 ppm) is highly conservative since humans tolerate up to 2 ppm with extreme discomfort as the only effect.
- Since the AEGL-2 protects from irreversible harm, a level of >0.5 ppm is appropriate, for example 1.5 ppm.

FMC

Comments on AEGL-3

- 4 hour AEGL-3 of 2.6 ppm is highly conservative. Human data show that the only consequence of exposure to this level is extreme discomfort after five minutes. **Reference: Fraser, JAL and Thorbinson, A. 1986. Fogging Trials with Tenneco Organics Limited (30th June, 1986) at Collards Farm.**
- Although there was no lethality in the human study, **it can still be used** to estimate an AEGL-3.
- The fogger study used aerosols which over-estimate the toxicity compared to the vapor.
- The liquid aerosol tends to stay on the mucous membranes longer and continues to produce irritancy.

FMC

Human Exposure to Peracetic Acid Aerosols during Fogging

Time: min	Concentration: ppm (as total H_2O_2)	Observed Effects
3.30 - 3.37	5	Extreme discomfort, irritation of nasal membranes, lacrimation
5.0	2.5	Extreme discomfort
5.1	3.0	Extreme discomfort
5.2	2.0	Irritation tolerable for 2 minutes
20	1 – 1.5	Discomfort of mucous membranes
30	0.5 – 1	Discomfort mild
35	0.5	No discomfort

Reference: Fraser, JAL and Thorbinson, A. 1986. Fogging Trials with Tenneco Organics Limited (30th June, 1986) at Collards Farm.

FMC

Human Exposure to Peracetic Acid Aerosols after Fogging

Time: min	**Concentration: ppm** (as total H_2O_2)	**Observed Effects**
5 – 10	2.0	Extreme discomfort of mucous membranes
15 - 20	1.0 – 1.5	Discomfort of mucous membranes
25	1.0	Discomfort tolerable
30	0.5 – 1.0	Discomfort mild
33 – 45	$\leq$ 0.5	No discomfort

Reference: Fraser, JAL and Thorbinson, A. 1986. Fogging Trials with Tenneco Organics Limited (30th June, 1986) at Collards Farm.

Comments on AEGL-3

- FMC 4-hour LC50 whole-body inhalation study in rats with 0.15% PAA aerosol/vapor at a maximum attainable concentration of 2466 ppm. There were **no** deaths. 4-hr LC50 > 2466 ppm.
- The animal LC0 is greater than 2466 ppm.
- If we apply standard inter- & intraspecies safety factor of 100-fold safety factor to the 4-hour LC50, we get 24.7 ppm.
- Janssen & van Doorn, 1994 (Solvay Report S-9408) exposed rats nose-only to 28 ppm PAA (Proxitane AHC, 15%) for 4 hours. There were **no** deaths at 28 ppm. The 4-hr LC50 was 66 ppm.

Comments on AEGL-3

FMC

- The use of animal data (LC50/LC01) for calculation of the AEGL-3 values is very conservative and does not take into account the more relevant human data.
- Examples of AEGLs on other irritants generally show higher AEGL-3 values:

  Chlorine: AEGL-3 = 20 ppm (1 hr)

  Nitric Acid: AEGL-3 = 92 ppm (1 hr)
- **Suggest AEGL-3 of 20 ppm be used for all time periods.**
  - $\simeq$ 4 hr **LC0** of 15% PAA in rats (28 ppm)
  - $\simeq$1/100th the 4 hr **LC0** of 0.15% PAA in rats
  - Irritant effects of PAA are **reversible** in animals (survivors of high doses) and humans.

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

December 10-12, 2003

Final Meeting-31 Highlights

La Mansion Del Rio
San Antonio, Texas

INTRODUCTION

Mr. Eric Stephens, Director of the Air Force Institute for Operational Health (AFIOH) welcomed the group to San Antonio and presented an overview of the AFIOH mission and the relevance of the AEGL process (Attachment 1). Mr. George Irving of Core 6 Solutions also welcomed the group and explained meeting logistics.

Ernie Falke announced that the AEGL public internet site should be up by January 5, 2004. The site will include proposed, interim, and final AEGL values, and .pdf files of the final documents; these files will be provided by the National Academy of Sciences and will be posted on the site. Ernie Falke also introduced Marquea King, a toxicologist on the EPA staff who is now working with the AEGL program.

The draft NAC/AEGL-30 meeting highlights were reviewed. Bob Benson pointed out that text was missing from the carbon monoxide discussion. Several committee members were concerned that no discussion was presented in the meeting summary text explaining the relationship of derived AEGL values for styrene, propane, and butane to the Lower Explosive Limit (LEL); explanation had only been included in the table footnotes. It was decided that the meeting highlights should be revised to include the LEL explanation in the text, while also maintaining the table footnotes. George Alexeeff pointed out that the AEGL-1 for propane was based on a NOAEL for vertigo; this needs to be added to the meeting summary. Marquea King explained that during NAC/AEGL-30, the AEGL-1 values for acetone cyanohydrin were not rounded correctly (AEGL-1 values were obtained by doubling the former AEGL-1 values after removing the modifying factor). The correct values should be 2.1 ppm (instead of 2.2 ppm) for the 10- and 30-min values and 0.69 ppm (instead of 0.70 ppm) for the 8-hour value. This modification was approved unanimously by a voice vote. A motion was made by John Hinz and seconded by Richard Thomas to accept the meeting highlights as presented with the aforementioned revisions. The motion passed unanimously by a voice vote. The final version of the NAC/AEGL-30 meeting highlights is attached (Appendix A) and was distributed to the NAC/AEGL by e-mail.

The highlights of the NAC/AEGL-31 meeting are summarized below along with the Meeting Agenda (Attachment 2) and the Attendee List (Attachment 3). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-31 Agenda.

RESPONSES TO *FEDERAL REGISTER* COMMENTS ON THE PROPOSED AEGL VALUES

Comments from the *Federal Register Notice* of July 18, 2003, on the proposed AEGL values for ammonia, xylenes, and methyl ethyl ketone were reviewed and discussed. The NAC/AEGL deliberation of these chemicals are briefly summarized as the following:

Ammonia (CAS No. 7664-41-7)

Chemical Manager: Larry Gephart, ExxonMobil
Staff Scientist: Kowetha Davidson, ORNL

Comments were received from William C. Herz (Director of Scientific Programs, The Fertilizer Institute (TFI)), Mary Lee Hultin (Michigan Department of Environmental Quality), George Alexeeff, and John Morawetz. TFI commented on AEGL-1, -2, and -3 values; comments concerned the consistency of points of departure with the AEGL definitions, over-application of uncertainty factors (UF), time-scaling to 4- and 8-hour exposure durations, and potential for incorrect interpretation and regulatory misuse of AEGLs. Dr. Hultin commented that points of departure appeared to be based on appropriate science; however, concern was expressed regarding the selection of the intraspecies UF of only 1. Dr. Alexeeff and Mr. Morawetz both expressed concern regarding AEGL-2 and AEGL-3 values and the use of an intraspecies UF on 1. Kowetha Davidson responded to the scientific issues raised by these comments (Attachment 4). Dr. William Herz (Director of Scientific Programs for The Fertilizer Institute) also participated in the discussion and thanked the NAC for their thorough consideration of the comments. Dr. Davidson then proposed revising the AEGL-1 values (Attachment 5) from 25 ppm at all time points to 50 ppm at all time points based on moderate irritation in humans. After considerable discussion, a motion was made by Nancy Kim and seconded by Tom Hornshaw to adopt AEGL-1 values of 30 ppm for all time points based on very mild irritation in humans exposed to ammonia for 10 minutes. The motion passed (YES: 15; NO: 0; ABSTAIN: 3) (Appendix B). A motion was then made by Ernest Falke and seconded by George Rodgers to have no further discussion regarding AEGL-2 or AEGL-3 and to elevate the ammonia TSD to interim status. The motion passed (YES: 16; NO: 1; ABSTAIN: 0) (Appendix B).

SUMMARY OF INTERIM AEGL VALUES FOR AMMONIA [ppm (mg/m^3)]							
Classification	Exposure Duration						Endpoint (Reference)
	5 min	10 min	30 min	1 hour	4 hours	8 hours	
AEGL-1 (Nondisabling)	30 (20)	30 (20)	30 (20)	30 (20)	30 (20)	30 (20)	Very mild irritation (MacEwen et al., 1970); Verberk, 1977
AEGL-2 (Disabling)	380 (266)	270 (189)	160 (112)	110 (77)	110 (77)	110 (77)	Irritation: eyes and throat; urge to cough (Verberk, 1977)
AEGL-3 (Lethal)	3800 (2657)	2700 (1890)	1600 (1119)	1100 (769)	550 (385)	390 (273)	Lethality (Kapeghian et al., 1982; MacEwen and Vernot, 1972)

Xylenes (CAS No. 1330-20-7)

Chemical Manager: Bob Benson, EPA
Staff Scientist: Claudia Troxel, ORNL

Comments were received from George Alexeeff, United Auto Workers (UAW) International Union, Clean Channel Association, Michigan Department of Environmental Quality (DEQ), and The American Chemistry Council (ACC). Dr. Alexeeff's comments suggested revising AEGL-1, -2, and -3 derivation descriptions to improve clarity. The UAW comments also concerned clarity in the derivation of AEGL-1 and AEGL-2 values, in addition to health effects noted at AEGL-2 and AEGL-3 concentrations being consistent with the AEGL definitions. The Clean Channel Association commented on needed notation when AEGL values approach the Lower Explosive Limit (LEL). The Michigan DEQ and the ACC both commented on the need to more thoroughly explain why separate AEGL values were not derived for individual xylene isomers. Claudia Troxel responded to issues raised by these comments (Attachment 6) and provided the committee with a revised text of the Summary and derivation sections of the TSD (Attachment 7). Dr. Troxel then discussed using PBPK modeling to refine the derived AEGL values (Attachment 8), pointing out that there is a flaw in the current TSD in that the assumption is made that a human and rat exposed to the same external xylene concentration will have the same internal dose. However, the rat will actually experience a greater xylene dose due blood: air partitioning and greater ventilation rate. Discussion then focused on whether to use modeling as support for values derived by SOP methodologies or to derive values based on modeling. After considerable discussion, a motion was made by Ernest Falke and seconded by Richard Thomas to accept AEGL-2 values of 1100 ppm for 10-min, 600 ppm for 30-min, and 400 ppm for 1-, 4-, and 8-hours based on PBPK modeling suggesting that values are below the threshold for CNS depression at 2 hours (Carpenter et al., 1975). Values were based on exposure at 50W of work for 10 and 30 minutes and 1 hour, and then held constant for the 4- and 8-hour time points because it was assumed that it is unlikely that any individual could maintain 50W work for 4 to 8 hours. An intraspecies UF of 3 was applied. The motion passed (YES: 14; NO: 1; ABSTAIN: 1) (Appendix

C). A motion was then made by Bob Benson and seconded by Ernest Falke to accept AEGL-3 values of 3300 ppm for 10-min, 1700 ppm for 30-min, and 1100 ppm for 1-, 4-, and 8-hours based on PBPK modeling with the endpoint of no lethality in rats exposed for 4 hours. Values again were based on exposure at 50W of work for 10 and 30 minutes and 1 hour, and then held constant for the 4- and 8-hour time points because it was assumed that it is unlikely that any individual could maintain 50W work for 4 to 8 hours. An intraspecies UF of 3 was applied. The motion passed (YES: 13; NO: 0; ABSTAIN: 3) (Appendix C). It was decided to pass the xylene values, but it was agreed that xylenes could come back to the committee if refinements on the PBPK model need to be made, particularly regarding the physiological parameters used for work.

Summary of Proposed AEGL Values for Xylenes (ppm)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1 (Nondisabling)	**130**	**130**	**130**	**130**	**130**	**Eye irritation in human volunteers exposed to 400 ppm mixed xylenes for 30 minutes (Hastings et al., 1986)**
AEGL–2 (Disabling)	**1100**	**600**	**400**	**400**	**400**	**Rats exposed to 1300 ppm mixed xylenes for 4 hours exhibited poor coordination (Carpenter et al., 1975)**
AEGL–3 (Lethal)	**3300**	**1700**	**1100**	**1100**	**1100**	**Rats exposed to 2800 ppm for 4 hours exhibited prostration followed by a full recovery (Carpenter et al., 1975)**

Methyl Ethyl Ketone (CAS No. 79-93-3)

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

Sylvia Talmage presented brief responses to comments to the Federal Register made by George Alexeeff, John Morawetz, the Michigan Department of Environmental Quality, and the Clean Channel Association (Attachment 9). New data, published since the development of AEGL values for methyl ethyl ketone (MEK) in December, 2001 and relevant to development of AEGL-1 values, were then discussed (Attachment 10). Based on three recent, well-conducted studies (Shibata et al. 2002; Muttray et al. 2002; Seeber et al. 2002) and the previously considered study of Dick et al. (1992), in which no irritation was reported at 200 ppm in healthy subjects, including subjects with self-reported multiple chemical sensitivity, the AEGL-1 was raised from 100 to 200 ppm. The motion to change the value was made by Loren Koller and seconded by Ernest Falke. The motion passed (YES:9 ; NO :3; ABSTAIN: 5) (Appendix D).

Prior to the meeting, a NAC member raised the question of whether the constant AEGL-2 value of 1700 ppm across time was realistic based on the fact that MEK reaches equilibrium in the blood fairly rapidly. The 1700 ppm value had been based on a 6 hr/day subchronic study with rats (Cavender et al. 1983). The endpoint was the threshold for narcosis. Several options were presented for time scaling. The NAC decided to time-scale the 1700 ppm concentration back to 10 minutes using the default value of n = 3. The 8-hour value was kept at 1700 ppm. The motion was made by Steve Barbee and seconded by John Hinz to time scale the values back to 10 minutes. The motion passed (YES: 13 ; NO: 0 ; ABSTAIN: 4) (Appendix D).

Sylvia Talmage then reported that the AEGL-3 10- and 30-minute value of 10,000 ppm had been based on a projected rather than a measured concentration (Hansen et al. 1992). Because two additional studies supported the derived value (Klimisch 1988; Zakhari 1977), she suggested keeping the value, but revising the basis. The suggestion was accepted by voice vote. A motion was made by Loren Koller and seconded by John Hinz to elevate methyl ethyl ketone to interim status. The motion passed (Appendix D).

Summary of Interim AEGL Values for Methyl Ethyl Ketone

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	200 ppm	200 ppm	200 ppm	200 ppm	200 ppm	NOAEL for subjective symptoms - humans (Dick et al. 1992; Shibata et al. 2002; Muttray et al. 2002; Seeber et al. 2002)
AEGL-2	4900 ppm*	3400 ppm*	1700 ppm	1700 ppm	1700 ppm	Threshold for narcosis - rats (Cavender et al. 1983)
AEGL-3	see below [a]#	see below [a]#	4000 ppm[b]*	2500 ppm[b]*	2500 ppm[b]*	Threshold for lethality - rat, mouse (Klimisch 1988; Zakhari 1977; La Belle and Brieger 1955)

[a]Based on Klimisch (1988); Zakhari (1977).

[b]Based on La Belle and Brieger (1955).

*: Concentrations are higher than 1/10 of the lower explosive limit of methyl ethyl ketone in air (1.8% = 18,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

#: The AEGL-3 value of 10,000 ppm (29,300 mg/m^3) for 10 and 30 minutes is higher than 50% of the lower explosive limit of methyl ethyl ketone in air (1.8% = 18,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

REVISIT OF CHEMICALS WITH SPECIFIC ISSUES

Acrylic Acid (CAS No. 79-10-7)

Chemical Manager: Ernest Falke, U.S. EPA
Staff Scientist: Peter Griem, FOBIG

Ernest Falke, Chemical Manager, explained a discrepancy between interim AEGL-2 values approved by the NAC and AEGL-2 values presented to the COT subcommittee (Attachment 11). This discrepancy resulted because the interim AEGL-2 values approved by the NAC were based on olfactory epithelial histopathology observed in monkeys and rats exposed to 75 ppm acrylic acid for *3 hours*, and the values presented to the COT subcommittee were based on similar histopathology noted in monkeys and rats exposed to 75 ppm for *6 hours*. After considerable discussion, a motion was made by Bob Benson and seconded by Loren Koller to reaffirm the AEGL-2 values based on the 3 hour point of departure and to revise the rationale to include concern about irreversibility of the histopathological lesions at the 6 hour time point. The motion passed (YES: 17; NO: 0; ABSTAIN: 0) (Appendix E).

Uranium Hexafluoride (CAS No. 7783-81-5)

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

George Rusch, Chemical Manager, explained a discrepancy between interim AEGL-3 values approved by the NAC and AEGL-3 values presented to the COT subcommittee (Attachment 12). This discrepancy resulted because the interim AEGL-3 values utilized a time-scaling exponent 'n' of 0.66, derived from rat lethality data ranging from 2- to 60-min, and the AEGL-3 values presented to the COT subcommittee utilized an n=1 (0.66 value rounded up). Using n=0.66 yielded 10- and 30-minute AEGL-3 values for uranium hexafluoride where exposure to HF alone approached the hydrogen fluoride AEGL-3 values. (Uranium hexafluoride hydrolyzes to hydrogen fluoride and uranyl oxyfluoride, so exposure to UF6 may actually represent an exposure to both hydrolysis products). Therefore, a proposal was made to utilize an 'n' of 1 (rounded up from 0.66) to scale AEGL-3 values across time. This provides more protective 10- and 30-minute AEGL-3 values. The 4- and 8-hour AEGL-3 values are slightly increased, but still considered protective. Also, the use of an 'n' of 1 for extrapolating from 1-hr to 4- and 8-hr is consistent with the NAC Standing Operating Procedures (SOP) default approach. A motion was made by George Alexeeff and seconded by George Rodgers to adopt AEGL-3 values of 220 mg/m^3 for 10-min, 72 mg/m^3 for 30-min, 36 mg/m^3 for 1-hr, 9.0 mg/m^3 for 4-hr, and 4.5 mg/m^3 for 8-hr. The motion passed (YES: 17; NO: 0; ABSTAIN: 0) (Appendix F).

REVIEW of PRIORITY CHEMICALS

Hydrogen Iodide (CAS No. 10034-85-2)

Staff Scientist: Sylvia Talmage, ORNL
Chemical manager: Ernie Falke, U.S. EPA

Sylvia Talmage discussed the poor database for hydrogen iodide (Attachment 13). In the absence of inhalation data for derivation of AEGL values for hydrogen iodide, the options were to either not derive values or base the values on the most chemically similar hydrogen halide, hydrogen bromide. Richard Niemeier stated that there is a need for AEGL values for hydrogen iodide. A motion was made by Richard Niemier and seconded by John Hinz to adopt the hydrogen bromide values as the values for hydrogen iodide, and to combine both chemicals into one document, with a clear presentation of the fact that data are unavailable for hydrogen iodide, and, in the absence of data, the values for hydrogen bromide should be consulted. The motion passed (YES: 12; NO: 5; ABSTAIN: 0) (Appendix G).

Summary of AEGL Values for Hydrogen Bromide/Hydrogen Iodide[a]

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm	Nose irritation in humans (CT Dept. Health 1955)
AEGL–2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm	Based on analogy with hydrogen chloride
AEGL–3	740 ppm	250 ppm	120 ppm	31 ppm	31 ppm	Threshold for lethality - rat (MacEwen and Vernot 1972)

[a] These values were derived based on empirical human and animal data for hydrogen bromide and other hydrogen halides. In the absence of inhalation data for hydrogen iodide, the values for hydrogen bromide should be consulted. Based on structure-activity relationships for the hydrogen halides, it is believed that hydrogen iodide is less toxic than hydrogen bromide. Therefore, application of the hydrogen bromide values for hydrogen iodide is conservative.

Sulfur Dichloride (CAS No. 10545-99-0)

Chemical Manager: Ernest Falke, U.S. EPA
Staff Scientist: Kowetha Davidson, ORNL

Kowetha Davidson presented information explaining that there are no human or animal data available to derive AEGL values for sulfur dichloride (Attachment 14). The chemical was placed in holding status (Appendix H).

Sulfur Chloride (CAS No. 10025-67-9)

Chemical Manager: Ernest Falke, U.S. EPA
Staff Scientist: Kowetha Davidson, ORNL

Kowetha Davidson reviewed the available data for sulfur chloride (Attachment 15). Data are limited to one rat study (Bomhard et al., 2000). After discussion, the chemical was placed in holding status (Appendix H), and an attempt will made to contact the study author to determine if more experimental detail can be obtained.

Chloroacetyl Chloride (CAS No. 79-04-9)

Chemical Manager: Steven Barbee, Arch Chemical
Staff Scientist: Sylvia Milanez, ORNL

The chemical review on chloroacetyl chloride was presented by Sylvia Milanez (Attachment 16). The proposed AEGL-1 values were based on mild eye irritation in rats exposed to 1 ppm chloroacetyl chloride for 6 hours (Dow, 1982). Intraspecies and interspecies UFs of 3 each (total UF = 10) were proposed because eye conjunctivitis due to local irritation is not expected to vary greatly between or within species. The proposed AEGL-1 value of 0.08 ppm was kept constant at all time points because mild irritant effects do not vary greatly over time.

The proposed AEGL-2 values were based on eye lacrimation and squinting (impaired ability to escape) in rats exposed to 32 ppm chloroacetyl chloride for 1 hour (Dow, 1986). An intraspecies UF of 3 was proposed to protect sensitive individuals, and an interspecies UF of 10 was proposed because data suggest humans are more susceptible to lacrimation than animals. Time scaling using n=3 for <1 hour and n=1 for >1 hour was proposed, except that the 4-hour value should be adopted as the 8-hour value because time scaling yields an 8-hour AEGL-2 value approaching the AEGL-1 value. Proposed AEGL-2 values were 1.9 ppm for 10-min, 1.3 ppm for 30-min, 1.1 ppm for 1-hour, and 0.27 ppm for 4- and 8-hours.

The proposed AEGL-3 values are based on an estimated lethality threshold of 215 ppm in rats (1/3 of the 1-hr rat LC_{50} value) (Dow, 1986). An intraspecies UF of 3 was proposed to protect sensitive individuals, and an interspecies UF of 3 was proposed because rat and mouse lethality studies suggest a steep concentration-response curve at concentrations within a factor of 2-3. Time scaling using n=3 for <1 hour and n=1 for >1 hour was proposed. Proposed AEGL-3 values were 39 ppm for 10-min, 27 ppm for 30-min, 21 ppm for 1-hour, 5.4 ppm for 4-hours, and 2.7 ppm for 8-hours.

After much discussion, a motion was made by John Hinz and seconded by Bob Benson to accept the AEGL-1 values as proposed (0.08 ppm for all time periods). The motion did not pass (YES: 11; NO: 6; ABSTAIN: 1) (Appendix I). A motion was then made by George Alexeeff and

seconded by Richard Niemier to adopt the AEGL-1 values as proposed with a modifying factor of 2 applied (0.04 ppm for all time points. This motion passed (YES: 11; NO: 4; ABSTAIN: 3) (Appendix I). A motion was then made by Bob Benson and seconded by John Hinz to adopt AEGL-2 values of 2.9 ppm for 10-min, 2.0 ppm for 30-min, 1.6 ppm for 1-hour, 0.40 ppm for 4-hours, and 0.20 ppm for 8-hours. The point of departure is that proposed above (32 ppm, 1-hr); however, inter- and intraspecies UFs of 3 each are applied and a MF of 2 (LOAEL to NOAEL) is also applied. Time scaling using n=3 for <1 hour and n=1 for >1 hour was proposed. The motion passed (YES: 10; NO: 4; ABSTAIN: 3) (Appendix I). A motion was then made by Bob Benson and seconded by John Hinz to adopt AEGL-3 values of 95 ppm for 10-min, 66 ppm for 30-min, 50 ppm for 1-hour, 13 ppm for 4-hours, and 6.5 ppm for 8-hours. The point of departure is the highest concentration (522 ppm) causing no deaths in rats exposed for 1 hour (Dow, 1986); inter- and intraspecies UFs of 3 each are applied. Time scaling using n=3 for <1 hour and n=1 for >1 hour was proposed. The motion passed (YES: 13; NO: 2; ABSTAIN: 3) (Appendix I).

Summary of AEGL Values for Chloroacetyl chloride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.04 ppm	0.04 ppm	0.04 ppm	0.04 ppm	0.04 ppm	Eye irritation in rats (Dow, 1986)
AEGL–2	2.9 ppm	2.0 ppm	1.6 ppm	0.40 ppm	0.40 ppm	Lacrimation and squinting in rats (Dow, 1986)
AEGL–3	95 ppm	66 ppm	50 ppm	13 ppm	6.5 ppm	Highest concentration causing No deaths in rats (Dow, 1986)

Dichloroacetyl Chloride (CAS No. 79-36-7)

Chemical Manager: Steven Barbee, Arch Chemical
Staff Scientist: Sylvia Milanez, ORNL

The chemical review on dichloroacetyl chloride was presented by Sylvia Milanez (Attachment 16). AEGL-1 values were not recommended due to insufficient data.

The proposed AEGL-2 values were based on coughing and notable discomfort in workers exposed to 1.6 ppm dichloroacetyl chloride for an estimated duration of 10 min (Dahlberg and Myrin, 1971). An intraspecies UF of 3 was proposed to protect sensitive individuals, because coughing and notable discomfort is not likely to be significantly worst in the general population than in repeatedly exposed workers. Time scaling using n=1 scaling from 10-min to 30 min and maintaining the same value from 30-min to 8-hr was proposed, because scaling to 1-, 4-, and 8-hour time periods yielded concentrations below those recognized by workers. Proposed AEGL-2 values were 0.53 ppm for 10-min, and 0.18 ppm for 30-min, 1-, 4-, and 8-hours.

The proposed AEGL-3 values are based on an estimated 4-hour lethality threshold of 500 ppm in rats (Smyth et al., 1951). An intraspecies UF of 10 because the cause of death in the key study was unknown and variability among humans cannot be reliably estimated. An interspecies UF of 10 was proposed because only one species was tested and the cause of death was unknown. Time scaling using n=3 for <4 hours and n=1 for >4 hours was proposed, except that the 30-min value should be adopted as the 10-min value. Proposed AEGL-3 values were 10 ppm for 10-min and 30-min, 7.9 ppm for 1-hour, 5.0 ppm for 4-hours, and 2.5 ppm for 8-hours.

After much discussion, a motion was made by Bob Benson and seconded by Loren Koller to not recommend AEGL-1 because of insufficient data. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix J). A motion was then made by Bob Benson and seconded by Ernest Falke to accept the AEGL-3 values as proposed. This motion did not pass. After considerable discussion concerning the relative toxicity of chloroacetyl chloride and dichloroacetyl chloride, a motion was made by George Alexeeff and seconded by Richard Thomas for AEGL-3 to combine the dichloroacetyl chloride TSD with the chloroacetyl chloride TSD, explain that dichloroacetyl chloride is less toxic than chloroacetyl chloride, and recommended adopting chloroacetyl chloride values for dichloroacetyl chloride. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix J). A motion was then made by Steve Barbee and seconded by Bill Bress to adopt chloroacetyl chloride AEGL-2 values as the AEGL-2 values for dichloroacetyl chloride, and combining the TSDs as was done for AEGL-3. The motion passed (YES: 14; NO: 0; ABSTAIN: 2) (Appendix I). A motion was then made by Richard Thomas and seconded by Loren Koller to reopen the AEGL-1 discussion; this motion passed by a show of hands. A motion was then made by Ernest Falke and seconded by Loren Koller to adopt the chloroacetyl chloride AEGL-1 values as the AEGL-1 values for dichloroacetyl chloride and present in the combined TSD. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix J).

Trichloroacetyl Chloride (CAS No. 76-02-8)

Chemical Manager: Steven Barbee, Arch Chemical
Staff Scientist: Sylvia Milanez, ORNL

The chemical review on trichloroacetyl chloride was presented by Sylvia Milanez (Attachment 16). AEGL-1, AEGL-2, and AEGL-3 values were not recommended due to insufficient data. A motion was made by Richard Thomas and seconded by Ernest Falke to not recommend AEGL-1, AEGL-2, or AEGL-3 values due to insufficient data and to include this information in the TSD for chloroacetyl chloride. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix K).

Acetyl Chloride (CAS No. 75-36-5)

Chemical Manager: Steven Barbee, Arch Chemical
Staff Scientist: Sylvia Milanez, ORNL

The chemical review on acetyl chloride was presented by Sylvia Milanez (Attachment 16). AEGL-1, AEGL-2, and AEGL-3 values were not recommended due to insufficient data. A motion was made by Ernest Falke and seconded by Richard Thomas to not recommend AEGL-1, AEGL-2, or AEGL-3 values due to insufficient data and to include this information in the TSD for chloroacetyl chloride. The motion passed unanimously by a show of hands (Appendix L).

Tetrachloroethylene (CAS No. 127-18-4)

Staff Scientist: Claudia Troxel, ORNL
Chemical Manager: Bill Bress, ASTHO

Tetrachloroethylene will be discussed at a future meeting after modeling is completed.

Oleum (CAS No. 8014-95-7)
Sulfuric Acid (CAS No. 7664-93-9)
Sulfur Trioxide (Cas No. 7446-11-9)

Staff Scientist: Johan Schefferlie, Netherlands
Chemical Manager: Loren Koller

Johan Schefferlie presented a progress report on sulfuric acid, sulfur trioxide, and oleum (Attachment 17). These three chemicals will be presented together in one TSD and values will be derived only for sulfuric acid. This TSD will be presented at a future NAC meeting.

Methacrylonitrile (CAS No. 126-98-7)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: George Rodgers

A brief history of the TSD and chemical review for methacrylonitrile was presented by Cheryl Bast (Attachment 18). The proposed AEGL-1 was based on transitory nasal, throat or ocular irritation in humans exposed to 2 ppm methacrylonitrile for 10 minutes (Pozzani et al., 1968). No uncertainty factor was applied to account for sensitive human populations because similar transitory irritation was noted in humans at 14 ppm. The 2 ppm concentration was held constant across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure time points. This approach is considered appropriate since mild irritant effects generally do not vary greatly over time.

The proposed AEGL-2 was based on a 13-15% decrease in fetal body weight in rats exposed to 100 ppm methacrylonitrile 6 hours/day on gestation days 6-20 (Saillenfait et al., 1993). An

uncertainty factor of 3 was applied to account for sensitive individuals. This uncertainty factor is considered sufficient because human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN (the metabolically-liberated toxicant) but the magnitude of these differences does not appear to be great (NRC, 2002). An interspecies uncertainty factor of 3 was also applied, because use of the full uncertainty interspecies factor of 10, would yield AEGL-2 values that are not consistent with the total data set. For time scaling, an *n* of 3 was applied to extrapolate to the 30-minute, 1-hour, and 4-hour time periods, and an *n* of 1 was applied to extrapolate to the 8-hour time period. The 30-minute value was adopted as the 10-minute value. Proposed AEGL-2 values were 22 ppm for 10- and 30-min, 18 ppm for 1-hr, 11 ppm for 4-hours, and 7.5 ppm for 8-hours.

The loss of consciousness, with no mortality noted, in rats exposed to 176 ppm for 3 hours was used as the basis of proposed AEGL-3 values (Pozzani et al., 1968). An uncertainty factor of 3 was applied to account for sensitive individuals, and interspecies uncertainty factor of 3 was also applied. Rationale for the UFs is the same as explained above for the AEGL-2 derivation. For time scaling, an *n* of 3 was applied to extrapolate to the 10-minute, 30-minute, 1-hour, and an n of 1 was used for extrapolation to the 4-hour time period. The 4-hour AEGL-3 value was also adopted as the 8-hour AEGL-3 value because time scaling would yield an 8-hour AEGL-3 value less that the 8-hour AEGL-2 value. The proposed AEGL-3 values were 32 ppm for 10-min and 30-min, 25 ppm for 1-hr, and 13 ppm for 4- and 8-hours.

After extensive discussion, a motion was made by George Rodgers and seconded by Loren Koller to accept the AEGL-3 values as presented. The motion passed (YES: 11; NO: 0; ABSTAIN: 3) (Appendix M). A motion was then made by Bob Benson and seconded by George Rodgers to derive AEGL-2 values by dividing AEGL-3 values by 2 (16 ppm for 10- and 30-min, 13 ppm for 1-hr, and 6.5 ppm for 4- and 8-hours). This approach is justified due to the relatively steep concentration-response curve, and dividing the AEGL-3 values by 3 (as per the SOP) for this chemical would yield AEGL-2 values in the range where only minor irritation was noted in humans. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix M). A motion was then made by George Rodgers and seconded by Loren Koller to adopt AEGL-1 values of 2.0 ppm for 10-min and 30-min, as proposed, and 1.0 ppm for 1-hr, 4-hr, and 8-hr due to the lack of human data beyond 10-minutes and the potential for a systemic effect. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix M).

Summary of AEGL Values For Methacrylonitrile [ppm (mg/m^3)]						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1	2.0 (5.5)	2.0 (5.5)	1.0 (2.8)	1.0 (2.8)	1.0 (2.8)	Transient nasal, throat, or ocular irritation in humans (Pozzani et al., 1968)
AEGL-2	16 (44)	16 (44)	13 (35)	6.5 (15)	6.5 (15)	AEGL-3 ÷ 2

AEGL-3	32 (88)	32 (88)	25 (69)	13 (36)	13 (36)	Loss of consciousness, no mortality in rats (Pozzani et al., 1968)

Benzonitrile (CAS No. 100-47-0)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: George Rodgers

The and chemical review for benzonitrile was presented by Cheryl Bast (Attachment 19).
The proposed AEGL-1 was based on irritation of extremities in rats exposed to 900 ppm for 1 hour (MacEwen and Vernot, 1974). An interspecies uncertainty factor of 10 was applied because the rat is not the most sensitive species. An uncertainty factor of 3 was applied to account for sensitive individuals. This intraspecies uncertainty factor of 3 is supported by the steep concentration-response curve, which implies little individual variability. A modifying factor of 2 was also applied to account for the sparse data base and potential delayed hepatic effects, such as the hepatic congestion evidenced in mice (MacEwen and Vernot, 1974). An *n* of 3 was applied to extrapolate to the 30-minute time period, and an *n* of 1 was applied to extrapolate to the 4- and 8-hour time periods. Proposed AEGL-1 values were 19 ppm for 10- and 30-min, 15 ppm for 1-hr, 3.8 ppm for 4-hours, and 2.0 ppm for 8-hours.

The proposed AEGL-2 was based on labored breathing and poor coordination in rats exposed to 900 ppm for 3 hours (MacEwen and Vernot, 1974). An interspecies uncertainty factor of 10 was applied because the rat is not the most sensitive species. An uncertainty factor of 3 was applied to account for sensitive individuals. This intraspecies uncertainty factor of 3 is supported by the steep concentration-response curve, which implies little individual variability. A modifying factor of 2 was applied to account for the sparse data base and to protect against potential delayed hepatic effects, such as the hepatic congestion evidenced in mice (MacEwen and Vernot, 1974). An *n* of 3 was applied to extrapolate to the 30-minute and 1-hour, time periods, and an *n* of 1 was applied to extrapolate to the 4- and 8-hour time periods. The 30-minute value was adopted as the 10-minute value. Proposed AEGL-2 values were 27 ppm for 10- and 30-min, 22 ppm for 1-hr, 11 ppm for 4-hr, and 5.6 ppm for 8-hr.

The exposure of mice to 890 ppm for 2 hours resulting in 1/7 deaths in mice was used as the basis of the proposed AEGL-3 values (MacEwen and Vernot, 1974). An interspecies uncertainty factor of 3 was applied, and an uncertainty factor of 3 was also applied to account for sensitive individuals. Uncertainty factor justifications are as described above for AEGL-2. A modifying factor of 2 was applied to account for the use of an endpoint where 1 of 10 animals died, the sparse data base, and to protect against potential delayed hepatic effects, such as the hepatic congestion evidenced in mice (MacEwen and Vernot, 1974). An *n* of 3 was applied to extrapolate to the 30-minute and 1-hour, time periods, and an *n* of 1 was applied to extrapolate to the 4- and 8-hour time periods. The 30-minute value was adopted as the 10-minute value due to the added

uncertainty of extrapolating from a 2-hour time point to 10-minutes. The proposed AEGL-3 values were 71 ppm for 10- and 30-min, 56 ppm for 1-hr, 23 ppm for 4-hr, and 11 ppm for 8-hr.

After discussion, a motion was made by Bob Benson and seconded by Ernest Falke to accept the AEGL-3 values as proposed except for the 10-min value which should be derived by time scaling per the SOP. Thus, the 10-min AEGL-3 value becomes 100 ppm. The motion passed (YES: 15; NO: 1; ABSTAIN: 0) (Appendix N). A motion was then made by George Rodgers and seconded by Bob Benson to accept the AEGL-2 values as proposed except for the 10-min value which should be derived by time scaling per the SOP. Thus, the 10-min AEGL-2 value becomes 39 ppm. The motion passed (YES: 14; NO: 2; ABSTAIN: 0) (Appendix N). A motion was then made by Bob Benson and seconded by Ernest Falke not to recommended AEGL-1 values due to the lack of data. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix N).

Summary of AEGL Values for Benzonitrile

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	NR	NR	NR	NR	NR	Insufficient data to derive AEGL-1 values
AEGL-2	39 (163)	27 (113)	22 (92)	12 (50)	5.5 (21)	Labored breathing, incoordination in rats (MacEwen and Vernot, 1974)
AEGL-3	100 (420)	71 (298)	56 (235)	23 (97)	11 (46)	14% death in mice (MacEwen and Vernot, 1974)

NR: Not Recommended.

Special Presentation

George Woodall presented information on a comparative survey of acute inhalation health reference values (Attachment 20).

Administrative Matters

The site and time of future meetings is as follows:

NAC/AEGL-32: April 19-21, 2004, Washington DC
NAC/AEGL-33: June 14-16, 2004, Netherlands
NAC/AEGL-34: September 21-23, 2004, Washington DC

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Cheryl Bast and Sylvia Talmage, Oak Ridge National Laboratory, with input from the respective chemical managers, staff scientists, and other contributors.

LIST OF ATTACHMENTS

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

Attachment 1. Overview of AFOIH
Attachment 2. NAC/AEGL-31 Meeting Agenda
Attachment 3. NAC/AEGL-31 Attendee List
Attachment 4. Response to Federal Register Comments for ammonia
Attachment 5. Proposed AEGL-1 revision for ammonia
Attachment 6. Response to Federal Register comments for xylenes
Attachment 7. Revised text for xylenes
Attachment 8. PBPK modeling for xylenes
Attachment 9. Response to Federal Register Comments for methyl ethyl ketone
Attachment 10. New AEGL-1 data for methyl ethyl ketone
Attachment 11. AEGL-2 issues for acrylic acid
Attachment 12. AEGL-3 time scaling issue for uranium hexafluoride
Attachment 13. Data Analysis of hydrogen iodide
Attachment 14. Data Analysis of sulfur dichloride
Attachment 15. Data Analysis of sulfur chloride
Attachment 16. Data Analysis of chloroacetyl chloride, dichloroacetyl chloride, trichloroacetyl chloride, and acetyl chloride
Attachment 17. Sulfuric acid, sulfur trioxide, and oleum progress report
Attachment 18. Data Analysis of methacrylonitrile
Attachment 19. Data Analysis of benzonitrile
Attachment 20. Comparative survey of acute inhalation health reference values

LIST OF APPENDICES

Appendix A. Final meeting highlights of NAC/AEGL-30
Appendix B. Ballot for ammonia
Appendix C. Ballot for xylenes
Appendix D. Ballot for methyl ethyl ketone
Appendix E. Ballot for acrylic acid
Appendix F. Ballot for uranium hexafluoride
Appendix G. Ballot for hydrogen iodide
Appendix H. Ballots for sulfur dichloride and sulfur chloride
Appendix I. Ballot for chloroacetyl chloride
Appendix J. Ballot for dichloroacetyl chloride
Appendix K. Ballot for trichloroacetyl chloride
Appendix L. Ballot for acetyl chloride
Appendix M. Ballot for methacrylonitrile
Appendix N. Ballot for benzonitrile

NAC/AEGL Meeting 32: April 19-21, 2004

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

Chemical Manager: ERNIE FALKE **Staff Scientist:** PETER GRIEM

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	Y		Y		Nancy Kim	N		Y	
Steven Barbee	Y		Y		Glenn Leach	Y		Y	
Lynn Beasley	Y		Y		John Morawetz	N		A	
Robert Benson	Y		Y		Richard Niemeier	A		A	
Jonathan Borak	A		A		Marinelle Payton	Y		Y	
William Bress	Y		Y		Susan Ripple	A		A	
George Cushmac	Y		Y		George Rodgers	A		A	
Ernest Falke	Y		Y		Marc Ruijten	Y		Y	
Alfred Feldt	A		A		George Rusch, Chair	Y		Y	
John Hinz	Y		Y		Robert Snyder	Y		Y	
Jim Holler	Y		Y		Richard Thomas	Y		Y	
Thomas Hornshaw	Y		A		George Woodall	Y		Y	
Warren Jederberg	Y		Y						
					TALLY	18/18-0		18/18	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	670 ,( )	670 ,( )	530 ,( )	340 ,( )	270 ,( )
AEGL 2	11,000 ,( )	4000 ,( )	2100 ,( )	720 ,( )	510 ,( )
AEGL 3	* ,( )	14,000 ,( )	9,100 ,( )	2200 ,( )	1400 ,( )
LOA	LOA = 8,9 PPM		UNANIMOUS		

~~* 40,000 ppm LEL MUCH 15,000 ppm~~

* 40,000 NOT LISTED IN TABLE SINCE IT IS GREATER THAN 50 % LEL (LEL = 55,000 ppm)

AEGL 1 Motion by: FALKE **Second by:** THOMAS

AEGL 2 Motion by: HINZ **Second by:** SNYDER

AEGL 3 Motion by: BENSON **Second by:** FALKE

LOA Motion by: Jederberg **Second by:** Benson

Approved by Chair: [signature] **DFO:** [signature] **Date:** 4/20/04

NAC/AEGL Meeting 32: April 19-21, 2004

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

Chemical Manager: **Staff Scientist:** PETER GRIEM

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	N	Y	Y		Nancy Kim	N	N		
Steven Barbee	Y	Y			Glenn Leach	Y	Y		
Lynn Beasley	Y	Y			John Morawetz	N	N		
Robert Benson	P	Y			Richard Niemeier	A	A		
Jonathan Borak	A	A			Marinelle Payton	N	Y		
William Bress	Y	Y			Susan Ripple	A	A		
George Cushmac	Y	Y			George Rodgers	A	A		
Ernest Falke	Y	Y			Marc Ruijten	Y	Y		
Alfred Feldt	A	A			George Rusch, Chair	Y	Y		
John Hinz	Y	P			Robert Snyder	Y	Y		
Jim Holler	Y	Y			Richard Thomas	Y	Y		
Thomas Hornshaw	N	Y			George Woodall	N	Y		
Warren Jederberg	Y	Y							
					TALLY	13/19	19/19		

APPROVED BY SHOW OF HANDS

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	19 ,( )	19 ,( )	15 ,( )	9.5 ,( )	6.3 ,( )
AEGL 2	47 ,( )	47 ,( )	37 ,( )	23 ,( )	12 ,( )
AEGL 3	,(*)	,( )	,( )	,( )	,( )
LOA	0.25				

* DO NOT SET AEGL, DUE TO LACK OF DATA

AEGL 1 **Motion by:** RUIJTEN **Second by:** HINZ

AEGL 2 **Motion by:** WOODALL **Second by:** ALEXEEFF

AEGL 3 **Motion by:** * HINZ **Second by:** BENSON

LOA **Motion by:** Norman **Second by:** Hinz

Approved by Chair: [signature] **DFO:** [signature] **Date:** 4/20/04

NAC/AEGL Meeting 32: April 19-21, 2004

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

Chemical Manager: **Staff Scientist:** SYLVIA TALMAGE

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff		Y	N		Nancy Kim		Y	Y	
Steven Barbee		Y	Y		Glenn Leach		Y	Y	
Lynn Beasley		Y	Y		John Morawetz		Y	N	
Robert Benson		Y	Y		Richard Niemeier		A	A	
Jonathan Borak		A	A		Marinelle Payton		Y	Y	
William Bress		Y	Y		Susan Ripple		A	A	
George Cushmac		Y	Y		George Rodgers		A	A	
Ernest Falke		Y	Y		Marc Ruijten		A	A	
Alfred Feldt		A	A		George Rusch, Chair		Y	Y	
John Hinz		Y	P		Robert Snyder		Y	Y	
Jim Holler		Y	Y		Richard Thomas		Y	Y	
Thomas Hornshaw		Y	Y		George Woodall		Y	Y	
Warren Jederberg		Y	Y						
					TALLY		19/19	16/18	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	8.1,( )	3.5,( )	2.0,( )	0.70,( )	0.41,( )
AEGL 3	84,( )	36,( )	21,( )	7.3,( )	[redacted],(7.3)
LOA					

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

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

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

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

Approved by Chair: _____ **DFO:** [signature] **Date:** 4/20/04

NAC/AEGL Meeting 32: April 19-21, 2004

Chemical: METHACRYLIC ACID **CAS Reg. No.:** 79-41-4

Chemical Manager: ~~FRITZ KALBERLAH~~ BOB BENSON **Staff Scientist:** SUSAN GFATTER FRITZ KALBERLAH

* HARALD MULLERSCHON

NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	A A	A	A	
Steven Barbee	Y Y	Y	Y	
Lynn Beasley	Y Y	Y	Y	
Robert Benson	P Y	Y	Y	
Jonathan Borak	A A	A	A	
William Bress	N Y	Y	Y	
George Cushmac	Y Y	Y	Y	
Ernest Falke	N Y	Y	Y	
Alfred Feldt	A A	A	A	
John Hinz	N Y	Y	Y	
Jim Holler	Y Y	Y	Y	
Thomas Hornshaw	Y Y	Y	Y	
Warren Jederberg	N Y	Y	Y	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y Y	Y	Y	
Glenn Leach	N Y	Y	Y	
John Morawetz	P P	P	Y	
Richard Niemeier	A A	A	A	
Marinelle Payton	A A	A	A	
Susan Ripple	A A	A	A	
George Rodgers	A A	A	A	
Marc Ruijten	Y N	P	Y	
George Rusch, Chair	P Y	Y	Y	
Robert Snyder	A A	A	A	
Richard Thomas	N Y	Y	Y	
George Woodall	N Y	Y	Y	
TALLY	7/14 *15/16	15/15	17/17	

*

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	10 ,(*6.7)	10 ,(*6.7)	10 ,(*6.7)	10 ,(*6.7)	10 ,(*6.7)
AEGL 2	76 ,( )	76 ,( )	61 ,( )	38 ,( )	25 ,( )
AEGL 3	280 ,( )	280 ,( )	220 ,( )	140 ,( )	71 ,( )
LOA					

* THOMAS

AEGL 1 Motion by: RUIJTEN **Second by:** FALKE BARBEE

AEGL 2 Motion by: HINZ **Second by:** WOODALL

AEGL 3 Motion by: BENSON **Second by:** HINZ

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 4/19/04

NAC/AEGL Meeting 32: April 19-21, 2004

Chemical: METHYL METHACRYLATE **CAS Reg. No.:** 80-62-6

Chemical Manager: BOB BENSON **Staff Scientist:** SUSAN GFATTER FRITZ KALBERLAH

NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	A A	A	A	
Steven Barbee	Y N	N	Y	
Lynn Beasley	Y P	P	Y	
Robert Benson	Y Y	Y	Y	
Jonathan Borak	A A	A	A	
William Bress	Y Y	Y	Y	
George Cushmac	Y Y	Y	Y	
Ernest Falke	A Y	Y	Y	
Alfred Feldt	A A	A	A	
John Hinz	Y P	P	Y	
Jim Holler	Y Y	Y	Y	
Thomas Hornshaw	Y Y	Y	Y	
Warren Jederberg	Y Y	Y	Y	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y Y	Y	Y	
Glenn Leach	Y Y	Y	Y	
John Morawetz	Y Y	Y	Y	
Richard Niemeier	A A	A	A	
Marinelle Payton	A A	A	A	
Susan Ripple	A A	A	A	
George Rodgers	A A	A	A	
Marc Ruijten	Y P	P	Y	
George Rusch, Chair	Y Y	Y	Y	
Robert Snyder	Y Y	Y	Y	
Richard Thomas	Y Y	Y	Y	
George Woodall	Y Y	Y	Y	
TALLY	17/17	14/15	18/18	

17-0-1

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	17, ( )	17, ( )	17, ( )	17, ( )	17, ( )
AEGL 2	150, ( )	150, ( )	120, ( )	76, ( )	50, ( )
AEGL 3	630, ( )	630, ( )	500, ( )	310, ( )	160, ( )
LOA	0.11 ppm (UNANIMOUS)				

AEGL 1 Motion by: RUIJTEN **Second by:** THOMAS

AEGL 2 Motion by: BENSON **Second by:** WOODALL

AEGL 3 Motion by: BENSON **Second by:** FALKE

LOA Motion by: Hinz **Second by:** Jederberg

Approved by Chair: [signature] **DFO:** [signature] **Date:** 4/19/04

Appendix G

NAC/AEGL Meeting 32: April 19-21, 2004

Chemical: ETHYL ACRYLATE **CAS Reg. No.:** 140-88-5

Chemical Manager: GEORGE WOODALL **Staff Scientist:** CAROL WOOD

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	N	A	A		Nancy Kim	Y	Y	P	
Steven Barbee	Y	Y	P		Glenn Leach	Y	Y	Y	
Lynn Beasley	Y	Y	Y		John Morawetz	N	N	Y	
Robert Benson	Y	Y	Y		Richard Niemeier	A	A	A	
Jonathan Borak	A	A	A		Marinelle Payton	A	A	A	
William Bress	Y	Y	Y		Susan Ripple	A	A	A	
George Cushmac	Y	A	A		George Rodgers	A	A	A	
Ernest Falke	Y	Y	Y		Marc Ruijten	Y	Y	Y	
Alfred Feldt	A	A	A		George Rusch, Chair	Y	Y	Y	
John Hinz	N	P	Y		Robert Snyder	Y	Y	Y	
Jim Holler	Y	Y	Y		Richard Thomas	Y	A	A	
Thomas Hornshaw	Y	Y	P		George Woodall	Y	Y	Y	
Warren Jederberg	Y	Y	Y						
					TALLY	19/19	15/15	13/13	
						16/19	15/16		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	~~28~~ 8.3 ,( )	8.3 ,( )	8.3 ,( )	8.3 ,( )	8.3 ,( )
AEGL 2	66 ,( )	45 ,( )	36 ,( )	19 ,( )	9.4 ,( )
AEGL 3	950 ,( )	410 ,( )	240 ,( )	71 ,( )	41 ,( )
LOA					

AEGL 1 **Motion by:** RUIJTEN **Second by:** HINZ

AEGL 2 **Motion by:** FALKE **Second by:** BENSON

AEGL 3 **Motion by:** SNYDER **Second by:** RUIJTEN

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 4/19/04

NAC/AEGL Meeting 32: April 19-21, 2004

Chemical: n- BUTYL ACRYLATE **CAS Reg. No.:**

Chemical Manager: GEORGE WOODALL **Staff Scientist:** CAROL WOOD

NAC Member	AEGL1	*	AEGL2	AEGL3	LOA
George Alexeeff	A	N	A	A	
Steven Barbee	Y	Y	Y	P	
Lynn Beasley	A	Y	A	A	
Robert Benson	N	Y	Y	Y	
Jonathan Borak	A	A	A	A	
William Bress	P	Y	Y	Y	
George Cushmac	A	Y	A	A	
Ernest Falke	N	Y	Y	Y	
Alfred Feldt	A	A	A	A	
John Hinz	N	Y	Y	Y	
Jim Holler	Y	Y	Y	Y	
Thomas Hornshaw	P	Y	Y	Y	
Warren Jederberg	Y	Y	Y	Y	

NAC Member	AEGL1		AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	Y	P	
Glenn Leach	P	Y	Y	Y	
John Morawetz	P	Y	Y	Y	
Richard Niemeier	A	A	A	A	
Marinelle Payton	A	A	A	A	
Susan Ripple	A	A	A	A	
George Rodgers	A	A	A	A	
Marc Ruijten	N	N	Y	Y	
George Rusch, Chair	Y	Y	Y	Y	
Robert Snyder	N	N	Y	Y	
Richard Thomas	A	Y	A	A	
George Woodall	Y	P	Y	Y	
TALLY	6/11		15/15	13/13	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	~~10~~ 8.3 ,( )	~~10~~ 8.3 ,( )	~~10~~ 8.3 ,( )	~~10~~ 8.3 ,( )	~~10~~ 8.3 ,( )
AEGL 2	160 ,( )	160 ,( )	130 ,( )	81 ,( )	53 ,( )
AEGL 3	820 ,( )	820 ,( )	480 ,( )	170 ,( )	97 ,( )
LOA					

* SECOND BALLOT

AEGL 1 Motion by: Bress / Woodall **Second by:** Hinz / Kim

AEGL 2 Motion by: FALKE **Second by:** RUIJTEN

AEGL 3 Motion by: RUIJTEN **Second by:** HINZ

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

Approved by Chair: [signature] **DFO:** [signature] **Date:** 4/19/04

NAC/AEGL Meeting 32: April 19-21, 2004

Chemical: METHYL CHLORIDE **CAS Reg. No.:** 74-87-3

Chemical Manager: GEORGE RODGERS **Staff Scientist:** SYLVIA TALMAGE

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	Y	Y	P		Nancy Kim	Y	Y	P	
Steven Barbee	P	Y	A		Glenn Leach	Y	Y	Y	
Lynn Beasley	Y	Y	Y		John Morawetz	A	A	A	
Robert Benson	Y	N	Y		Richard Niemeier	A	A	A	
Jonathan Borak	A	A	A		Marinelle Payton	N	Y	Y	
William Bress	N	Y	Y		Susan Ripple	A	A	A	
George Cushmac	Y	Y	Y		George Rodgers	A	A	A	
Ernest Falke	Y	Y	Y		Marc Ruijten	A	A	A	
Alfred Feldt	A	A	A		George Rusch, Chair	Y	Y	Y	
John Hinz	N	Y	Y		Robert Snyder	Y	N	Y	
Jim Holler	Y	Y	Y		Richard Thomas	Y	Y	Y	
Thomas Hornshaw	N	Y	Y		George Woodall	Y	Y	Y	
Warren Jederberg	Y	Y	Y						
					TALLY	13/17	16/18	15/15	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	*,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	1100 ,( )	1100 ,( )	910 ,( )	570 ,( )	380 ,( )
AEGL 3	3800 ,( )	3800 ,( )	3000 ,( )	1900 ,( )	1300 ,( )
LOA					

*NR DUE TO LACK OF DATA TO SET AEGL-1

AEGL 1 Motion by: FALKE **Second by:** THOMAS

AEGL 2 Motion by: HORNSHAW **Second by:** HINZ

AEGL 3 Motion by: WOODALL **Second by:** THOMAS

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

Approved by Chair: [signature] **DFO:** Paul Tobin **Date:** 4/21/04

NAC/AEGL Meeting 32: April 19-21, 2004

Chemical: METHYL BROMIDE **CAS Reg. No.:** 74-83-9

Chemical Manager: GEORGE RODGERS **Staff Scientist:** SYLVIA TALMAGE

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff		N	N		Nancy Kim		N	P	
Steven Barbee		A	A		Glenn Leach		Y	Y	
Lynn Beasley		Y	Y		John Morawetz		A	A	
Robert Benson		Y	P		Richard Niemeier		A	A	
Jonathan Borak		A	A		Marinelle Payton		A	Y	
William Bress		N	Y		Susan Ripple		A	A	
George Cushmac		Y	Y		George Rodgers		A	A	
Ernest Falke		Y	Y		Marc Ruijten		A	A	
Alfred Feldt		A	A		George Rusch, Chair		Y	Y	
John Hinz		Y	Y		Robert Snyder		Y	Y	
Jim Holler		Y	Y		Richard Thomas		Y	Y	
Thomas Hornshaw		A	Y		George Woodall		N	Y	
Warren Jederberg		Y	Y						
					TALLY		11/15	14/15	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR ,( )	NR ,( )	NR ,( )	NR ,( )	NR ,( )
AEGL 2	940 ,( )	380 ,( )	210 ,( )	67 ,( )	67 ,( )
AEGL 3	3300 ,( )	1300 ,( )	740 ,( )	230 ,( )	130 ,( )
LOA					

NR = LACK OF DATA

AEGL 1 Motion by: ALEXEEFF **Second by:** BENSON

AEGL 2 Motion by: FALKE **Second by:** HINZ

AEGL 3 Motion by: HINZ **Second by:** FALKE

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

Approved by Chair: [signature] **DEO:** Paul S. Tobin **Date:** 4/21/04