Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

18-Apr-2001

English - Or. English

ENV/JM/MONO(2001)2
Unclassified

ENVIRONMENT DIRECTORATE

JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

REPORT OF THE OECD EXPERT MEETING ON ACUTE EXPOSURE GUIDELINE LEVELS (AEGLS)

Paris, 7 - 8 June, 1999

JT00106208

English - Or. English

REPORT
of the OECD EXPERT MEETING ON ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

(Paris, 7 - 8 June, 1999)

Some other OECD publications related to chemical accident prevention, preparedness and response:

Guiding Principles for Chemical Accident Prevention, Preparedness and Response: *Guidance for Public Authorities, Industry, Labour and Others for the Establishment of Programmes and Policies related to Prevention of, Preparedness for, and Response to Accidents Involving Hazardous Substances* (1992) [Under Revision]

International Directory of Emergency Response Centres (first edition, 1992) [prepared as a joint publication with UNEP-IE; under revision]

Report of the OECD Workshop on Strategies for Transporting Dangerous Goods by Road: Safety and Environmental Protection (1993)

Health Aspects of Chemical Accidents: *Guidance on Chemical Accident Awareness, Preparedness and Response for Health Professionals and Emergency Responders* (1994) [prepared as a joint publication with IPCS, UNEP-IE and WHO-ECEH]

Guidance Concerning Health Aspects of Chemical Accidents. *For Use in the Establishment of Programmes and Policies Related to Prevention of, Preparedness for, and Response to Accidents Involving Hazardous Substances* (1996)

Report of the OECD Workshop on Small and Medium-sized Enterprises in Relation to Chemical Accident Prevention, Preparedness and Response (1995)

Guidance Concerning Chemical Safety in Port Areas. *Guidance for the Establishment of Programmes and Policies Related to Prevention of, Preparedness for, and Response to Accidents Involving Hazardous Substances. Prepared as a Joint Effort of the OECD and the International Maritime Organisation (IMO)* (1996)

New OECD Series on Chemical Accidents:

No. 1, Report of the OECD Workshop on Risk Assessment and Risk Communication in the Context of Chemical Accident Prevention, Preparedness and Response (1997)

No. 2, Report of the OECD Workshop on Pipelines (Prevention of, Preparation for, and Response to Releases of Hazardous Substances (1997)

No. 3, International Assistance Activities Related to Chemical Accident Prevention, Preparedness and Response: Follow-up to the Joint OECD and UN/ECE Workshop to Promote Assistance for the Implementation of Chemical Accident Programmes (1997)

No. 4, Report of the OECD Workshop on Human Performance in Chemical Process Safety: Operating Safety in the Context of Chemical Accident Prevention, Preparedness and Response (1999)

No. 5, Report of the OECD Workshop on New Developments in Chemical Emergency

Preparedness and Response, Lappeenranta, Finland, November 1998 *(*2001)

No. 6, Report of the OECD Expert Meeting on Acute Exposure Guideline Levels (AEGLs) (2001)

About the OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 30 industrialised countries in North America, Europe and the Pacific, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised Committees and subsidiary groups made up of Member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's Workshops and other meetings. Committees and subsidiary groups are served by the OECD Secretariat, located in Paris, France, which is organised into Directorates and Divisions.

The work of the OECD related to chemical accident prevention, preparedness and response is carried out by the Working Group (formerly Expert Group) on Chemical Accidents, with Secretariat support from the Environment, Health and Safety Division of the Environment Directorate. The objectives of the Chemical Accidents Programme include exchange of information and experience, analysis of specific issues of mutual concern in Member countries, and development of guidance materials related to chemical accident prevention, preparedness and response. As a contribution to meeting these objectives, over a dozen Workshops have been held since 1989.

As part of its work on chemical accidents, the OECD has issued several Council Decisions and Recommendations (the former legally binding on Member countries), as well as numerous Guidance Documents and technical reports (see partial list on page 5 and 6). Publications include the OECD's *Guiding Principles for Chemical Accident Prevention, Preparedness and Response*; *Guidance Concerning Chemical Safety in Port Areas* (a joint effort with the IMO); *Guidance Concerning Health Aspects of Chemical Accidents*; the joint IPCS/OECD/UNEP/WHO publication, *Health Aspects of Chemical Accidents*; and the joint OECD/UNEP *International Directory of Emergency Response Centres* (currently being revised by the OECD, UNEP-TIE and the Joint UNEP/OCHA Environment Unit).

The Environment, Health and Safety Division produces publications in seven series: **Testing and Assessment**; **Good Laboratory Practice and Compliance Monitoring**; **Emission Scenario Documents, Pesticides**; **Risk Management**; **Harmonisation of Regulatory Oversight in Biotechnology**; and **Chemical Accidents.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's web page.

This publication was produced within the framework of the Inter-Organisation Programme for the Sound Management of Chemicals (IOMC).

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, FAO, WHO, UNIDO and the OECD (the Participating Organisations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. UNITAR joined the IOMC in 1997 to become the seventh Participating Organisation. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

TABLE OF CONTENTS

Report of the OECD Expert Meeting on Acute Exposure Guideline Levels (AEGLs)

(Paris, 7 - 8 June, 1999)

INTRODUCTION

1. This report contains a summary of the discussions at the OECD Expert Meeting on Acute Exposure Guideline Levels (AEGLs), held on 7 – 8 June 1999 in Paris. A copy of the Agenda for the meeting is attached as Annex I.

2. The 8th Meeting of the OECD Working Group on Chemical Accidents ("Working Group") organised this special meeting as a follow-up to the consultation of experts held in December 1998. The purpose of the meeting was three-fold:

   - to reach consensus on the scientific methods used to develop AEGLs;
   - to identify the specific needs of policy makers and industry in Member countries; and
   - to identify options for developing an international approach to AEGLs.

3. In advance of the meeting, the US made available the draft Standing Operating Procedures (SOPs)[1] manual of the National Advisory Committee on AEGLs (NAC AEGL) as well as technical support documents (TSDs) for five chemicals. It was suggested that all participants review these documents in advance of the meeting and provide comments via the Secretariat.

4. The June Expert Meeting consisted of two parts:

   - the first part addressed scientific and technical issues. This included a discussion of the approach being followed by the NAC AEGL and presentations concerning related initiatives in other OECD Member countries.
   - the second addressed policy issues, with the AEGL experts meeting together with the Extended Bureau of the Working Group. This part of the meeting focussed on ways and means of obtaining participation of OECD Member countries in the AEGL programme.

5. During the first part of the meeting, there were approximately 40 participants, representing ten OECD Member countries, as well as other interested international organisations and the Business and Industry Advisory Committee to the OECD (BIAC). It was chaired by Marc Ruijten from the Netherlands. A copy of the participants list is attached as Annex II to this report.

6. This report also contains, in annexes, copies of:

   - a summary of the comments to the SOPs provided in advance of the meeting (see Annex III);
   - the presentations related to initiatives in other countries (see Annex IV). These are listed in paragraph 40.

[1] Available on the OECD web site at http://www.oecd.org/ehs/ehsmono/index.htm

PART 1: SCIENTIFIC AND TECHNICAL ISSUES

Introductory Presentations

7. The Chairman of the Meeting, Marc Ruijten from the Netherlands, opened the meeting noting that there is an urgent need to develop specific guidance concerning health impacts of acute exposure to chemicals. Such guidance is needed in order to provide support to governments and the response community for emergency planning and response. The AEGL programme in the U.S. is a good candidate for developing such guidance, which could become internationally acceptable.

8. He congratulated the US on its efforts, and commended its willingness to open the process to other countries and to put the development of specific AEGL values "on hold" in order to allow for comments from other interested countries.

9. He noted that there is a window of opportunity for others to get involved in the AEGL programme. He asked experts and members of the Extended Bureau to be prepared to:

- consider their need for AEGL values;
- reach a conclusion on their level of confidence in the AEGL development procedure and on the willingness of the NAC AEGL to accommodate the views of others; and
- provide preliminary views on whether they would like to join in the AEGL programme.

10. The OECD Secretariat (Peter Kearns) welcomed all the participants and thanked the US for taking the lead in this effort. He said that it is still an open question as to what role OECD should play in moving the AEGL programme to an international project. He said that it is dependent, in part, on Member countries' interests as well as on what mechanism is chosen to internationalise the AEGL programme. He noted that the OECD could provide a brokering or facilitating role by, for example, helping to establish the means by which countries can join the AEGL programme. In the short-term, it will not likely be an OECD activity, since it is expected that not all countries will reach a decision about whether to participate in the near future. However, he mentioned that there is an opportunity to establish "rules of the game" now.

Overview of the AEGL Programme and Committee

11. The US experts[2] provided an overview of the AEGL programme being undertaken in the US, and described the draft SOPs. They pointed out that the SOP manual contains much of the history and background concerning AEGL development as well as a detailed description of the derivation of AEGL values. It was noted that the SOP manual is a living document, subject to revision on an ongoing basis.

[2] A number of experts from the US responsible for different aspects of the AEGL programme, participated in this meeting including Roger Garrett and Ernest Falke from the US EPA, George Rusch Chairman of the NAC AEGL, and Po-Yung Lu from the Oak Ridge National Laboratory. This report does not identify which individual made specific presentations at the meeting. They are referred to collectively as "a US AEGL expert".

12. AEGLs are defined to be the concentration of a substance in the air that causes a specific level of biological effects in a defined population after a specified duration of exposure. AEGLs are intended to represent biological threshold exposure values for the general population. The availability of these levels provides guidance to those responsible for emergency planning and response to chemical accidents, as well as for prevention of accidents with possible adverse health effects.

13. AEGLs are being established for single exposures during four different time periods, i.e., 30 minutes, and one, four, and eight hours. For each time period, three levels of effects are considered:

- AEGL - 1 is the level of a chemical in air at or above which the general population could experience notable discomfort;

- AEGL - 2 is the level of a chemical in air at or above which there may be irreversible or other serious long-lasting effects or impaired ability to escape; and

- AEGL – 3 is the level of a chemical in air at or above which the general population could experience life-threatening health effects or death.

14. It was pointed out the AEGL development process intends to develop realistic threshold levels, since if the AEGLs are set too high then the public will not be adequately protected. On the other hand, if AEGLs are set too low, then the zones considered to be vulnerable will be excessive and could create hindrances to effective planning and response (including, e.g., injuries occurring from evacuations).

15. It was also noted that it is possible that the lowest concentration leading to an AEGL – 1 endpoint could be higher than the lowest concentration leading to an AEGL – 2 endpoint (i.e., for some chemicals once the chemical can be detected, exposure has occurred at a level at which serious adverse effects may have been induced). The NAC AEGL is open to ideas on how to deal with this issue.

16. The objectives of the process used to develop AEGL values were described. These include:

- continuous improvement of the scientific rigour of the development process;

- continuous development of scientifically credible values;

- broad application of AEGL values;

- development of final AEGL values, at the rate of more than 40 chemicals per year (which will require as much collaborative effort as possible); and

- international acceptance and application of AEGL values.

17. It was noted that there are four stages in the development of AEGLs: draft; proposed; interim; and final.

- Following a review and evaluation of published scientific literature, as well as non-published data that can be collected from the private sector or any other source, a

technical support document is developed containing "draft" AEGLs. The draft AEGLs are circulated to all Committee members for review and comment.

- The draft AEGLs are elevated to "proposed" status once approved by the Committee by a 2/3 majority. These are then published for public review and comment (in the US Federal Register).

- Following resolution of relevant issues raised through public comment, and approval by the Committee, the AEGL values are classified as "interim". The interim AEGL value represents the best efforts of the Committee to establish exposure limits. These values are made available for use as deemed appropriate on an interim basis.

- The interim values are submitted to the National Academy of Sciences (NAS) for its review and concurrence. If there is no concurrence, then the Committee reviews the issues of the NAS Committee. When concurrence is achieved, the AEGL values are considered "final" and are published by the NAS.

18. The involvement of the NAS is considered important for a number of reasons. For example, the NAS provides a cohesive factor among stakeholders and it performs as an arbiter for scientific issues. It also establishes a mechanism for peer review, encourages one set of uniform values, and promotes public confidence.

19. The NAC AEGL includes representatives from a range of stakeholders, including representatives of a variety of U.S. Federal Agencies, industry, labour, states, academia and a number of interested organisations. The Committee meets four times a year and the meetings are open to the public. Thirty days before a meeting, the agenda is published in the Federal Register.

20. The US AEGL experts emphasised the value of the joint, co-operative effort for the development of AEGLs. Such an effort results in standardised exposure limits, development of more scientifically sound limits (with more people and resources, credibility increases), lower cost for each stakeholder, increased productivity (i.e., numbers of chemicals addressed), and broader acceptance in all sectors.

21. It was noted that there is a priority list of chemicals for AEGL development, developed with input from the current stakeholders. The next priority list is subject to amendment/addition by the international community. The current master list has more than 1000 chemicals, with a focus on 85 initially.

22. The process for the development of AEGL values starts with the chemical in issue being assigned to a member of the NAC AEGL (the Chemical Manager). The Chemical Manager, along with two additional NAC AEGL members (chemical reviewers) and a staff scientist from a "TSD development centre" (currently Oak Ridge National Laboratory) are the AEGL development team for that chemical. A technical support document (TSD) is then developed using all data that appear scientifically credible, including both published and non-published data. The development team collaboratively works on data selection and evaluation. The TSD is drafted by the staff scientist from the TSD development centre (not a member of the NAC AEGL). The TSD identifies the key study to be relied upon in developing each draft AEGL level, as well as supporting studies, background information and non-relevant data. Modifying/uncertainty factors, and scaling methodologies, are applied in relation to the weaknesses of data. This is then reviewed by the development team and draft AEGL values are developed.

23. For each chemical, a TSD is circulated to NAC AEGL members for review and comment before meetings, providing an opportunity to build a consensus. Based on comments received, the TSD and draft AEGL may be revised. The chemical is then considered at the Committee meeting, in order to discuss the revised TSD and AEGL values. The meeting adopts "proposed values" by consensus or 2/3 majority.

24. The proposed values, along with a summary of the TSD, are published in the Federal Register for a thirty-day review and comment period. The Committee reviews any public comments, resolves relevant issues and seeks a 2/3 majority on any modified AEGL value and supporting rationale. At this point the AEGL values are classified as "interim" and are sent, along with the revised TSD and supporting rationale to the National Academy of Sciences (NAS).

25. As of the date of the meeting, the NAC AEGL had reviewed 62 chemicals, 12 summaries had been published in the federal register, and 10 chemicals had been submitted for review by the NAS.

26. There are numerous scientific and technical considerations in developing AEGL values. As indicated, the NAC AEGL takes account of published, as well as non-published, industry data, other sources, and special toxicity studies. It was noted that unpublished data is often very reliable, when developed in conformance with Good Laboratory Principles (GLP). While human data is preferable, this is generally not available. It was noted that only inhalation data is used, i.e., route-to-route extrapolation has not been used so far.

27. In evaluating data, a number of other factors are taken into account including, for example, exposure concentration and duration (there is a need for data points over a large concentration and time range), analytical procedures used, number of subjects in the study, the species studied and animal weights, concentration/dose selection, observation period, signs and symptoms of toxicity, data for the establishment of an AEGL - No Observed Effect Level (AEGL-NOEL), and the number of concentrations or doses, etc.

28. No AEGL values are derived based on cancer risks, as a result of the uncertainty in extrapolating from lifetime to short-term exposures. There is very little data available concerning the risks of cancer from a single exposure or a small number of exposures. Furthermore, emergency responders tend to focus on minimising the immediate toxic effects of an accident. It was noted that this is a question of policy: the current policy is based on the assumption that increasing the number of people considered at risk in the event of an accident because of the possibility of causing cancer may do more overall harm than the statistical risk of cancer. However, in the future, the Committee may choose to give additional weight to cancer concerns. Calculations for cancer risk are taken up in the TSDs as a separate annex to the document.

29. The process for the calculation of AEGL values begins by selecting one or more empirical time and concentration data points for the AEGL level under consideration. Then adjustments are made to the experimental value. An uncertainly factor is used to account for variability between species (interspecies UF), and to account for individuals in the population who are sensitive but not hypersensitive (intraspecies UF). In addition, a modifying factor (MF) has occasionally been used to account for uncertainties in the database, study design or other factors. The experimental value is scaled across time for the AEGL periods of 30 minutes, and one, four and eight hours. The AEGL is then calculated using the following formula:

$$\text{AEGL} = \frac{\text{scaled experimental value}}{(\text{interspecies UF}) \times (\text{intraspecies UF}) \times (\text{MF})}$$

30. It was noted that the use of uncertainly factors needs to be balanced, taking into account the fact that larger uncertainly factors lead to a more conservative AEGL value. When applied in the context of preparedness and response it results in a greater degree of action. As noted above, this is a concern because it could divert limited resources from more critical aspects, and it may cause increased damage and injury (e.g., the greater the extent of an evacuation, the more people are hurt from the evacuation process).

31. The Committee seeks to apply an uncertainty factor that results in an AEGL value that best fits the supporting data. As a rule of thumb, for the interspecies UF, a factor of "10' is used where there is a need to address a number of limitations in the data. Such limitations could result from, for example, the fact that mechanism of action of the chemical is unknown, from the variability in responses between species and in those cases in which humans are more sensitive than animals. The factor may be reduced to "3' if the data indicate that there is little interspecies variability, primates or the most sensitive species was used, the mechanism of action is unlikely to differ across species, the use of "10" conflicts with human data that is available, or a multiple exposure study is used. The uncertainty factor might be reduced to "1" where there is remarkable agreement of the data for a well-defined toxic endpoint, or if using another factor would conflict with human data.

32. The intraspecies UF is used to protect sensitive populations recognising that, according to NAS guidance, the AEGLs should not strive to protect everyone under all circumstances. Therefore, sensitive, but not hypersensitive, individuals are considered in the development of AEGL values. Again, the starting point for the intraspecies UF is "10" which may be reduced according to the specific situation. The UF of 10 is used when, for example, young people are more sensitive to the chemical than adult populations or there is a broad range of responses, when the mechanical actions or metabolism are uncertain, or when a large number of systems may be impacted by the chemical. The UF would be reduced to "3" or "1" when these factors are limited or do not appear to be important.

33. The modifying factor, ranging from more than 0 and less than 10, may be applied based on an assessment of the uncertainties of the studies used in developing the AEGL values including, for example, the completeness of the available data set and the number of species used.

34. Interested parties are invited to develop actual data to influence the choice of uncertainty and modifying factors.

35. Time scaling is used to help develop AEGL values for the four different time periods. Where data are available for the time periods of interest, then this data are used. Since it is rare that empirical data are available for all AEGL-specified time points, an approach has been developed to extrapolate within and outside the time range of reported data. A regression analysis is used to establish an "n" value, which determines the slope of the concentration-time-response curve, allowing for an estimate of the AEGL values for the time periods of interest. If supporting data are available, these numbers can be evaluated for reasonableness. Where empirical data are limited for deriving the "n" value, and there are limited supporting data, then a more conservative approach is used in developing the AEGL values for the different time periods. For example, n=1 is used for extrapolation from short to longer durations and n=3 is used for long to shorter durations.

36. It was emphasised that there is a "reasonableness" approach used in the application of uncertainty and modifying factors. Once the uncertainty and modifying factors and time scaling are applied,

the resultant AEGL values are passed through a "reasonableness test", i.e., a consideration of whether the results make sense given data and expert knowledge. The process of determining the AEGL values should be transparent as the Committee is paying attention to documenting the rationale for picking specific values.

37. Mr. Ten Berge from BIAC demonstrated a software programme to estimate variables for acute toxicity studies (i.e., the value of "n"), that takes into account duration of exposure, body weight, sex, and numbers of animals in the experiment.

Comments on the AEGL Programme

38. The participants in the expert meeting were invited to provide written comments on the SOP in advance of the meeting. These were summarised in a document circulated at the meeting and were discussed in some detail. Further comments were provided on the results for specific chemicals including arsine and chlorine. The summary of the comments received in advance of the meeting, as prepared by the US delegation, is included as Annex III.

39. Discussion at the meeting focussed on the following issues: AEGL endpoints; key data selection; uncertainty factors; modifying factors; time scaling; carcinogenicity; human data; dosimetry corrections; and miscellaneous procedural issues. The following summarises some of the points raised:

a) AEGL endpoints:

- A question was raised whether a change in air rate resistance is a sufficient basis for setting AEGL values and how severe a change in pulmonary function is needed to be taken into account for this purpose. A US AEGL expert noted that this is an open question. He said that the reasoning behind the current approach is that the AEGL – 1 level is based not on adverse effects but rather on detectability. An AEGL -1 level is an alert, linked to preventing hysteria, not physical harm.

- It was suggested that consideration be given to the odour properties of the chemical under consideration since substances with a bad smell may induce anxiety at a lower level above the detection limit compared to other substances. The US AEGL experts welcomed this comment and said that they would discuss it in the future.

- It was noted that the threshold limit values (TLVs) established by the American Conference of Governmental Industrial Hygienists (ACGIH) are values designed to protect healthy workers. A question was raised as to whether these might be used to develop AEGL-1 values. A US AEGL expert noted that the TLVs are looked at, but are not relied on by themselves since the TLVs are often not well-documented.

- It was suggested that it is not valid to set the AEGL-2 value based on the highest level causing reversible effects when the level causing irreversible effects cannot be established. A US AEGL expert agreed that this is a valid comment but the alternative is to not have any value. The values have been changed where better data have been made available.

- There was considerable discussion concerning the calculation of the LC01, the calculated concentration that is expected to produce 1% lethality in the test animals. A number of

experts questioned the use of 1/3 of the LC50 to approximate the LC01. It was noted that the rationale for this approach was lacking, and that others divide the LC50 by 4 rather than 3. A US AEGL expert noted that 1/3 is used when the dose-response curve is steep. The use of 1/4 may also be appropriate, and more conservative than the approach chosen by the NAC AEGL.

- It was noted that the SOP manual does not discuss handling the reproductive effects toxicity endpoint. A US AEGL expert explained that the Committee has not used reproductive effects to set an AEGL level, as it has not thus far been the most sensitive endpoint although it would be used were it the most sensitive.

It was also pointed out that the question of developmental toxicity will be discussed at the September 1999 meeting of the Committee and that any suggestions on this subject would be very welcome.

b) Key Data Selection

- It was suggested that the AEGL development process should prefer studies that include variations in concentration and time period of exposure. Furthermore, there should be an opportunity for interested parties to provide better data than is currently available. A US AEGL expert said that the Committee regularly seeks industry input during the development of TSDs, and industry are also invited to provide input during the Committee meetings and during the comment period. The Committee will postpone (and has done so) establishing AEGL values when they were informed that better data are forthcoming. They will also adjust values if new information is made available. Furthermore, in the future the Committee will advertise the chemicals on the priority list a year in advance in order to facilitate new testing.

- It was explained that the key study is usually the one with the most sensitive animal species unless there are grounds indicating that it is not relevant. This approach improves transparency and consistency in methodology. A US AEGL expert said that the most appropriate study is used as the key study for developing AEGL values. While the most sensitive species is one parameter that is considered, it is important to recognise that in, certain cases, other data are more appropriate (e.g., human or primate data are generally preferable). It was agreed that it should always be clearly documented when the key study is one using a species other than the most sensitive species.

c) Uncertainty Factors

- There was considerable discussion concerning the use of uncertainty factors and the way the choice is made about what level to apply in the development of AEGL values. One concern was that the existing approach might result in too conservative AEGLs. Another concern was that there was no clear justification for a default of "10" for the interspecies UF as indicated in the SOP since, in some cases, humans are less sensitive to toxic effects than smaller animals. There were also discussions concerning the use of terminology "uncertainty" and "modifying" factors and the relationship between these factors and the application of the AEGL values (e.g., in risk assessment, in emergency planning, and in response).

- A US AEGL expert noted that the application of uncertainty factors is decided on a case-by-case basis and, in fact, it is very rare that a "10" is used for both uncertainty factors, resulting in a 100 fold safety factor (10 x 10) incorporated into an AEGL value. The default values are only used if information is not available to indicate that an alternative would be preferable. In addition, in developing AEGL values, they are reviewed in the context of supporting data and, therefore the application of uncertainty factors should not lead to very conservative values.

- It was also noted that that the uncertainty factor for interspecies extrapolation actually consists of two parts: scaling and variability.

- For intraspecies uncertainties, "10" was considered to be an appropriate default level and, in fact, there are cases where "10" may not be large enough. Therefore, it was suggested that the SOP allow for an intraspecies uncertainly value of greater than "10" in those specific cases where it is warranted. In any event, the uncertainty value should be adjusted to reflect actual data. It was also pointed out that the range of sensitivity in humans depends, in part, upon the toxicological endpoint in question.

- Another question that was raised is whether uncertainty factors only address lack of good data or whether they also seek to incorporate a margin of safety. A US AEGL expert noted that AEGLs are biological reference points, based on toxicology, which take into account uncertainty or absence of data through the application of the uncertainty factors. AEGLs can be used in a variety of applications and how they are used is a policy matter. Those responsible can adjust the values to change the margin of safety, as considered appropriate in a given context.

- It was also pointed out that part of the confusion concerning the uncertainty and modifying factors might stem from terminology. The term "uncertainty factors" as used in the AEGL programme are considered extrapolation factors in other countries/organisations. Furthermore, AEGL "modifying factors" are called uncertainty factors elsewhere.

- In conclusion, it was generally agreed that the issue discussed was, to some degree, a wording problem, rather than a scientific one. Since the use of "10" as an uncertainty factor has to be justified, then it is not actually a default value. Rather, the NAC AEGL uses a range between 1 and 10 (and perhaps outside the range), applied on a case-by-case basis, in light of the data available. It was also pointed out that as long as the uncertainty factors need to be justified, then there should be confidence that the outcome will be reasonable. A US AEGL expert agreed that the SOP might be rewritten to avoid an appearance of a bias towards the use of a factor of 10. To the extent that there exists disagreement about the wording of the SOP, then comments should be provided to the Committee for their consideration.

d) Time Scaling

- AEGL values need to be developed for 4 different time periods. In most cases, the data used to develop the AEGL values are not available for all these time periods. The simple approach, where the product of exposure duration and concentration required to produce a certain adverse health effect is assumed to be constant, is invalid. Some effects appear to be driven by the concentration level rather than by exposure time. One convenient

mathematical description of the degree of time- and concentration dependence is:

$C^n * t$ = constant, where

constant = a well defined (adversity and proportion of population affected) health effect;
C = concentration level;
t = exposure duration;
n = scaling factor.

If n > 1, the effect is more concentration- than time-dependent. Haber's rule (C*t = constant) is the special case where n=1.

- There was extensive discussion about the use of time scaling to extrapolate AEGL values for the four time periods. Distinctions were made between the case where there is good data (a study in one species for one endpoint with various concentrations of the chemical for various time periods) and where there is no or limited data. There was some disagreement about the ability to derive AEGL values beyond the existing data (e.g., for time periods beyond the range used in the test or for applying the data for different endpoints).

- It was suggested that it might be helpful to use more than one key study for a chemical, where valid studies exist for different endpoints. A US AEGL expert noted that the Committee is flexible and that more than one study could be used but to date they have not seen two or more robust studies that could be used for a particular chemical. He agreed that it would be possible to take more than one study into account to develop AEGL values for different time intervals.

- There was also discussion about the validity of the procedure to use of LC50 values instead of raw data to determine the value of "n". It was noted that LC50 is not actually data. Where the data underlying the LC50 values are not available, it may or may not be possible to determine the slope of the curve. Where raw data is available, a computer programme should be used to develop the slope of the curve.

- The meeting also discussed whether a specific n-value used for time scaling defined for a particular AEGL-level (e.g., a value derived for lethality (AEGL-3)) should or could be used for other AEGL-levels comprising different effects. This may result in different studies/endpoints to be used for an AEGL level at different time-points. Although, in most cases, only lethality data will be available to derive an n-value, the SOP will be changed to explicitly address this issue.

- One expert noted that there is a lot of data available for 30-minute combustion toxicity, from which were generated LC50 figures. He agreed to send the study to Peter Kearns at the OECD.

- There was a question raised about deriving AEGL numbers for less than 30 minutes. It was noted that limited data is available for exposures shorter than 30 minutes. A US AEGL expert stated his view that is that it is possible to extrapolate from 30 down to 10 minutes but not below that. The Committee does not have a specific policy on this issue.

- Based on the suggestions made, a US AEGL expert stated that if the data is available then it is possible to develop the variable needed to determine the slope of the curve using either the current methodology or the more sophisticated computer programmes. The latter should be reviewed carefully. In the absence of chemical-specific data a conservative approach is used for the extrapolation (i.e., n=1 for short to long; and n=3 for long to short) and this should be evaluated against any supporting data. If it does not pass the reasonableness test, then the resulting AEGL values should be adjusted.

e) Dosimetry

- It was suggested that use should be made of known differences in metabolism, oxygen consumption, breathing rates, respiratory tract surface area and geometry when extrapolating between species. In addition, allometric scaling and the mode of action of the chemical should be taken into account. It was agreed that these should be explored further since, in general, there are no validated generic methods for applying these and there are significant differences between substances, as well as differences between systemically and locally acting toxic chemicals.

f) Modifying Factors

- It was suggested that modifying factors might be superfluous in light of the application of uncertainty factors. A US AEGL expert noted that a modifying factor had only been used three or four times, for example when they only had one study that had not been reproduced, or where there was a study on one isomer that was to be applied to another known to have a difference in toxicity. When use has been made of a modifying factor, this was made transparent in the TSD, with a clear justification.

- It was pointed out that a modifying factor could be avoided by asking for additional tests. It was agreed that critical data gaps provide an incentive for testing. Furthermore, interested parties are motivated to perform additional testing when it might lead to a reduction in the uncertainty and modifying factors applied in the development of AEGL values.

g) Carcinogenicity

- It was noted that carcinogenicity has not been used as a basis for the development of AEGL values, although it was acknowledged that there is a possibility that a single exposure to a particular chemical might cause cancer. One question is: to what extent does the data justify the development of AEGL values based on cancer risk, when adverse effects from a single exposure are the primary concern. Given the level of risk and the number of people estimated to be exposed in any typical release in the US, the use of cancer data will lead to a very large vulnerable zone.

- It was pointed out that consideration of cancer is important for the protection of public health and that the public has a high level of concern about cancer. In fact, anxiety after an accident about cancer risks can produce various pathologies from the stress involved. Therefore, it should be taken into account as an important end-point.

- A US AEGL expert indicated that the Committee is still trying to formulate a position on cancer and a protocol for dealing with cancer data is in progress. For those chemicals that are carcinogens, the TSD includes an appendix containing the cancer risk assessment. The Committee has hired a contractor to gather a database to evaluate the risk from single exposure and they are trying to persuade the National Testing Program to conduct additional studies. He said that the Committee welcomed opinions on this matter, including the level of risk that should be considered and for which AEGL level carcinogenicity should be an endpoint. The Dutch delegates pointed out that a report on this subject, including a literature review, has been published by the Dutch Health Council which proposes the use of Dose Rate Correction Factors.

- One suggestion was that the NAC AEGL take account of cancer data, but handle it differently since cancer information is important for planning purposes but perhaps not as much for response. Another suggestion was that for those chemicals that are both toxic and carcinogenic, then the focus should be on toxicity. But where there is no toxicity, then the carcinogenicity should be used.

h) Miscellaneous

- Route-to-route extrapolation: A question was raised about why there was no reference in the SOP about route-to-route extrapolation. It was also noted that while the focus has been on vapour exposure, dermal exposure should also be a substantial concern. A US AEGL expert noted that the Committee has preferred using inhalation data, but agreed that this is a concern and in one case dermal exposure was recognised.

- Sensitisation: Another issue concerned the fact that sensitisation has not been addressed in the SOP. It was pointed out that sensitisation is generally an issue in multiple exposures and therefore not a concern for AEGLs, which generally relates to a single accidental exposure.

- Rounding: One expert suggested that it does not make sense to round the AEGLs to two significant figures, given that large uncertainty factors are used. A US AEGL expert agreed that the point is well taken and that there are arguments for both options. He said that the choice was made to use two figures since rounding to one figure can make a big difference when the AEGLs are used in models for planning purposes, and to differentiate between different AEGL levels and time periods.

- Absence of Data: It was noted that in absence of adequate data, no AEGL value is established. It was suggested that instead the Committee should come up with their best guess and clearly identify it as provisional. A US AEGL expert noted that this is a judgement call and that the Committee is uncomfortable setting an AEGL level without reasonable data. However, they do recognise that their collective experience can provide a better guess than emergency responders and, therefore, they make an effort to establish AEGLs whenever possible. Where a critical need is identified, the Committee will push industry to develop data (as all testing is done by the private sector on a voluntary basis). Thus far, the Committee considered eight chemicals for which they decided to not develop numbers, but most of these chemicals had little production volume.

- Ceiling or Weighted Average: One expert asked whether the interpretation of the AEGL value is a ceiling value, or a time-weighted average. A US AEGL expert stated that an

AEGL value is a ceiling, i.e., at or above the level certain effects will occur. However, there is a concern that this will be interpreted to mean that an exposure level below the value will be "safe"; therefore, the term threshold may be used.

This leads to the question of how to interpret the case where during the time period being addressed there is a temporary spike of exposure above the AEGL level. It was noted that the issue of short excursions above the AEGL level will be discussed at the September 1999 NAC AEGL Meeting.

Initiatives Related to AEGLS in Other OECD Member Countries

40. A number of participants made presentations concerning related initiatives, i.e.:

(a) EPRGs ("Emergency Response Planning Guidelines") of the American Industrial Hygiene Association, presented by David Kelly (representing BIAC);

(b) UK SLOTs ("Specified Level of Toxicity"), presented by Maureen Meldrum;

(c) French Initiative: Detailed methodology for setting up lethal and irreversible threshold effects, presented by Joelle Jarry and Annick Pichard;

(d) German Initiatives, presented by Fritz Kalberlah;

(e) ECETOC Emergency Exposure Indices for Industrial Chemicals, presented by Fritz Kalberlah;

(f) Dutch Initiative: Rotterdam temporary emergency number program, presented by Marc Ruijten.

See Annex IV for copies of the presentations.

41. In addition to the scheduled presentations, the Italian expert described related work in his country. He noted that a document has been published on civil planning and rapid assessment. It uses the LC50 values, based on the manual published by the International Atomic Energy Agency related to classification and prioritisation of risks due to major accidents. He noted that he expects a proposal to be developed in his country to undertake further research in this area. In this regard, he suggested that a co-operative, international AEGL effort is one of the best ways to make progress in this area.

Concluding Statement

42. The Chairman concluded the first part of the meeting by congratulating all participants for all their hard work and constructive discussions. He suggested that such an open "brainstorming" session should be held every one or two years.

43. He reminded participants that AEGLs have a wide range of applications in chemical emergency prevention, preparedness and response. Once there is a consensus on the AEGL levels, based upon good information, they can be applied in different contexts, as appropriate.

44. He also pointed out that since there is a real need for such short-term exposure guidance in all countries, it would be inefficient for different countries to undertake the effort separately. He noted that the interest demonstrated at this meeting is evidence of the need for realistic numbers, based on good data. He suggested that there is a need to address about 500 chemicals. For these reasons, it is logical to pursue international co-operation to share the burden and responsibility.

45. The Chairman reminded participants that the first part of the meeting involved technical discussions and it was not intended that the experts reach consensus on the issues considered. Rather, the objective was to exchange opinions, data and procedures. He indicated that he had the impression that there is a fair amount of confidence in the existing AEGL development procedure. Furthermore, the NAC AEGL appears to have flexibility in its procedures, including a willingness to consider and possibly accommodate the views of others and to apply new science and data as it becomes available.

46. In conclusion, he said that he hoped that the meeting provided the technical experts with the confidence to recommend to the policymakers that they participate in the AEGL programme. He pointed out that the second part of the meeting will focus on how to internationalise the programme. A truly international effort would increase the likelihood of the worldwide acceptance and application of the AEGLs. He recognised that achieving this will likely be a step-by-step process, with the OECD providing a forum to facilitate that development and with the US acting as lead country.

PART 2: POLICY ISSUES

47. This part of the meeting was designed to consider policy issues and, in particular, how to facilitate international co-operation in the development and application of AEGL values. It included the technical experts from the first part of the meeting, along with the members of the Extended Bureau of the Working Group. It was chaired by Gunnar Hem from Norway, Chairman of the Working Group.

48. Mr. Garrett of the U.S. opened this part of the meeting. He emphasised that the US NAC AEGL is extending a sincere invitation to Member countries to participate in the AEGL programme. The meeting of technical experts made it very clear that an international effort would make a dramatic contribution to the existing programme.

49. The question, he pointed out, is how to move toward international participation. He noted that this should be an evolutionary process. He identified five ways for other Member countries to participate and provide support for the AEGL programme:

- provide input into the development of the priority lists of chemicals including mechanisms for identifying such chemicals (for example through the Pollutant Release and Transfer Registers);
- share published and unpublished data on chemicals;
- become a member of the NAC AEGL;
- provide resources to support the development of TSDs (either financial or in-kind); and
- participate in the review and comment process.

50. In addition, he noted that there may be the opportunity to add one or two new members, from other OECD countries, to the National Academy of Sciences subcommittee providing oversight for the AEGL programme. There has already been a member selected from Canada.

51. Mr. Garrett further elaborated on what is involved in being a member of the NAC AEGL. Any new Committee member from outside the US would be expected to provide substantial financial, or in-kind, support for the development of TSDs. In addition, there is a significant "human resources" contribution by the individual on the Committee. This includes the time involved in: reviewing and commenting on approximately 50 draft AEGLs each year; participating in Committee meetings; and being a chemical manager and a chemical reviewer. In addition, the Committee member would be expected to provide a liaison with the organisation that he/she represents. There are also travel costs associated with participation in the AEGL meetings which are scheduled four times a year.

52. Mr. Garrett identified a number of the benefits to participating in the NAC AEGL. For example, members of the Committee can help focus work on chemicals of specific interest and influence decisions on prioritisation. They can also influence the resolution of AEGL scientific issues and AEGL values. Participation will also help to increase overall production of AEGLs, and provides the members with an educational opportunity.

53. Mr. Garrett noted that some countries expressed an interest in providing a contribution to the programme through an AEGL Development Centre. He noted that, from a practical perspective, there is a need to limit the number of AEGL Development Centres internationally, in order to maintain quality and co-ordination.

54. He described the role of an AEGL Development Centre (currently found at, for example, the US Oak Ridge National Laboratory). A Development Centre must have:

- availability of capable scientific staff with low turnover;
- availability of facilities, equipment, and personnel to undertake the literature search and data gathering needed for the TSDs, AEGL development and communication and co-ordination; and
- willingness to assume the "contractor" role.

55. The Secretariat noted that the OECD is open to suggestions as to the future role of OECD in the AEGL programme. Based on the discussions thus far, it appears that OECD could be most effective in facilitating international participation and communication and serving as a broker. If there is an interest, the OECD could publish the AEGL numbers although this would not imply that countries are required to use the numbers.

56. The Chairman identified a number of issues for discussion:

- should this be an international activity and what are possible obstacles to this (formal, scientific, financial);
- if there is an international effort, how should it be structured and how can OECD facilitate the process; and
- what should the next steps be and who should take the initiative.

57. There was a consensus on the need for the development of AEGL-like numbers for a number of purposes, in both a domestic and transboundary context, related to chemical accident prevention, preparedness and response. It was agreed that it is clearly more efficient to undertake this work as an international effort. In addition, it was noted that industry is interested in having internationally-agreed numbers. The meeting expressed strong support for the AEGL programme, as being implemented in the US. It was recognised that the US has established an effective structure for moving forward with the development of acute exposure values.

58. Two countries (Germany and the Netherlands) indicated their intent to participate in the NAC AEGL. A couple of others indicated an interest in observing the AEGL programme and several others noted that, while they support the work, they need to discuss the matter further in capitals.

59. Several delegates raised a number of points related to the provision of financial or in-kind contributions. The Dutch delegate confirmed that his country would provide support in the form of a Development Centre capable of preparing TSDs. In this regard, several delegates asked about how many Centres could be accommodated in light of the need to ensure quality and co-ordination.

60. It was pointed out that there are advantages and disadvantages of having a number of Development Centres. Among the advantages is that there is access to expertise from around the world, and a greater commitment to the programme.

61. The delegate from the IPCS suggested that it may be possible to have a network of participating institutions to help develop the TSDs. The process could be aided by agreement on the structure for the documents.

62. A couple of delegates noted that one issue which should be further discussed is the use of uncertainty factors. In particular, there was a question of whether different countries could use different safety factors in the application of AEGLs. It was pointed out that AEGLs are biological reference values. When applied, they can be modified or adapted to the particular use. However, it was noted that there may be a need to reach agreement in how they would be applied in the context of transboundary accident prevention, preparedness and response.

63. In a related comment, several delegates emphasised the need for the process of developing AEGLs to be very transparent so that it is clear what part is based on science and what on other factors. It was also suggested that more use be made of human data.

64. A question was raised about how to ensure co-ordination among the European Union countries. It was agreed that this would be further considered among the relevant countries.

65. The meeting also discussed the role of other international organisations in taking the results of the AEGL programme beyond the OECD region. The representatives of both UNEP and IPCS expressed appreciation for the initiative and offered to provide a mechanism for disseminating the results to non-OECD countries. It was pointed out that in less developed countries, one concern is how to ensure that they have the capacity to use the numbers in a meaningful way.

66. The delegate from the US suggested that the focus should not be on whether the numbers are "perfect" (an unattainable goal at this point) but rather whether this work provides a good foundation for developing very good values. Furthermore, countries should take steps as quickly as possible to decide whether, and how, to participate in the AEGL programme in order that they can help to shape the process.

67. In conclusion, there was agreement that the meeting made significant progress and that there was a high level of interest in virtually all countries. The question which remained was how, not whether, to proceed with this work on an international basis.

68. With respect to next steps, it was emphasised that the NAC AEGL is open to various ways of contributing to the process. Each country should figure out what would work best for them. Therefore, the US offered to meet with other delegations on a bilateral basis, in order to provide any additional information that is needed and to develop an appropriate mechanism for that country. Countries were also asked to develop their priority lists of chemicals requiring AEGL values and provide these lists to the NAC Committee.

69. It was agreed that the Working Group should continue to discuss this matter further. If there is an expansion of the AEGL activity, then there may be a need to address the more formal aspects of joining and ensuring an active commitment, including financial aspects. The OECD should continue to facilitate participation of Member countries and other international organisations.

ANNEX I

AGENDA
OECD Expert Meeting on Acute Exposure Guideline Levels

OECD Annex Chardon Lagache,
94, rue Chardon-Lagache, Paris 75016

Paris, 7-8 June 1999, beginning at 09:30

(To be combined with Extended Bureau Meeting of the Working Group on Chemical Accidents, 8-9 June 1999)

Monday, 7 June 1999

Morning session: Scientific aspects 1

09:30 Chair (Marc Ruijten)

09:45 OECD (Peter Kearns)

10:00 AEGL's Programme (Roger Garrett)

10:45 AEGL's Committee (George Rusch)

11:15 Development of AEGL values (Ernest Falke)
informative questions / clarification only

12:30 Lunch

Afternoon session: Scientific aspects 2

14:00 Presentations and Discussion of Comments of Scientists from OECD Member countries

- 14:00 Wil ten Berge: MLE processing of data. Consequences for time scaling and interspecies extrapolation.
- 14:20 General discussion on the basis of written comments

15:30 Coffee break

16:00 Presentations and Discussion of Comments of Scientists from OECD Member countries - general discussion continued

18:00 Adjourn for the day

Tuesday, 8 June 1999

Morning session: Scientific aspects 3

09:00 Presentations and comments from scientists from OECD countries - general discussion continued

10:00 Related Initiatives to AEGLs in other OECD countries (includes informative questions)

- 10:00 ERPGs (David Kelly)
- 10:10 UK SLOTs (Maureen Meldrum)
- 10:20 France (Joelle Jarry or Mrs Pichard)

10:30 Coffee break

11:00 Related Initiatives to AEGLs in other OECD countries (includes informative questions)

- 11:00 Germany (NN)
- 11:10 Netherlands (Leon de Bruijn or Marc Ruijten)

11:20 Response by AEGL team to alternative approaches presented.

11:40 General discussion on alternative approaches.

12:00 Closure - AEGL team comments on:

- critique from scientists from OECD countries;
- AEGL team's conclusions concerning validity of the current development methodology based on previous discussion;
- procedure to consider possible amendments of SOP on the basis of the discussions.

12:25 Closure scientific session (Marc Ruijten).

12:30 Lunch

Afternoon session: Policy aspects (To be combined with the Extended Bureau meeting)

14:00 Chair (Gunnar Hem).

14:05 Proposed internationalisation of the AEGL program (Roger Garrett).

1. Invitation to OECD or OECD Countries to participate in the AEGL program.
2. Areas of participation and support:
   a. Contributing chemicals to the priority list.
   b. Sharing relevant published/unpublished data.
   c. Membership on the NAC/AEGL Committee.
   d. Providing financial resources.
   e. Conducting review and comment process.
   f. At least one additional member on the NAS subcommittee for AEGLs.
3. Benefits of participation:
   a. Availability of AEGLs and TSDs for chemicals of interest.
   b. Influence in prioritisation of chemicals.
   c. Influence on scientific issues related to AEGL development.
   d. "Voting rights" in NAC/AEGL Committee
   e. At lest one additional OECD representative on NAS Subcommittee for AEGLs.
   f. Capacity building in emergency guideline development.

14:40 Discussion and response of OECD Member countries to (amongst other things) the following.

- proposed areas of application;
- prioritising chemicals;
- public review process;
- mechanism for an international procedure to determine final values;
- identification of competent TSD drafting centres.

15:30 Coffee break

16:00 Discussion and response of OECD member countries - continued.

17:30 Conclusion and intent to participate in AEGL program and/or adopt AEGLs by OECD member countries

18:00 Closure of Session.

ANNEX II

OECD EXPERT MEETING ON ACUTE EXPOSURE GUIDELINE LEVELS

Paris, 7 – 8TH JUNE, 1999

PARTICIPANTS LIST

ALLEMAGNE	GERMANY
Mr JÄCKH, Rudolf BASF AG, Ludwigshafen HAT/D, Z470 D-67056 Ludwigshafen	Tel: 49 621 60 56716 Fax: 49 621 60 51734 E-mail: rudolf.jackh@basf-ag.de
Mr BENDER, Herbert BASF-AG, Ludwigshafen DUS/TD M940 D-67056 Ludwigshafen	Tel: 49 0621 60 56 455 Fax: 49 621 60 74 140 E-mail: herbert.bender@basf-ag.de
Mr GRIEM, Peter FoBiG - Forschungs und Beratungsinstitut Gefarnstoffe GmbH Werderring 16 D-79098 Freiburg	Tel: 49 761 38608 12 Fax: 49 761 38608 20 E-mail: fobiggmbh@aol.com
Mr KALBERLAH, Fritz Research Institut for Dangerous Materials and Toxicology (FoBiG GmbH) Werderring 16 D 79098 Freiburg	Tel: 49 761 38608 11 Fax: 49 761 3860 820 E-mail: fobiggmbh@aol.com
Mr. PAULUHN, Jürgen BAYER AG Dept. of Toxicology Build. 514 D-42096 Wuppertal	Tel: 49 202-368909 Fax: 49 202-364589 E-mail: jurgen.pauluhn.jp@bayer-ag.de
Mr PETTELKAU, Hans-Jürgen Federal Ministry for Environment Nature Conservation and Nuclear Safety Schiffbauer damm 15 D-10117 Berlin	Tel: 49 30 28550 4347 Fax: 49 30 28550 4375 E-mail: pettelkau.hans@bmu.de
Mr SCHAEFER, Heinz-Guenter VCI (Chemical Producers Association) Karlstr. 16 D-60329 Frankfurt/Main	Tel: 49 69 255 61 1536 Fax: 49 69 255 61 1607 E-mail: schaefer@vci.de

Mr WINKELMANN-OEI, Gerd
Federal Environment Agency
Seecktstr. 6-10
PO Box 330022
D-13581 Berlin

Tel: 49 30 8903 3298
Fax: 49 30 8903 3099
E-mail: gerhard.winkelmann-oei@uba.de

AUTRICHE / AUSTRIA

Mr GIDALY, Gottfried
Federal Ministry for the Environment,
Youth and Family Affairs
Department I/3
Stubenbastei 5
A-1010 Vienna

Tel: 43-1 515 22 2342
Fax: 43-1 513 1679 1086
E-mail: gottfried.gidaly@bmu.gv.at

CANADA / CANADA

Mr BISSETT, Wayne
Environmental Emergencies Branch
Environmental Protection Service
Environment Canada
Place Vincent Massey
Hull, Quebec K1A 0H3

Tel: 1-819 997 2981
Fax: 1-819 997 5029
E-mail: Wayne.Bissett@ec.gc.ca

Mr LACOURSIERE, Jean-Paul
J.P. Lacoursiere Inc.
35 Avenue Lemoyne
Repentigny, Québec, J6A 3L4

Tel: 1 450 581 2315
Fax: 1 450 581 4539
E-mail: jpla@sympatico.ca

Mr REISS, Robert
Emergency Prevention Officer
Environment Canada
Environmental Protection Service
4th Floor 105 McGill
Montreal Quebec H2Y 2E7

Tel: 1 514 283 0822
Fax: 1 514 496 1157
E-mail: Robert.Reiss@ec.gc.ca

ETATS-UNIS / UNITED STATES

Mr FALKE, Ernest
US Environmental Protection Agency
(Mailcode 7403)
Risk Assessment Division
Office of Pollution Prevention & Toxics
401 M Street SW
Washington DC 20460

Tel: 1 202 260 34 33
Fax: 1 202 401 28 63
E-mail: falke.ernest@epa.gov

Ms BEAL, Diane Deputy Counsellor for International Affairs Office of Prevention, Pesticides and Toxic Substances (7101) 401 M Street SW Washington DC 20460	Tel: 1 202 260 1822 Fax: 1 202 240 1847 E-mail: beal.diane@epa.gov
Mr GARRETT, Roger Director, Special Science Programs US EPA (Mailcode: 7403) Risk Assessment Division Office of Pollution Prevention & Toxics 401 M Street, S.W. Washington D.C. 20460	Tel: 1 202 260 4302 Fax: 1 202 401 2863 E-mail: garrett.roger@epa.gov
Mr LU, Po-Yung Oak Ridge National Laboratory Toxicology and Risk Assessment 1060 Commerce Park, MS 6480 Oak Ridge TN 37830	Tel: 1 423 574 7587 Fax: 1 423 241 0397 E-mail: lpy@ornl.gov
Mr MAKRIS, Jim Director US-EPA Office of Solid Waste and Emergency Response CEPPO 5104 401 M Street, S.W. Washington, D.C. 20460	Tel: 1-202 260 86 00 Fax: 1-202 260 79 06 E-mail: makris.jim@epa.gov
Mr RUSCH, George Department of Toxicology & Risk Assessment Allied Signal, Inc 101 Columbia Road Morristown NJ 07962 1139	Tel: 1 973 455 36 72 Fax: 1 973 455 5405 E-mail: george.rusch@alliedsignal.com
FRANCE	**FRANCE**
Mr CHAPRON, Marcel Direction de la prévention des pollutions et des risques Ministère de l'aménagement et de l'environnement 20, avenue de Ségur F-75302 Paris 07 SP	Tel: 33 1 42 19 14 07 Fax: 33 1 42 19 14 67 E-mail: marcel.chapron@environnement.gouv.fr
Ms JARRY, Joelle Direction de la prevention des pollutions et des risques Service de l'environnement industriel Bureau des risques technologiques et des industries chimiques et petrolieres 20 avenue de Segur 75302 Paris 07 SP	Tel: 33 1 42 19 14 16 Fax: 33 1 42 19 14 67 E-mail: joelle@environnement.gouv.fr

Mr MOCHE, Laurent Chef Bureau des Risques technologique indusries chimiques et pétrolières Ministere de l'amenagement du territoir et de l'environnement 20 avenue de Segur 75007 Paris	Tel: 33 1 42 19 14 34 Fax: 33 1 42 19 14 67 E-mail: laurent.moche@environnement.gouv.fr
Ms PICHARD, Annick INERIS Parc technologique ALATA Direction des risques chroniques BP 2 60550 Verneuil en halatte	Tel: 33 3 44 55 65 13 Fax: 33 3 44 55 66 05 E-mail: Annick.Pichard@ineris.fr
ISLANDE **ICELAND**	
Mr VIDARSSON, Fridjon Mar Administration of Occupational Safety and Health PO Box 12220 132 Reykjavik	Tel: 354 567 2500 Fax: 354 567 4086 E-mail: fmv@ver.is
ITALIE **ITALY**	
Mr DRAICCHIO, Francesco ISPESL Lab of Physiology and Ergonomics Via Fontana Candida, 1 00040 Monteporzio Catone Roma	Tel: 39 06 94 181 453 Fax: 39 06 9418 1410 E-mail: dray@flashnet.it
Mr LUDOVISI, Giancarlo Istituto Superiore per la Prevenzione e la Sicurezza del Lavoro (ISPESL) Via Urbana 167 00184 Roma	Tel: 39 06 471 42 35 Fax: 39 06 474 18 31 E-mail: ludovisi@tin.it
Mr PAPALEO, Bruno ISPESL Dipartimento Medicina del Lavoro Via Fontana Candida, 1 Monteporzio Catone 00040 Roma	Tel: 39 06 9418 14 56 Fax: 39 06 9418 1410 E-mail: papbru@flashnet.it

NORVEGE	**NORWAY**
Mr HEM, Gunnar (WG Chairman) Head of Corporate Legal Affairs The Norwegian Directorate for Fire and Explosion Prevention P.O. Box 355, Sentrum Nedre Langgt. 20 3101 Tonsberg	Tel: 47-33 39 89 05 Fax: 47-33 39 89 43 E-mail: gunnar.hem@dbe.dep.telemax.no
PAYS-BAS	**NETHERLANDS**
Mr LOMMERS, Gérard Ministry of Housing, Physical Planning and the Environment (IBV 655) 8, Rijnstraat, P.O. Box 30945 2500 GX The Hague	31-70 339 47 03 31-70 339 1314 E-mail: Lommers@DSVS.DGM.minvrom.nl
Mr RUIJTEN, Marc (CHAIRMAN) Municipal Health Service Rotterdam Environmental Health Office Post Box 70032 3000 LP Rotterdam	Tel: 31 10 4339 405 Fax: 31 10 4339 343 E-mail: ruijtenm@ggd.rotterdam.nl
Mr VAN RAAIJ, Marcel RIVM (National Institute of Public Health and the Environment), Centre for Substances and Risk Assessment PO Box 1 3720 BA Bilthoven	Tel: 31 30 274 3615 Fax: 31 30 274 4401 E-mail: MTM.van.Raaij@rivm.nl
ROYAUME UNI	**UNITED KINGDOM**
Ms McCREADY-SHEA, Susan HM Principal Specialist Inspector Health & Safety Executive Safety Policy Directorate Nuclear & Haz. Installations Policy Div Daniel House, Trinity Road Bootle Merseyside L20 7HE	Tel: 44 151 951 4725 Fax: 44 151 951 3418 E-mail: susan.mccready-shea@hse.gov.uk
Ms MELDRUM, Maureen Health and Safety Executive Toxicology Unit Room 147 Magdalen House Stanley Precinct Bootle, Merseyside L20 3QZ	Tel: 44 151 951 3805 Fax: 44 151 951 3317 E-mail: maureen.meldrum@hse.gov.uk

SUISSE **SWITZERLAND**	
Mr SCHIESS, Martin Office fédéral de l'environnement, des forêts et du paysage Section sécurité des installations Hallwylstrasse 4 CH 3003 Berne	Tel: 41-31 322 54 34 Fax: 41-31 323 03 70 E-mail: Martin.Schiess@buwal.admin.ch
BIAC	
Mr de GERLACHE, Jacques Senior Toxicologist SG/Corporate Communications SOLVAY SA Rue du Prince Albert, 33 1050 Brussels, Belgium (also representing ECETOC)	Tel: 32 2 509 64 54 Fax: 32 2 509 72 40 Email: jacques.degerlache@solvay.com
Mr KELLY, David DuPont Haskell Lab Elkton Road PO Box 50 Newark DE 19714, USA	Tel: 1302 366 5330 Fax: 1 302 366 6420 E-mail: david.p.kelly@usa.dupont.com
Mr BERGE, W. Ten DSM P.O. Box 6500 6401 JH Heerlen, Netherlands	Tel: 31 455 787 128 Fax: 31 455 787 112 E-mail: wil.berge-ten@dsm-group.com
UNEP	
Dr GOLDSCHMITT, Ernst United Nations Environment Programme Industry and Environment Office Tour Mirabeau 39-43 Quai André-Citroën 75739 Paris Cedex 15, France	Tel: 33 1 44 37 30 07 Fax: 33 1 44 37 14 74 E-mail: ernst.goldschmitt@unep.fr

OCHA/UNEP

Mr SAKHAROV, Vladimir
Chief
Joint UNEP/DHA Environment Unit
UN Office for the Coordination of Humanitarian Affairs
Disaster Response Branch
Palais des Nations
8-14 Avenue de la Paix
CH Geneva 10, Switzerland
Tel: 41-22 917 11 42
Fax: 41-22 917 00 23

WHO/IPCS

Mr COLEMAN, Gary
Director
WHO Collaborating Centre,
University of Wales Institute
Western Avenue
Cardiff CF5 2YB, UK
Tel: 44 1222 506 851
Fax: 44 1222 506 803
gcoleman@uwic.ac.uk

Mr HAINES, John A.
IPCS / World Health Organisation
20, avenue Appia
CH-1211 Genève 27, Switzerland
Tel: 41-22 791 35 73
Fax: 41-22 791 48 48
E-mail: Hainesj@who.ch

SECRETARIAT DE L'OCDE — OECD SECRETARIAT

DIVISION ENVIRONNEMENT, SANTE ET SECURITE

ENVIRONMENT, HEALTH AND SAFETY DIVISION

2 rue André-Pascal
75775 Paris Cedex 16
France
Internet site: http://www.oecd.org/ehs/
Fax: 33 (0) 1 45 24 16 75

Mr Peter KEARNS - Principle Administrator
Tel: 33 (0) 1 45 24 16 77
Fax: 33 (0) 1 45 24 16 75
Peter.Kearns@OECD.ORG

Ms Francine SCHULBERG - Consultant
237 22nd Avenue
San Francisco CA 94121
United States
Tel: 1 415 668 22 39
Fax: 1 415 752 41 20
Fschulberg@aol.com

Ms Jenny GRIFFIN - Secretary
Tel: 33 (0) 1 45 24 98 43
Fax: 33 (0) 1 45 24 16 75
Jennifer.Griffin@OECD.ORG

ANNEX III

Categorisation of Comments (in CAPITAL LETTERS) and Comment Response on the Draft Standing Operating Procedures, for 7 - 8 June, 1999 OECD Meeting, Paris

AEGL ENDPOINTS

SHOULD AN AEGL-1 LEVEL BE SET BASED UPON A MINOR CHANGE IN PULMONARY FUNCTION? Comment from Ten Berge

The AEGL-1 is a detection level when people may begin to experience some slight discomfort It is a level at which the effects of the chemical are detectable.

WHEN DERIVING THE AEGL-1 LEVEL FOR "DETECTABILITY" IT WOULD BE USEFUL TO INCLUDE DIFFERENT CRITERIA FOR SUBSTANCES WITH HEDONIC ODOR PROPERTIES. SUBSTANCES WITH A BAD SMELL MAY INDUCE ANXIETY AT MUCH LOWER LEVELS. Comment by van Raaij

This is an interesting point and is certainly worth discussing further. Specific suggestion about how to incorporate this concept would be welcome.

THE RATIONALE FOR A METHEMOGLOBIN LEVEL OF 22% AND PULMONARY FUNCTION IS NOT CLEAR. Comment by van Raaij

The 22% level was seen at a specific exposure level in rats. Methemoglobin levels in humans of 15-20 % resulted in clinical cyanosis but no hypoxic symptoms. This was chosen as the AEGL-1 level. A more complete rationale is in Appendix E 1.17.

The pulmonary function changes are explained more fully in Appendix E 1.18.

IT IS NOT VALID TO SET THE AEGL-2 BASED ON THE HIGHEST LEVEL CAUSING REVERSIBLE EFFECTS WHEN THE LEVEL WHICH IS DISABLING CANNOT BE ESTABLISHED. Comment by van Raaij

While the true NOEL for disabling effects is not know in the above case, the current methodology is the best the Committee can do with limited data. The alternative is to derive no value. At the least the level developed would be protective of public health. It could later be raised if more definitive data are developed.

A NOEL FOR LETHALITY WOULD BE USED FOR THE AEGL ENDPOINT. THIS LEAVES NO ROOM FOR CONSIDERATION OF MODE OF ACTION OR STRUCTURE ACTIVITY RELATIONSHIPS.
Comment from Ten Berge

The AEGL endpoints are based upon a biological effect. A NOEL for death can be used to set an AEGL-3 endpoint in an experiment in which the next higher dose caused lethality. This would also require a reasonable spread in dose selection so the NOEL was not artificially too low because of widely spaced doses.

THE NAC/AEGL COMMITTEE USES 1/3 THE LC_{50} WHICH ISAPPROXIMATELY THE LC_{01}. THIS IS THE ASSUMED DISTRIBUTION FOR SENSITIVITY IN THE POPULATION. Comment from Ten Berge. THE RATIONALE FOR THIS DETERMINATION IS LACKING. Comment by van Raaij. WITHIN HEALTH AND SAFETY EXECUTIVE (GREAT BRITAIN) THE LC_{50} IS DIVIDED BY 4. THIS APPROACH IS SUPPORTED BY A NUMBER OF STUDIES. Comment from Meldrum

The NAC/AEGL Committee uses 1/3 of the LC_{50} only when the dose response curve is very steep and we have no more reliable means to set the approximate AEGL-3 NOEL.

The use of a factor of 4 is certainly appropriate. As noted above this approach is only taken when there is an indication of a steep dose response curve. As an aside, the value of 4 is more conservative than the approach taken by the NAC/AEGL Committee.

WHEN COMPUTING AN LC_{01} THE METHOD OF FINNEY SHOULD BE USED. RELIANCE SHOULD NOT BE PLACED ON THE LOWER CONFIDENCE LIMIT. Comment from ten Berge. ALTERNATIVE METHODS TO A NOEL SHOULD BE EXPLORED. Comment by van Raaij

When computing an LC_{01} a probit analysis is performed. The NAC/AEGL Committee uses the Maximum Likelihood Estimate (MLE), not a lower confidence limit when determining the LC_{01}. Any value generated is compared with supporting data and must pass a "reasonableness test" before it is accepted. If a computed LC_{01} seems artificially low, other methods to determine an AEGL-3 NOEL are used.

Reference is made to an RIVM methodology by Slob and Pieters, 1997. What is the reference.

The U.S. Environmental Protection Agency has developed a public domain software program for Benchmark Dose determination which uses a number of different models.

THE SECTION FOR THE AEGL-3 SHOULD PRESENT A STATISTICAL EVALUATION OF THE RAW DATA USING THE PROBIT ANALYSIS ACCORDING TO FINNEY (1977). Comment from Ten Berge

Key studies are sometimes evaluated using probit analysis. There is a balance between the benefit gained by performing statistical analyses on raw data and the monetary cost of doing so. This is usually only done on data which is used for critical conclusions.

THERE IS NO DISCUSSION FOR HANDLING THE REPRODUCTIVE EFFECTS TOXICITY ENDPOINT. comment from Ruijten

The SOP is a statement of the history of the methodologies used by the NAC/AEGL Committee to the present. We have not used reproductive effects to set an AEGL level. However, it is likely that effects on the reproductive system would be treated as reversible or irreversible like any other effect and assigned to the appropriate AEGL level.

Another issue is the question of how to assess developmental toxicity (frank teratogenic effects, fetal mortality, functional deficits, lower weight). This issue will probably be addressed for two chemicals in the NAC/AEGL Committee meeting in September 1999.

THERE SHOULD BE SOME AGREEMENT ABOUT THE WHICH LEVEL OF CHANGE (PULMONARY FUNCTION CHANGES, % INHIBITION, ETC.) IS ASSOCIATED WITH AN AEGL LEVEL. Comment by van Raaij

The NAC/AEGL Committee is captive to the spectrum of data which is available. As a result determinations of effects associated with the different AEGL levels are made on a case by case basis. If we have data which is useful for a specific endpoint, for example methemoglobin formation, on one chemical (e.g. aniline), and another chemical acts through the same mechanism, we would use the same methodology.

THE AEGL-2 FOR METHYL HYDRAZINE IS 1/3 THE AEGL-3 & THE AEGL-3 IS 1/3 THE LC_{50}. THIS ASSUMES THE AEGL-2 IS 10 FOLD LOWER THAN THE LC5O. Comment from Ten Berge. A STANDARD FACTOR OF 3 IS NOT APPROPRIATE IN THE ABSENCE OF DATA. Comment by van Raaij

The dose response curve for methyl hydrazine is very steep. There were no data available from which to derive an AEGL-2 level yet it was felt important to provide one for planning purposes. Dividing the AEGL-3 by 3 seemed reasonable given the steepness of the dose-response curve. In fact, with the inclusion of Uncertainty Factors, the AEGL-2 is 273 fold lower than the LC_{50}. This has been done only once. If it were done again the determination of the divisor would be made based upon the available data on the specific chemical.

KEY DATA SELECTION

RAW EXPERIMENTAL DATA SHOULD BE ANALYZED USING FINNEY'S PROBIT ANALYSIS. STUDIES SHOULD BE PREFERRED WHICH INCLUDE VARIATION IN CONCENTRATION AND TIME PERIOD OF EXPOSURE. THERE SHOULD BE AN OPPORTUNITY FOR INDUSTRY TO PROVIDE BETTER DATA. Comment from Ten Berge

Key studies are sometimes evaluated using probit analysis. There is a balance between the benefit gained by performing statistical analyses on raw data and the monetary cost of doing so. This is usually only done in on data which is used for critical conclusions.

We prefer studies with variation in concentration and time.

In fact industry has provided valuable data to the NAC/AEGL Committee which has been used to adjust AEGL values. For example, the 10 minute HF numbers are based upon industry data submitted at an NAC/AEGL Committee meeting. The silane industry repeated an old study. The new study was reviewed and the AEGL values adjusted according to the new data. The propylene oxide industry submitted information on human exposures which resulted in the NAC/AEGL Committee raising the AEGL-1 values. All well run studies which are relevant will be considered.

THE KEY STUDY SHOULD INVOLVE THE MOST SENSITIVE SPECIES UNLESS THERE ARE GROUNDS TO INDICATE THAT THE RESPONSES SEEN IN THIS SPECIES ARE NOT RELEVANT FOR HEALTH. Comment from Meldrum

The most sensitive species is often used to develop AEGL values. Other factors such as the conduct of the study, number of animals used, analytical chemistry determinations of exposure, relatedness to humans, reporting of effects relevant to the AEGL level under consideration, agreement with other data, etc. are also considered when selecting the key study.

THE USE OF ONLY 3 ANIMALS PER EXPOSURE GROUP IS NOT A RELIABLE BASIS FOR DETERMINATION OF AN LC_{50} OR ANY SPECIFIED POINT ON THE EXPOSURE RESPONSE CURVE. Comment from Meldrum

Agreed. However, primate data which is the most relevant to humans, often have few data points. This is on the order of 2-4 animals per dose group. This information may be used as supporting data. If it is used as a key study, the data are compared with other information on the chemical to make sure that the conclusions are consistent with the spectrum of data on the compound.

UNCERTAINTY FACTORS - GENERAL

TOO CONSERVATIVE AEGL VALUES MAY KILL NEW INDUSTRIAL ACTIVITIES AND CAUSE UNNECESSARY EVACUATIONS WHICH WOULD INCUR A RISK OF THEIR OWN. Comment from Ten Berge. Comment from Ruijten. THE BUILT IN CONSERVATISM INCORPORATING THE USE OF UNCERTAINTY FACTORS MAY UNDERMINE THE VALUE OF THE AEGL VALUES TO EMERGENCY PLANNERS. USE OF UNCERTAINTY FACTORS CAN LEAD TO LESS ACCURATE PREDICTION IN HUMANS. Comment from Meldrum

Generally the AEGL-2 is considered a planning and action level although that is a policy issue which is determined by the user. The NAC/AEGL Committee recognizes the need to develop realistic biological reference values, yet still be protective of public health. The NAC/AEGL Committee walks a very difficult balancing act between two extremes. One the one hand the goal is to derive values which are biologically meaningful and close to a level at which a sensitive individual will respond yet not be to high to prevent action in a dangerous situation. On the other hand the values should be such that, while protective of human health, they are not too low to have any meaningful biological relevance to serve as the basis for action. At one extreme action would not be taken at the appropriate time. At the other extreme, unnecessary actions and evacuations, which incur a risk of their own, might be taken.

THE UNCERTAINTY FACTORS ARE ARBITRARY WITH NO CLEAR JUSTIFICATION FOR THE DEFAULT FACTOR OF 10. REDUCING THE UNCERTAINTY FACTOR FROM 10 TO 3 TO REFLECT CONFIDENCE IN THE DATA MAY LEAD TO DECISIONS BASED UPON SUBJECTIVE JUDGEMENTS AND A LACK OF TRANSPARENCY. Comment from Meldrum

Historically the default uncertainty factor of 10 has been used and is supported by a number of reviews. Although appropriate for setting “safe” levels for chronic exposure it may be overly conservative when trying to set biologically relevant levels for emergency response. See comments above. The rationale for using lower uncertainty factors is always included in the Technical Support Documents so there should be no loss of transparency. As noted elsewhere, default factors of 10 are usually not used.

Subjective, or professional, judgements, supported by a scientific rationale, are used because there is rarely a spectrum of data available with which to make highly accurate predictions of inter- and intraspecies variability.

INTERSPECIES UNCERTAINTY FACTORS

AN INTERSPECIES UNCERTAINTY FACTOR OF 10 SHOULD NOT BE USED FOR ETHYLENE OXIDE BECAUSE THE MOST SENSITIVE SPECIES WAS NOT USED. HUMANS ARE RELATIVELY INSENSITIVE TO ETHYLENE OXIDE. Comment from Ten Berge

The only species with data appropriate to setting the AEGL-2 level was the rat. The rat LC_{50} is about 3 fold higher than the mouse. Since the most sensitive species was not used the uncertainty factor was kept at 10.

THE MECHANISM OF ACTION IS UNLIKELY TO DIFFER BETWEEN SPECIES AND MUCH OF THE DIFFERENCE CAN BE ADDRESSED BY ALLOMETRIC SCALING. Comment from Ten Berge

See comments in dosimetry section on allometric scaling. Currently there are no models for scaling doses between species for single inhalation exposures to gases which have been validated with experimental data.

MECHANISM OF ACTION IS USUALLY KNOWN. Comment from Ten Berge

Although the mechanism of action is usually known there are cases in which we will be uncertain about the mechanism of action or in the ability of the organism to detoxify the chemical. In this case we may use a higher uncertainty factor.

HIGH VARIABILITY DOES NOT JUSTIFY THE USE OF A HIGH UNCERTAINTY FACTOR. USE THE MOST RELIABLE STUDY. Comment from Ten Berge

Where the data indicate a high degree of variability which cannot be explained, a larger uncertainty factor may be used.

HUMANS LESS SENSITIVE THAN ANIMALS. COMMENT IS THAT IT IS IMPROBABLE THAT HUMANS ARE MORE SENSITIVE THAN ANIMALS WITH A FEW EXCEPTIONS. Comment from Ten Berge

This section title should read “Humans More Sensitive than Animals” and will be corrected.

When the NAC/AEGL Committee has information which indicates that humans are more sensitive than animals they will generally use a higher uncertainty factor. A case in point is aniline.

INTERSPECIES UNCERTAINTY FACTORS ARE OFTEN TOO CONSERVATIVE BECAUSE:

- THE STARTING POINT FOR CALCULATIONS IS THE MOST SENSITIVE SPECIES. Comment from Ruijten

  When the most sensitive species is used the UF is usually reduced to 3.

- OFTEN A NOEL IS USED. Comment from Ruijten

- The NOEL used is an AEGL-NOEL. So the AEGL-3 NOEL might be the highest dose which did not cause lethality. However, this is usually a significant and highly adverse effect level. For example, the AEGL-3 NOEL for fluorine is % of the LC_{50} with severe lung effects.

- THERE IS INSUFFICIENT JUSTIFICATION FOR THE APPLICATION OF UNCERTAINTY FACTORS. SUCH JUSTIFICATION WOULD BE TO FIGURE WHO IS MOST SUSCEPTIBLE AND BY HOW MUCH. Comment from Ruijten

  Agreed. Professional judgement of Committee members is used when considering all of the data on a chemical. Any help in this area would be most appreciated.

- UNCERTAINTY FACTORS ARE USED MULTIPLICATIVELY. WHY NOT USE THE RMS? Comment from Ruijten

  Multiplying uncertainty factors by each other assumes the worst case in each case. This is certainly a problem which should be addressed. Some workshops have been held on this issue in the United States. Any proposal, which is backed by experimental data is most welcome and would receive serious consideration.

- CONSERVATIVE USE OF TIME SCALING FACTORS. Comment from Ruijten

  This is only done when the NAC AEGL Committee has insufficient data to derive a time-concentration relationship. What alternative would you suggest?

IN MOST CASES ONE DOES NOT KNOW IF THE MOST SENSITIVE SPECIES HAS OR HAS NOT BEEN USED. IT IS NOT VALID TO MAKE THIS ASSUMPTION. Comment by van Raaij

This rationale is rarely used. When it is used there is a clear rationale justifying its use. For this rationale to be used there would have to be data available on different species which demonstrated that the species used was not the most sensitive.

IF THE DETERMINATION IS MADE THAT HUMANS ARE MORE SENSITIVE, THEN THERE MUST BE DATA AVAILABLE ON HUMANS. IN THIS CASE ONE SHOULD USE THE HUMAN DATA. Comment by van Raaij

When human data are available and relevant to the specific AEGL endpoint they are used. This determination was made for aniline based upon limited studies and case reports (see section 4.4.2 of the aniline document) which were inadequate to derive AEGL levels.

INTRASPECIES UNCERTAINTY FACTORS.

THIS IS NOT NEEDED. HIGHER VARIABILITY CAN BE REPRESENTED IN A FLAT DOSE-RESPONSE RELATIONSHIP. Comment from Ten Berge. SUSCEPTIBLE BUT NOT NECESSARILY HYPERSUSCEPTIBLE INDIVIDUALS WILL BE PROTECTED BY THE AEGL VALUES. HOW CAN THE COMMITTEE SET NUMBERS WITHOUT DETERMINING WHICH EFFECTS SHOULD BE PREVENTED IN WHICH PEOPLE AND HOW WILL IT GENERATE OR USE DATA TO SUPPORT DECISION MAKING ON THIS ISSUE? Comment from Ruijten

When the data present a flattened dose-response curve a higher uncertainty factor would be considered - not to exceed 10. Most intraspecies uncertainty factors used by the NAC/AEGL Committee are between I and 3.

This is one of the most difficult areas for the Committee to address. When considering intraspecies uncertainty factors one must consider both within group variability and between group variability.

Within group variability. Animal studies are typically performed on inbreed strains for the express reason to reduce variability. The fact that a well fed, generally not pregnant, adult, healthy, non-asthmatic, nonalcoholic or otherwise compromised inbred strain exhibits little variability does not mean that the variation in humans would be as little. Occasionally data exist on normal and asthmatic individuals. In this case the NAC/AEGL Committee may use an intraspecies uncertainty factor of I because a sensitive

individual has been tested. For irritants and data on healthy individuals the intraspecies uncertainty factor is typically 3.

Between group variability. Typically studies are performed on adult animals or adult humans in reasonably good health. They do not consider separate groups such as children, infants, pregnant females, elderly, asthmatic, alcoholic, smokers, etc. It is rare to have data within a single species which provides a means of comparing different potentially sensitive groups, much less identifying which may be the most sensitive group.

For the above reasons, and the lack of data to provide a reliable guide to sensitivities within the human population, Intraspecies Uncertainty Factors are typically used when setting AEGL-values. These are either 1, 3, or 10 (in the case of aniline infants are clearly much more sensitive than adults). The effect is presumed to be the same between all groups but it is rarely possible to identify the most sensitive group from the limited data usually available on a chemical.

Data from which to make reliable estimates of within and between group variability from acute inhalation exposures are extremely limited. We continue to review the literature and drug studies on humans to help refine the information used to make intraspecies uncertainty factor determinations. The NAC/AEGL Committee would be very interested in any information, reviews, or evaluations on this subject.

A DEFAULT FACTOR OF 10 SHOULD NOT BE USED TO ACCOUNT FOR THE SENSITIVITY OF YOUNG. Comment from Ten Berge

The NAC/AEGL Committee usually does not use an Intraspecies Uncertainty Factor of 10 to account for the sensitivity of young. See above.

RESPONSE BY NORMAL AND SENSITIVE INDIVIDUALS IS UNLIKELY TO DIFFER. THE DEFAULT FACTOR OF 3 IN THIS CASE IS NOT NEEDED BECAUSE IT IS CONSIDERED IN THE DOSE RESPONSE RELATIONSHIP. Comment from Ten Berge

This rationale is used to reduce the default factor of 10 to a 3. See also discussion above about variability.

MECHANISM OF ACTION IS UNKNOWN. Comment from Ten Berge

See discussion above in MECHANISM OF ACTION IS USUALLY KNOWN.

THE DEFAULT FACTOR OF 10 IS NOT VALID FOR AEGL DETERMINATIONS. THE WORK OF THE RIVM INDICATES THAT THE VARIABILITY IN KINETIC RESPONSES BETWEEN “MEAN” AND “SUSCEPTIBLE” HUMANS ARE DISTRIBUTED WITH A MEAN FACTOR OF 2-3. THE P99 IS ABOUT 10. A PART OF THE INTRASPECIES VARIABILITY IS INCLUDED IN THE DOSE RESPONSE RELATIONSHIPS. A DEFAULT FACTOR OF 10 IS OVERLY CONSERVATIVE. IN CASES WHERE INTERINDIVIDUAL VARIABILITY IS UNLIKELY WHY USE A FACTOR OF 3? Comment by van Raaij

The default factor of 10 is commonly accepted practice in the United States. In fact, most intraspecies uncertainty factors used to date fall in the range of I and 3. In special cases, such as aniline where a sensitive population has been clearly identified, an uncertainty factor of 10 may be used.

Please provide the RIVM reference. The Committee is always looking for ways to improve its methodologies.

See discussion above about within group variability in response the comment about the dose response relationships.

When intraspecies variability is considered unlikely a standard uncertainty factor of 3 is used because the time/concentration level used to derive an AEGL value is usually based upon data from a healthy animal or human. It is assumed that more sensitive individuals exist. If the data is from a sensitive human the intraspecies uncertainty factor is often reduced to 1.

HUMAN DATA SHOULD BE CONSIDERED FROM THE BEGINNING WHEN ESTABLISHING A POSSIBLE INTRASPECIES FACTOR. Comment by van Raaij

In fact human data is always considered first. However, it is rare that human data are sufficient to establish the sensitive population and the difference in response threshold between that population and the "normal" population. As mentioned above, if data from testing in sensitive humans is used to set an AEGL level the intraspecies uncertainty factor is usually reduced to 1.

MODIFYING FACTORS

THIS CHAPTER IS SUPERFLUOUS ALTHOUGH IT HAS THE ADVANTAGE OF ENCOURAGING DEVELOPMENT OF DATA. Comment from Ten Berge. Comment from Ruijten

If not considered as a Modifying Factor, the topic would be considered in one of the uncertainty factors. For example, the existence of only one study in one laboratory with no repeated study information may raise uncertainty. Also known differences in isomer toxicity have to be accounted for at some point in the development of AEGL values. Modifying factors are rarely used, about 3-4 times in 55 chemicals assessed.

TIME SCALING

PAGE 35 IN THE SOP IS NOT A GOOD PRESENTATION OF THE WORK OF TEN BERGE (1986). Comment from Ten Berge

Agreed. The SOP will be changed to reflect the concept that the entire data set was analyzed in the Ten Berge reference and that 95% confidence limits were established.

SECTION 2.7.3. IT IS POSSIBLE TO EXTRAPOLATE OUTSIDE THE EXPERIMENTAL PERIOD OF EXPOSURE AND ESTIMATE CONFIDENCE LIMITS. THE BASIS FOR THIS IS PROBIT ANALYSIS WITH TIME AND CONCENTRATION AS INDEPENDENT VARIABLES. Comment from Ten Berge

Agreed. The probit analysis is performed on the computed LC_{50} values. It would be useful for the NAC/AEGL Committee to explore the Finney methodology if the software can be made available to us.

SECTION 2.7.4. EVEN IF EMPIRICAL DATA ARE AVAILABLE FOR THE AEGL TIME POINTS THEY SHOULD BE SUBJECTED TO PROBIT ANALYSIS TO CHECK ON THE CONSISTENCY OF THE DATA WHICH MAY HAVE SOME ERRORS. Comment from Ten Berge

Actually, we have not had data sufficient to establish all time periods and have had to make extrapolations. However, the point is well taken and should be considered in the future. In all cases a reasonableness test will be applied to the derived values to determine how well they fit the empirical, supporting, and modeled data.

SECTION 2.7.5. IF TOXICITY DATA DO NOT FALL WITHIN THE RANGE OF 30 MINUTES TO 8 HOURS THEY SHOULD NOT BE USED TO DERIVE AN AEGL VALUE. Comment from Ten Berge

Almost all of the data used in time extrapolation have fallen within the 30 minute to 8 hour time period and is the preferred time period to be used. However, when time data occasionally fall outside this time interval the NAC/AEGL Committee must weigh the uncertainties involved in making an extrapolation from the data at hand and the need for the development of the AEGL value.

GENERATE AEGL VALUE FOR TIME(S) <30 MINUTES. comment from Ten Berge. Comment from Ruijten

Generate a 10-15 minute number. This is a topic which the NAC/AEGL Committee should consider. Which value is most useful to users of these numbers and what scientific issues are involved in the choice of a 10 or 15 minute number?

USE THE FINNEY 1977 (IS THIS 1977 OR 1971?) MAXIMUM LIKELIHOOD ESTIMATION TO GENERATE THE MLE AND CONFIDENCE LIMITS. Comment from Ten Berge. THE CURRENT METHODOLOGY IS STATISTICALLY INVALID SINCE AN LC_{50} IS NOT AN OBSERVATION BUT A STATISTICAL ESTIMATOR. Comment from Ruijten. USE PROBIT ANALYSIS ON CONCENTRATION AND TIME AS VARIABLES. Comment by van Raaij. THE VALUE OF n SHOULD BE DERIVED FROM DATA IN THE SAME SPECIES, STRAIN, AGE OF ANIMALS, UNDER FIXED CONDITIONS. Comment from Meldrum

Where data are sufficient the NAC/AEGL Committee will explore the use of this methodology (Finney). It would be helpful if the program developed by Ten Berge were made available to the Committee.

Often LC_{50} values are expressed in publications without the accompanying data needed to perform a detailed statistical analysis. In this case the methodology presented in the SOP will be used. Although not as elegant as the Finney methodology, without the requisite individual data points it is the best we can do at this time. Although it is not possible to estimate the variance around the projected line, the use of a regression analysis on derived data has the advantage of using a consistent methodology which can be repeated for different experiments and for different evaluators. This use of this approach is strengthened by the fact that the data used are usually from the same experiment in the same laboratory. The bottom line is that extrapolation to time points outside the data region is usually necessary and this extrapolation must be made to develop the AEGL values. Using the current approach when all we have are LC_{50} values seems the best utilization of available data. The alternative is to make conservative assumptions when performing the time extrapolation. As always, the NAC/AEGL Committee will evaluate any methodology which will enable it to improve the scientific derivation of AEGL values.

THERE IS NO DISCUSSION ABOUT APPLYING THE VALUE OF n DERIVED FROM LETHALITY DATA TO OTHER, NON-LETHAL, ENDPOINTS. Comment from Ruijten. WHEN LETHALITY IS THE ENDPOINT OF INTEREST THE USE OF LC_{50} VALUES FOR DIFFERENT EXPOSURE TIMES PERMITS THE MOST RELIABLE DETERMINATION OF n. Comment from Meldrum

Currently the only means we have of determining the value of n is from lethality data because this is the only data we typically have from which one can derive a concentration of equal effect at different times (LC_{50}), and for which the qualitative effect and degree of effect is identical (death). Although the AEGL-2 endpoint for irreversible damage could follow a different time-concentration relationship it is the best the NAC/AEGL Committee can do at this time to estimate the value of n for non-lethal effects. The AEGL-2 value is often close to the AEGL-3 value (about 3 fold) so in these cases the value of n probably does not

differ too much from the n determined from lethality data. The NAC/AEGL Committee is always interested in better ways to estimate the AEGL values. The discussion in the SOP will be changed to explicitly address this issue.

SECTION 2.7.5.1 LAST PARAGRAPH. THE ONLY GAS FROM WHICH N COULD BE DERIVED FOR AN AEGLI VALUE IS CHLORINE. Comment from Ten Berge

Please provide the references to Anglen 1982, and Verberk 1976 so we can look at them.

SECTION 2.7.5.2. IF THERE ARE THREE DATA POINTS WITHIN THE TIMEFRAME 30 MINUTES TO 8 HOURS, PROBIT ANALYSIS CAN BE USED TO GENERATE A REGRESSION EQUATION FROM WHICH THE CONCENTRATION FOR ANY RESPONSE AND EXPOSURE DURATION CAN BE DERIVED. Comment from Ten Berge

Agreed.

SECTION 2.7.5.3. THE CHAPTER SHOULD BE REWRITTEN WITH THE PREFERRED METHOD BEING THE PROBIT ANALYSIS ACCORDING TO FINNEY (1977). Comment from Ten Berge

The NAC AEGL Committee would be willing to explore the use of the Finney (1977) methodology when the data are sufficiently robust if the software is made available.

THE SUMMARY TABLES SHOULD PRESENT THE REGRESSION EQUATION ORIGINATING FROM THE PROBIT ANALYSIS ACCORDING TO FINNEY (1977). Comment from ten Berge

This should be done with our current methodology. If the NAC AEGL Committee adopts the method of Finney, or some other form of statistical analysis, the regression equation should be presented.

SOME ANALYSES HAVE COMBINED DATA FROM DIFFERENT STUDIES AND NOT TAKEN THE QUALITY OF THE STUDIES INTO ACCOUNT. Comment from Meldrum

Usually data from a single study are analyzed to determine a value for n. This is often the best quality study. When robust data are not available, the Committee must choose between using the available data to derive the most reasonable estimate or use general assumptions and a conservative methodology. It is often a matter of choosing the lesser of a number of evils.

SOME ENDPOINTS, SUCH AS EYE IRRITATION, ARE DEPENDENT ON THE CONCENTRATION AND NOT TIME. THE “FLAT-LINED” AEGL-1 VALUES ARE APPROPRIATE IN THIS CASE. Comment from Meldrum

Agreed.

CARBON MONOXIDE BINDING TO HEMOGLOBIN IS A SATURABLE PROCESS WHICH REACHES A STATE OF EQUILIBRIUM DEPENDENT ON EXPOSURE CONCENTRATION. A Cnt RELATIONSHIP DOES NOT HOLD FOR CARBON MONOXIDE AND CANNOT BE USED TO EXTRAPOLATE TO LONG EXPOSURE PERIODS. Comment from Meldrum

This is an interesting point and should be investigated further to determine the impact on the AEGL methodology of time scaling. Please provide references.

IRRITANT GASES DO NOT ALWAYS HAVE AN n OF 2. IN THE ABSENCE OF DATA A DEFAULT APPROACH IS NEEDED. IT MUST BE STATED AND CONSISTENTLY FOLLOWED TO ALLOW FOR TRANSPARENCY. Comment from Meldrum

Agreed.

CARCINOGENICITY

HUMAN DATA

DOSIMETRY CORRECTIONS

SOME USE SHOULD BE MADE OF KNOWN DIFFERENCES IN METABOLISM, OXYGEN CONSUMPTION, BREATHING RATES, RESPIRATORY TRACT SURFACE AREA AND GEOMETRY WHEN EXTRAPOLATING BETWEEN SPECIES - ALLOMETRIC SCALING AND MODE OF ACTION SHOULD BE TAKEN INTO ACCOUNT. Comment from Ten Berge. Comment by van Raaij

Where methodologies exist which have been validated by experimental data for the type of chemical under consideration, they will be considered to help refine extrapolation between species. This is a difficult area in which one must distinguish between systemic and respiratory toxic chemicals.

Other compounding factors include dose-dependant differences in the pattern of deposition in the respiratory tract which differ both within and between species. There are no models for gases which have been validated with empirical data.

For the oral route of exposure, systemic toxicity seems to scale between species according to the body weight to the 2/3 to 3/4 power for multiple exposures. Since minute volumes scale according to the same relationship this would argue for no dosimetry correction because the two relationships would cancel each other out. However, recent work seems to indicate that for single oral exposures, toxicity scales according to the body weight. This would argue for a minute volume correction between species. However, it is unknown whether this relationship would hold true for inhalation exposure.

Therefore, without clear data on interspecies dosimetry corrections the ambient exposure for gases is not corrected when extrapolating between species.

DO NOT DISCARD OUT OF HAND BECAUSE SOME EXAMPLES DO NOT FIT A MODEL. USE A REASONABLENESS TEST WHICH IN FACT THE COMMITTEE DOES. Comment from Ruijten

Agreed.

EXTRAPOLATION FROM ANIMALS TO HUMANS IS DIFFICULT. HOWEVER, ASSUMING EQUAL SENSITIVITY BETWEEN ANIMALS AND HUMANS SEEMS TO OFFER THE HIGHEST PROBABILITY OF AN ACCURATE PREDICTION. Comment from Meldrum

Agreed. In the absence of validated dosimetry correction methodologies for gases this is the approach taken by the Committee.

MISCELLANEOUS PROCEDURES AND COMMENTS

THERE IS NO SECTION IN THE SOP ABOUT USING ROUTE TO ROUTE EXTRAPOLATION. Comment from Ruijten. Comment by van Raaij

Correct. The NAC/AEGL Committee has not used route to route extrapolation to date. Inhalation data is much preferred because of the uncertainties associated with portal of entry, local effects, the impact of a bolus dose from oral exposure in comparison to exposure over time from inhalation, the effects of peak levels vs area under the curve, and the uncertainty of how to scale over time.

ROUNDING. IT DOES NOT MAKE SENSE TO USE 2 SIGNIFICANT FIGURES WHEN LARGE UNCERTAINTY FACTORS ARE USED. Comment from Ruijten

Trivial differences in numbers can give large differences if only one significant figure is used. For example, values of 14.9 and 15.1 would yield AEGL values of 10 and 20 respectively. This is a two fold difference for a very small difference in computed AEGL values. Values of 18, 14, 11, and 6 ppm for 30 minute, 1, 4, and 8 hours would give values of 10, 10, 10, and 20 ppm for the time points. It would not give the appearance of a logical progression. These numbers will be used in exposure models to make decisions. The use of 2 significant figures will allow for a more reasonable progression when different exposure scenarios are considered.

HOW WILL COMMITTEE MEMBERSHIP AND VOTING RIGHTS BE EFFECTED BY THE INFLUX OF SCIENTISTS FROM OTHER OECD COUNTRIES? Comment from Ruijten

We currently envision that each OECD member would have one vote at the table. This is the same as any current member. The number of OECD participants is negotiable.

IN THE ABSENCE OF ADEQUATE DATA NO AEGL VALUE IS DETERMINED. IN THIS CASE THE COMMITTEE SHOULD COME UP WITH THE BEST GUESS OF AN AEGL VALUE AND CLEARLY IDENTIFY IT AS PROVISIONAL. Comment by van Raaij

This situation occurs in about 10-15% of the cases considered. The NAC/AEGL Committee does not feel confident with generating values from inadequate data. When this occurs, every effort is made to contact industry and search further for adequate data. The Committee does its best to use available data to come up with reasonable numbers. This often involves professional judgement applied to very limited data sets. We provide the rationale used to generate the values. In some cases this has resulted in industry performing testing or providing information in their files to provide data which will enable us to generate a more refined AEGL value estimate. This has been especially helpful for silanes, propylene oxide, hydrogen fluoride, and currently I ,2-dichloroethane.

SPECIFIC CHEMICALS

ARSINE

SECONDARY LITERATURE IS CITED WHICH IS INCONSISTENT WITH THE SOP CHARGE TO USE PRIMARY SOURCES. THIS IS IMPORTANT FOR THE MONKEY STUDY SINCE IT IS USED TO SUPPORT AN UNCERTAINTY FACTOR. Comment from Ruijten

The secondary sources are used as background information. Only primary sources are used to set AEGL values. This should be clarified in the SOP.

The monkey study was from a secondary source. It is a valid comment and the author of the document is tracking the original study to ensure that the conclusions are valid.

THE KEY STUDY IS CUT IN TWO AND DISCUSSED IN TWO SECTIONS. THIS IS CONFUSING. ALSO FIGURES FROM STUDIES SHOULD BE INCLUDED FOR CLARITY. Comment from Ruijten. The Technical Support Document is organized into a standardized format organized around effect (which is directly related to AEGL endpoint), and species. It represents the best of many format evils in structuring such a document.

Where possible figures which clarify the material should be included. As always, every enhancement represents an increase in monetary resources. We continually try to balance budget against clarity.

THE OVERSIGHT TABLES PRESENT A COLUMN WITH THE CT PRODUCT WHICH IMPLIES AN n OF 1 WHEN THE DOCUMENT USES AN n OF 2. Comment from Ruijten

Agreed. This is confusing. The column should be deleted.

WHY IS THE FACT THAT AN EFFECT IS DELAYED A MATTER OF ADDITIONAL CONCERN IN THE DEVELOPMENT OF AEGL VALUES? Comment from Ruijten

The delayed effect is noted. It is not used to derive an AEGL value.

THERE IS NO RATIONALE FOR USING THE FLURY AND ZERNIK DATA IN THE AEGL RATIONALE. Comment from Ruijten

The Flury and Zernik data were not used in the development of an AEGL value. In fact, their data were rejected for use. It is included as background material.

IT DOES NOT MAKE SENSE TO USE A LARGE COMPOSITE UNCERTAINTY FACTOR OF 30 FOR THE AEGL-2 ENDPOINT (NO HEMOLYSIS) AND AEGL-3 ENDPOINT (40% HEMOLYSIS). HUMAN EXPERIENCE WITH MALARIA AND MEDICATION SHOULD BE USED. Comment from Ruijten

Given the data sets available, the variability in response among species and the fact that a less sensitive species was used, a total uncertainty factor of 30 was deemed prudent by the NAC/AEGL Committee. Another reason for the uncertainty factor of 30 was the steepness of the dose response curve. The 1 hour exposure of 15 ppm which cause 40% hemolysis but no deaths was used as the AEGL-3 NOEL. At 26 ppm, 100% of the animals died. The difference between the AEGL-3 NOEL and 100% mortality is less than a factor of 2 so there is little margin for error.

The use of human experience data on hemolysis would be useful to consider if a rationale for it's use is presented.

THE AEGL-1 SHOULD BE NA SINCE THE ODOR THRESHOLD IS ABOVE THE AEGL-2 LEVEL. THIS IS IMPORTANT INFORMATION FOR A RESPONDER SINCE IF EXPOSED PEOPLE REPORT SMELLING THE CHEMICAL THE RESPONDER KNOWS THE AEGL-2 LEVEL HAS BEEN EXCEEDED. Comment from Ruijten

The AEGL-1 level is NA.

This is an important issue which probably bears further discussion. The definition of the AEGL-1 only deals with sensory perception and ignores the possibility of a severe toxic effect. The implication is that the AEGL-1 level is "safe" whereas in the case of arsine, an AEGL-1 value which is based upon the verbal definition of the AEGL-1 level is above the AEGL-2 value and is indeed dangerous. The public perception will always be that an AEGL-1 level is "safer" than an AEGL-2 level regardless of the definition. To use a sophisticated rationale for the development of an AEGL-1 level for an emergency responder to use in an expert manner requires a high level of sophistication on the part of the user of the information. How might we express "Dangerous AEGL-1" levels so they would be of use to sophisticated users of the AEGL values but not misleading to naive users?

CHLORINE

THE SCALING FOR THE AEGL-1 ENDPOINT ASSUMES THE SAME TIME DEPENDENCY AS OBSERVED FOR LETHALITY HOWEVER, DIFFERENT BIOLOGICAL PROCESSES UNDERLIE THESE EVENTS. Comment from Meldrum

There is some evidence for time dependency for the AEGL-1 endpoint. However, the point is well taken - see comments under time scaling. The endpoint of irritation is similar but to a different in degree for the two AEGL levels. The same comment applies to the AEGL-2.

THE MONKEY STUDY SUPPORTS THE SAFETY OF THE AEGL-2 VALUE. HOWEVER, THE AEGL-2 IS NOT MEANT TO INDICATE "SAFETY". A 2 HOUR EXPOSURE TO 2 PPM (ANGLEN) DID NOT CAUSE ANY EFFECT. IT IS UNCLEAR THAT EXPOSURE TO 2 PPM FOR 1 HOUR WOULD CAUSE ANY HARM IN A HUMAN POPULATION. Comment from Meldrum

The monkey study and the Anglen study were performed on healthy subjects. The Rotman study showed effects at I ppm exposure for 4 hours in a sensitive individual. This was used as the basis for the AEGL-2 determination. Since a sensitive individual was used the intraspecies uncertainty factor was reduced to 1.

THE MOUSE APPEARS TO BE THE MOST SENSITIVE SPECIES AND IF THE MOUSE WERE USED THERE WOULD BE NO NEED TO USE AN INTRASPECIES UNCERTAINTY FACTOR. Comment from Meldrum

The mouse was considered to be overly sensitive so a value between a non-lethal concentration in the mouse and rat was chosen as the AEGL-3 NOEL. The fact that the LC_{50} values differ by a factor of about 2 was used as a rationale for reducing the interspecies uncertainty factor to 3. The NAC/AEGL Committee rarely uses an interspecies uncertainty factor of 1. Since a normal, adult, healthy population of animals was tested there is no justification for reducing the intraspecies uncertainty factor to 1. The fact that chlorine is highly reactive to biological tissue and therefore individual response would not be expected to vary greatly was used as a rationale to reduce the intraspecies uncertainty factor from 10 to 3.

THE TECHNICAL SUPPORT DOCUMENT SUGGESTS THERE IS LITTLE LIKELIHOOD THAT THERE WOULD BE DIFFERENCES IN RESPONSE TO CHLORINE YET THERE ARE DIFFERENCES IN SITES OF TOXICITY BETWEEN SPECIES. Comment from Meldrum

See comments in Dosimetry section. It is difficult to use this type of information in a meaningful way to adjust for dose and effect between species. At the higher doses one would see a different spectrum of deposition than at lower doses. Often at high doses the toxic irritant penetrates to the lung. How would one use this information for chlorine and other irritant gases?

THERE IS SOME LACK OF CONSISTENCY ACROSS STUDIES. SINCE THE DATA POINT TO THE MOUSE AS THE MOST SENSITIVE SPECIES IT MIGHT BE PRUDENT TO USE THE MOUSE TO SET THE AEGL-3 VALUES. Comment from Meldrum

There was a great deal of discussion on this matter. The consensus of the NAC/AEGL Committee was to use a value between the mouse and rat AEGL-3 NOELs and to use an interspecies uncertainty factor of 3. LC_{50} values did not differ between species by a large factor.

THE REASON FOR VARIATION BETWEEN STUDIES IN RELATION TO THE TIMING OF DEATHS IS UNCLEAR. Comment from Meldrum

Agreed.

THE O'NEILL STUDY, BEING RECENT, MAY OFFER THE MOST RELIABLE BASIS FOR DETERMINATION OF LETHALITY RESPONSES IN MICE. Comment from Meldrum

The O'Neill study was considered in setting the AEGL-3 values along with the rat data. There was a great deal of discussion around this issue.

ALTHOUGH CONTACT IRRITATION IS NOT LIKELY TO VARY BETWEEN INDIVIDUALS THE CONSEQUENCES OF "CONTACT IRRITATION" MIGHT VARY BETWEEN NORMAL INDIVIDUALS AND THOSE WITH COMPROMISED PULMONARY FUNCTION. Comment from Meldrum

Agreed. That is why an intraspecies uncertainty factor of 3 was used for the AEGL-3 derivation. An intraspecies uncertainty factor of I was used for the derivation of the AEGL-2 value because a sensitive person was used as the basis for the derivation.

THE AEGL-3 VALUES SEEM QUITE LOW IN RELATION TO THE ANIMAL LETHALITY DATA. FROM THE SCHLAGBAUER AND HENSCHLER STUDY THE PREDICTED MOUSE LC_{01} WOULD BE 60 PPM FOR 30 MINUTES. Comment from Meldrum

Actually the 30 minute AEGL-3 value of 28 ppm is not that far from the predicted LC_{01} of 60 ppm. The NAC/AEGL Committee walks a very difficult balancing act between two extremes. On the one hand the goal is to derive values which are biologically meaningful and close to a level at which a sensitive individual will respond, yet not be too high to prevent action in a dangerous situation. On the other hand the values should be such that, while protective of human health, they are not too low to have any meaningful biological relevance to serve as the basis for action. At one extreme, action would not be taken at the appropriate time. At the other extreme, unnecessary actions and evacuations, which incur a risk of their own, might be taken.

ANNEX IV

Presentations on Related Initiatives

(a) EPRGs ("Emergency Response Planning Guidelines") of the American Industrial Hygiene Association, presented by David Kelly (representing BIAC);

(b) UK SLOTs ("Specified Level of Toxicity"), presented by Maureen Meldrum;

(c) French Initiative: Detailed methodology for setting up lethal and irreversible threshold effects, presented by Joelle Jarry and Annick Pichard;

(d) German Initiatives, presented by Fritz Kalberlah;

(e) ECETOC Emergency Exposure Indices for Industrial Chemicals, presented by Fritz Kalberlah;

(f) Dutch Initiative: Rotterdam temporary emergency number program, presented by Marc Ruijten.

(a) EPRGS ("Emergency Response Planning Guidelines") of the American Industrial Hygiene Association, presented by David Kelly (representing BIAC)

Slide 1

HISTORY OF ERPGS

First Meeting in 1987

First Publications in 1988

American Industrial Hygiene Association

George M. Rusch, First Chairman

Slide 2

ERPG Process

Literature

New Literature Review

Use Primary References

Document all Sources of Information

A Copy of All References Available for Inspection at AIHA

Use Guidelines as a Framework

Slide 3

Consensus Process

1. Verbal Approval at Meeting
2. Balloted by Mail
3. Ballot Comments Addressed, Final Differences Resolved

Slide 4

Publication Process

Publish New Documents Yearly

Open to Revisions

Updated As Needed
(At least 7 to 10 years)

Slide 5

ERPG Document Sources

Government Organizations

Trade Groups

Individual Companies

ERP Committee Members

Slide 6

ERPG-2 Criteria

-NO IMPAIRMENT OF ESCAPE

-NO IRREVERSIBLE EFFECTS

-RARE OCCURRENCE

Slide 7

DATA USED IN DETERMINING ERPGs

1. HUMAN DATA

   CONTROLLED STUDIES

   EPIDEMIOLOGY

   ANECDOTAL

(ACCIDENTS ETC.)

2. ANIMAL STUDIES

   LC50 VS TIME

   RD50

   BEHAVIORAL STUDIES
   (CNS EFFECTS)

   PATHOLOGY (TARGET)

ORGANS)

   METABOLISM STUDIES

Slide 8

Special Considerations

Developmental Toxins

Carcinogens

Slide 9

Developmental Toxins

Effect Window Concept

Assume Effects Can Occur in One Hour

Classified as ERPG-2 Type Effect

(Ethylene Oxide)

Slide 10

ERPG-1:

The maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient, adverse health effects or without perceiving a clearly defined objectionable odor.

ERPG-2:

The maximum airborne concentration below which, it is believed, nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious adverse health effects or symptoms which could impair an individual's ability to take protective action.

ERPG-3

The maximum airborne concentration below which, it is believed, nearly all individuals could be exposed for up to one hour without experiencing or developing life threatening health effects.

Slide 11

Some Users of ERPGs

Rotterdam (GGD)

US Department of Energy

US EPA Risk Management Plan

US Department of Transportation

Used Woldwide by Many Corporations

Slide 12

ERPG - AEGL Relationship

***Present State**: AIHA and ERP Committee Assisting with AEGL Program*

Resource Sharing
Mutual Benefits
Parallel Efforts
ERPGs Used as Benchmarks in AEGL Development
Values are Generally in Agreement

***Future State:** Relationship Evolving as AEGL Effort Grows*

Maximize Productivity through Cooperation
ERPGs will be Complementary with AEGLs
ERPGs will Focus on Special or Lesser-Used Chemicals not Covered by AEGLs

Slide 13

AIHA ERP COMMITTEE 1999

David P. Kelly	*DuPont, Chairman*
Finis Cavender, Ph.D.	*I.V. Co./ Univ. North Carolina, Vice Chair*
Doan Hansen, Ph.D.	*Brookhaven National Laboratory , Secretary*
Larry A. Gephart	*Exxon, Past Chairman*
Dennis R. Anderson, Ph.D.	*Dow Corning Co.*
Jeffery L. Burgess, MD	*University Arizona*
Keith H. Jacobson, Ph.D.	*Retired, (NIOSH)*
Mark S. Johnson, Ph.D.	*US Army*
Everett Langford, Ph.D.	*Huntsman Chemical*
Rashmi S. Nair, Ph.D.	*Monsanto*
Anthony S. Panepinto, CIH	*Proctor and Gamble*
Frank M. Renshaw, Ph.D.	*Rohm and Haas*
Susan D. Ripple, CIH	*Dow Chemical*
Marc Ruijten, Ph.D.	*GGD, Rotterdam*
George M. Rusch, Ph.D.	*Allied-Signal*
Richard Schlesinger, Ph.D.	*New York Univ. Med. Center*
Allan S. Susten, Ph.D.	*US Agency Tox Sub and Disease Registry*
Richard D. Thomas, Ph.D.	*Intl. Center for Environ & Health*
Paul Tobin, Ph.D.	*US Environmental Protection Agency*
Lindsay E. Booher, CIH	*AIHA Board Coordinator*

Slide 14

ERPG PROGRAM STATUS

Published *87*

Documents being reviewed *30*

Slide 15

Carcinogens
ERPGS

Considered ERPG-2 Type Effect
Use NRC Model with $1/10^4$ Risk
Very Conservative
(Assumes effects can occur after one hour exposure)
Rarely Decides ERPG-2 Value

Slide 16

AEGLs

AEGLs are Based on Non-Cancer Endpoints
Information Provided on Cancer Risk in Appendix
Values Provided for Risk at $1/10^4$, $1/10^5$, and $1/10^6$
User has Information to Adjust Values as Needed

Slide 17

AEGLs and ERPGs

Different Committees, Both Balanced, but AEGL is Larger and Has Wider Representation
Different Sponsors
ERPG Sponsored by AIHA
AEGLs Sponsored by Government Agencies through EPA
AEGLs Authored by Oak Ridge National Laboratory, ERPGs Authored by Various Groups, Mainly Industry and US Dept of Energy
AEGLs SOPs More Detailed and Explicit
ERPGs Don't Use Explicit Safety Factors
AEGLs Have Additional Review Through NRC

(b) UK SLOTSs ("Specified Level of Toxicity"). presented by Maureen Meldrum

Slide 1

TOXICOLOGY FOR MAJOR HAZARDS

HSE **MAUREEN MELDRUM**

Slide 2

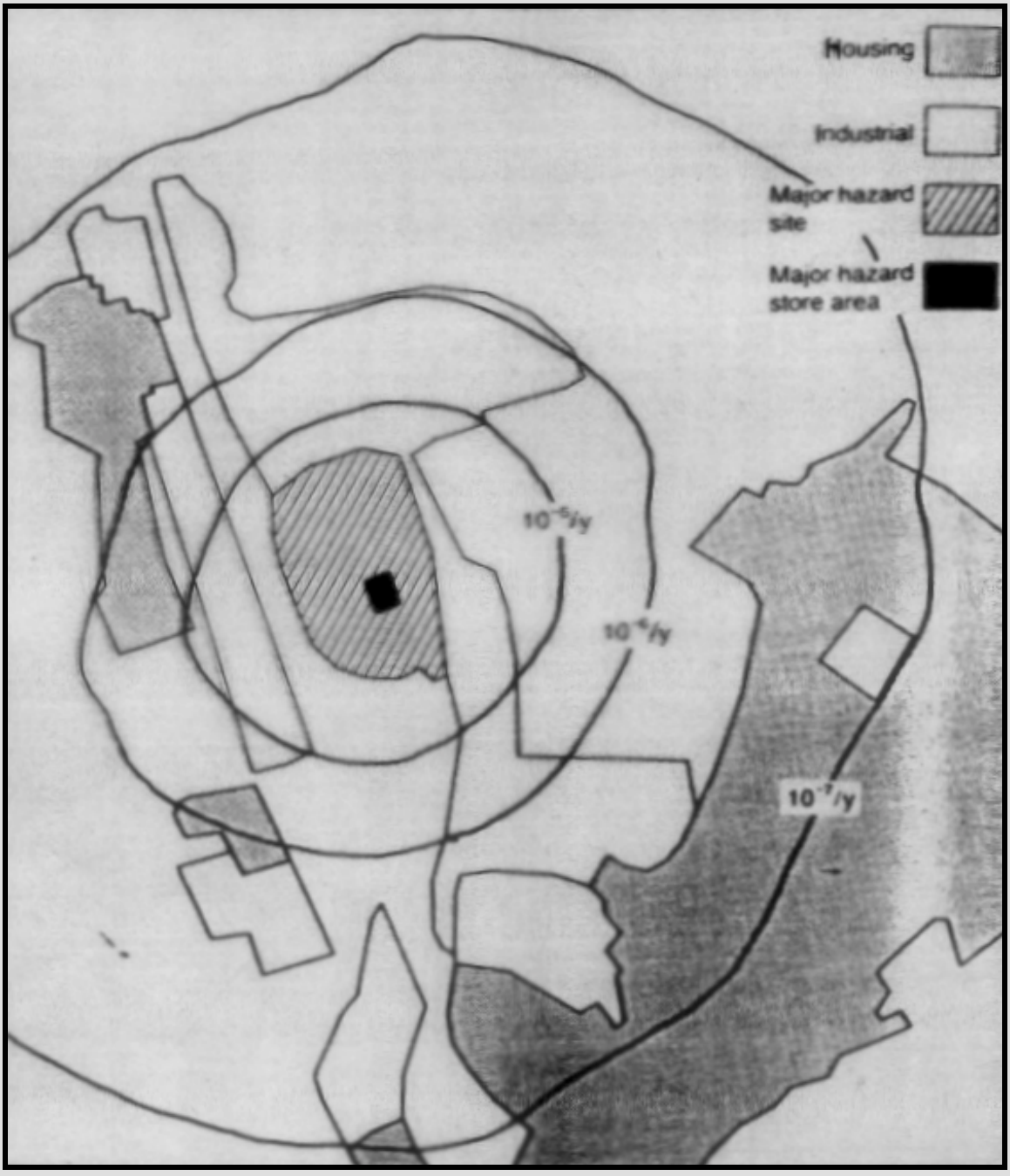
TOXICOLOGY FOR MAJOR HAZARDS

Specified Level of Toxicity (SLOT) for land-use planning applications

- Severe distress to almost everyone; with
- A substantial fraction requiring medical attention; and
- Some people being seriously injured, requiring prolonged treatment; and
- The most susceptible members of the population possibly being killed

Slide 3

TOXICS RISK AT OUTPUT CONTOURS OF INDIVIDUAL RISK



Slide 4

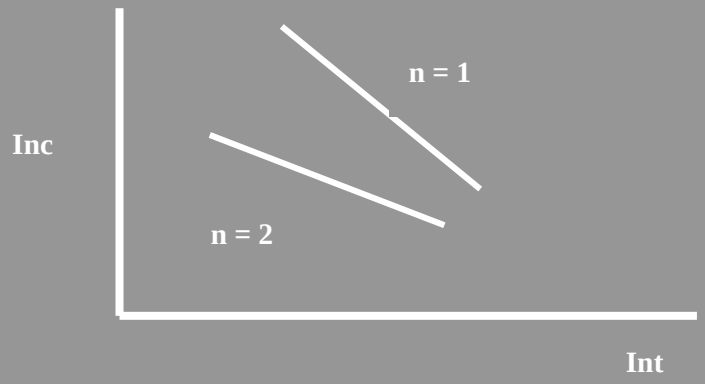
DANGEROUS TOXIC LOAD RELATIONSHIPS FOR INDIVIDUAL SUBSTANCES

Acrylonitrile	9600	ppm.min
Ammonia	3.76×10^8	ppm^2.min
Chlorine	108 000	ppm^2.min
Hydrogen Fluoride	12 000	ppm.min
Hydrogen Sulphide	2×10^{12}	ppm^4.min
Nitrogen Dioxide	96 000	ppm^2.min
Sulphuric Acid Mist	2.16×10^5	$(mg/m^3)^2$ min

Slide 5

RELATIONSHIP BETWEEN ATMOSPHERIC CONCENTRATION, DURATION OF EXPOSURE AND TOXICITY

$c^n t$ = CONSTANT
SLOPE = -1/n



Slide 6

TOXICOLOGY FOR MAJOR HAZARDS

Derivation of "n" value

The way in which C and t are related in producing a "dangerous toxic load" can only be examined within a collection of data from

- Same study, involving the
- Same species and
- Same type of toxic effect

If data from different studies using different species are combined in an analysis, the, inter-laboratory + interspecies variation will exert an unknown influence on the derived relationship between C and t.

Slide 7

TOXICOLOGY FOR MAJOR HAZARDS

Principles of such toxicological assessments in HSE:

1. Uses principles and practices of mainstream regulatory toxicology
2. Transparent.
3. A bottom-line prediction must be made; fence-sitting is not an available regulatory option.

Slide 8

TOXICOLOGY FOR MAJOR HAZARDS

HSE provides advice to local authorities for land-use planning purposes

Advice is based on calculations of the risk to an individual or community of being exposed to amounts of released substance(s) which would result in a specific level of toxicity (SLOT).

Slide 9

TOXICOLOGY FOR MAJOR HAZARDS -Problems

Rely on default assumptions in absence of data

- Default n = 1
- Default - use rat when only species tested
- Default - extrapolate from oral data when no inhalation data available
- Default - assume $LC_{1\text{-}5}$ is 1/4 of LC_{50} when no fractional mortality data available

Slide 10

TOXICOLOGY FOR MAJOR HAZARDS

Considerations:

1. Is the site capable of creating a Specified Level of Toxicity (SLOT) in the surrounding population?
2. If so, what is the risk that conditions producing the SLOT will occur?

Slide 11

TOXICOLOGY FOR MAJOR HAZARDS

Stages:

- Identify most appropriate animal model -usually this is the most sensitive species as judged by LC_{50} values
- Using data from this animal model identify "SLOT" conditions (~LC_{01})
  - probit analysis -eyebaling -1/4LC_{50}
- Derivation of DTL equation and constant (n)
- Reflect back to available human data-see if it makes sense

Slide 12

TOXICOLOGY FOR MAJOR HAZARDS

The "Dangerous Toxic Load" concept

The aim of the toxicology assessment is to identify exposure conditions (pairs of values of C and t) predicted to produce the SLOT

$$F(C,t) = \text{the constant}$$

$$C^n t = DTL$$

(c) French Initiative: Detailed Methodology for Setting up Lethal and Irreversible Theshold Effects,
Presented by Joelle Jarry and Annick Pickard

Accidental Chemical Release

Methodology for setting up lethal and irreversible threshold effects

Joëlle JARRY
French Ministry of Environment
Direction de la Prévention de la Pollution et des Risques

Annick PICHARD
Institut National de l'Environnement Industriel et des Risques
Département Toxicologie et Ecotoxicologie

- April 22, 1999 -

INTRODUCTION

The law dated July 19th, 1976, pertaining the classified facilities for the protection of the environment, foresees that delivery of a permit to operate can be subject to a compulsory order for the establishment of dangerous or potentially harmful facilities.

The authorisation request is based on a safety report. With this regulation, French Authorities, before the European Directive Seveso (1982) had taken into account the technological risk and the control of the major accidents.

The aim of the safety study is to define accidental scenarios leading to a reduction in the origin of the risk, to manage the land use planning and to organise the emergency planning.

Among the retained scenarios, some of them assess the health consequences for the general population surrounding the establishment when submitted to various exposures (chemicals, thermics, mechanics) using human threshold effects.

In order to harmonize the thresholds of French level, the Ministry in charge of the Environment has developed toxicity thresholds which are taken into account for the management of the land use planning around the high risk sites.

So, in the case of the accidental release of a chemical, the safety report defines:
the « lethal effects distance »,
the « irreversible effects distance ».

The distance calculations are founded for each chemical on lethal and irreversible threshold values.

This document describes the methodology for establishing, for each chemical, lethal and irreversible threshold effects.

The definitions of these toxicity thresholds have been enacted during the consultation meeting June 4th, 1998, between the French authorities, INERIS and the Chemical Industry.

1. GENERAL REMARKS

For each chemical substance, threshold effects are established in a **consensus group** to which the French Environment Ministry, INERIS and French Chemical Industry participate.

To assess consequences for the general population of a chemical accidentally released in the atmosphere, the criteria for threshold establishment used in the French methodology are:

- a single exposure,
- a duration of exposure up to one hour,
- a concentration of the chemical which may be high (lethal effects) and low (irreversible effects).

The **general population** is divided into various susceptibility groups. These are young and elderly persons, pregnant women, people in good health and adults with chronic illness.

The nature and severity of **toxic effects** are different. Systemic effects result chiefly from inhalation and local effects involve eyes, skin and respiratory tract.

Chronic or long term effects are not taken account (mutagens, carcinogens, reproductive toxicants etc.).
Regarding the accidental chemical scenario, 3 types of effects have been defined from June, 4th, 1998.

- "lethal effects" which correspond to the outcome of the death among most of the persons exposed.
- "reversible effects" which correspond to return to the same health status as before the accident.
- "irreversible effects" which correspond to the lasting of a lesional or functional impairment directly related to an accidental exposure situation (single or short exposure duration).

The characteristics of these effects make it possible to determine:

- the **« lethal effects threshold »** which corresponds to the maximum airborne concentration of a pollutant for a specific exposure duration below which no lethal effects are observed in the most exposed population.
- the **« irreversible effects threshold »** which corresponds to the maximum airborne concentration of a pollutant for a specific exposure duration below which no irreversible effects are observed in the most exposed population.

The terms « the most exposed population » excludes « hyper-susceptible » groups (for example, pulmonary impaired subjects).

2. TOXICOLOGICAL DATA

From a literature study, this stage reviews the available human and animal toxicity data.

After a critical analysis, a grading is proposed and the best studies are retained.

2.1. Human toxicity data

For each published study, type of effects, number of subjects involved, exposure conditions (concentration - duration).

Two kinds of human toxicity are available : case reports presentations and healthy volunteers experimental studies.

In the first case, the physician observes effect without specific information available on the exposure conditions. Usually, concentrations are high and the nature of the effects may be death, or eye, skin, respiratory tract irritation.

In the healthy volunteer studies, the effects are reversible and exposure duration is checked. These studies describe the symptoms at low concentrations which are always well below human hazardous concentrations.

When this methodology is applied, these data are very useful to establish the irreversible effects threshold.

2.2. ANIMAL EXPERIMENTAL DATA

2.2.1 General remarks

The number is higher than for human data and they are often used for the human risk assessment.

Only acute effects are considered. This may be immediate or delayed death, systemic effects, skin, eye and respiratory tract irritation. A critical data analysis takes into account the species, the publications and studies quality (date of experimentation, GLP, etc.). A grading of each study allows the retention of the best of them.

In fact, the most recent studies describe with more precision the nature of the toxic effect, the animals concerned by the effects in percentage, exposure conditions (duration-concentration).

Each study is examined considering these criteria.

2.2.2. Mortality Data Analysis

So, the keys studies are kept.

For each study, experimental points are placed on a concentration-duration diagram.

Mortality curves for CL 50% and CL 1% are plotted.

For that, Haber's law is used : for a specific effect (for example: mortality), a relationship between exposure duration (T) and airborne concentration (C) exists the original law C x T = K has been extended for easy use and is now written :

$$C^n \; x \; T = K$$

- C = Concentration
- T = exposure duration
- K = constant
- n = a number above zero

The Haber law interpolation to the low doses is discussed within the consensus groups.

When possible with the data quality, the Probit analysis is used to examine the effect/dose data and plot the mortality curves CL 50% and CL 1%.

The probit analysis extrapolation to the low risk is kept but it is more important to insist on the uncertainty which comes from the fact that this extrapolation is not justified by measured data.

2.2.3. Irreversible effects analysis

That is the most difficult analysis.

Most often, data is limited and various types of effects are observed. In the case of irritating chemicals, the main effects are consequences on respiratory tract (asthma), ocular (cornea). But they may be systemic effects (liver, kidneys etc.).

It must be founded on human toxicity data. For lack of them, relevant experimental data may be retained. Moreover, quality of data and complex analysis are assumed to express the relationship between the severity of one or several irreversible effects and concentration.

Usually, only or two relevant studies are kept.

RESULTS REVIEW - SETTING UP EFFECTS THRESHOLD

3.1. ANIMAL DATA EXTRAPOLATION TO HUMANS

When, animal and human data are of the same quality, human data have priority.

Animal data extrapolation to humans is made taking special account of the species respiratory tract physiology, of the species sensitivity and of the mechanism of action of the substance.

When considering the ammonia and fluorhydric acid examples, the consensus group has decided that animal data can be used without any safety factors.

3.2. HUMAN LETHAL EFFECT THRESHOLD

From key studies for lethal effects, threshold airborne concentrations are proposed for exposure duration from 10 minutes to 60 minutes.

Usually, these durations are 10, 20, 30 minutes.

3.3 HUMAN IRREVERSIBLE EFFECTS THRESHOLD

When sufficient human data exist, the establishment of the irreversible effects threshold is based on expert judgement within the consensus group.

If only animal experimental data are available and if these data show a dose-effect relationship, the Haber law can be applied and the Probit model may be used.

This irreversible effect threshold is established for exposure durations which vary from 15 to 30 minutes.

(d) German Initiatives, Presented by Fritz Kalberlah
and
(e) ECETOC Emergency Exposure Indices for Industrial Chemicals, Presented by Fritz Kalberlah

Acute
Exposure
Guideline
Levels

AEGL alternatives in Germany

Störfallbeurteilungswerte

Hazardous incidence evaluation values

History: initiated at the beginning of the 90ies by VCI, Verband der Chemischen Industrie (Association of the Chemical Industry)

Aim: for planning of industrial plants and chemical accident prevention

Definition: a 60-minute exposure should not lead to life-threatening or other severe, especially irreversible health effects,
1 exposure period, 1 severity level

Documentation: short (one page) support document

Current: values for 37 substances were derived, have to be updated

Comparison: most values range between ERPG-2/ERPG-3 and 1-hour AEGL-2/AEGL-3

Folie_VCIdef

FoBiG GmbH, 1999

Acute
Exposure
Guideline
Levels

AEGL alternatives in Germany

Einsatztoleranzwerte

Action tolerance levels

History: initiated by the Federal Agency for Civil Defense in 1995/96, used in guideline 10/01(1998) of the vfdb, Vereinigungzur Förderung des deutschen Brandschutzes (Federation for the Advancement of German Fire Prevention)

Aim: health hazard evaluation of substance air concentrations during fires

Definition: a 4-hour exposure should not lead to health hazards for unprotected fire fighters and the general population, 1 exposure period, 1 severity level

Documentation: short (one page) support document

Current: values for 33 substances derived

Comparison: most values are above MAK and between ERPG-1/ERPG-2 and 4- hour AEGL-1/AEGL-2

Folie_VCldef FoBiG GmbH, 1999

Acute
Exposure
Guideline
Levels

AEGL alternatives
Emergency Exposure Indices for Industrial Chemicals

History: initiated by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) in 1991 (Technical Report No. 43)

Aim: health hazard evaluation of substance air concentrations during emergencies

Definition: values for 3 severity levels (discomfort, EEI-1;disability, EEI-2; incapacity, EEI-3) and 3 exposure periods (15, 30 and 60 minutes)

Documentation: extensive support document

Current: example derivations for 2 substances

Comparison: largely comparable to AEGL severity levels; no explicit use of safety/ uncertainty factors

Folie_EEIdef

FoBiG GmbH, 1999

(f) Dutch Initiative: Rotterdam Temporary Emergency Number Programme, Presented by Marc Ruijten

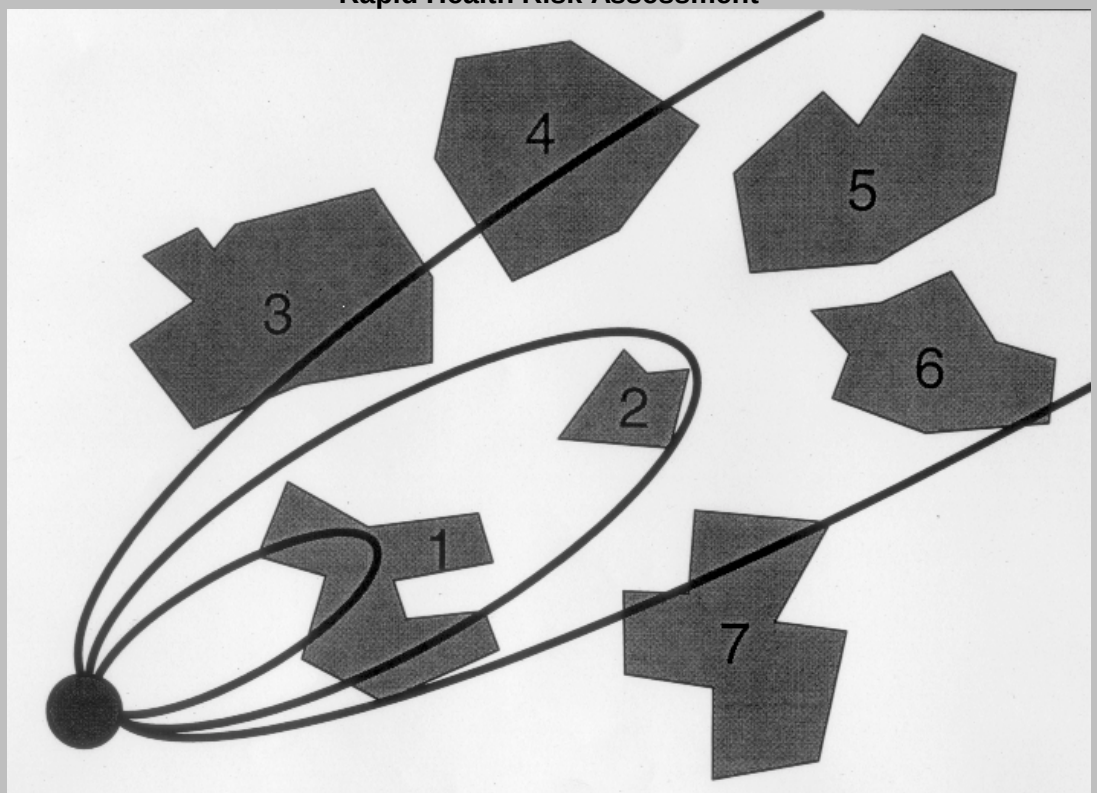
Slide 1

Rotterdam Temporary Emergency Number Programme

Marc Ruijten
Environmental Health Unit
Municipal Health Service Rotterdam

Slide 2

Rapid Health Risk Assessment



Slide 3

Local requirements

- *Phase 1: identification of priority chemicals*

production
storage
transportation
volatility
toxicity

- *Result: 280 priority chemicals identified*

Slide 4

Levels of ambition

- *Level 1: generic methods*

STEL - LC

- *Level 2: quick and dirty evaluation of data*

- *Level 3: thorough evaluation of data*

ERPG
AEGL

Slide 5

The KISS principle

K Keep
I It
S Simple
S Stupid!

Slide 6

Local emergency response numbers

- *ERPG methodology, but: secondary literature*
- *Choice of fixed levels (..- 1 - 2 - 5 - 10 - 20 -..)*

limited precision of other input data
limited precision of analytical devices
limitations toxicological database

Slide 7

Expert health effect assessment

- *Selection of experts according to strict criteria*
- *Acrylonitrile, 1-hour exposure*

nose/throat irritation: 9 - 70 ppm (10 ppm)
wheezing: 11 - 300 ppm (120 ppm)
death: 68 - 1000 ppm (300 ppm)

- *Hydrogen fluoride, estimation of ERPG-levels*

ERPG-1 (5 ppm): 2 - 10 ppm (5 ppm)
ERPG-2 (20 ppm): 5 - 60 ppm (27 ppm)
ERPG-3 (50 ppm): 40 - 300 ppm (100 ppm)

Slide 8

Local emergency response numbers

- *ERPG methodology, but: secondary literature*
- *Choice of fixed levels (..- 1 - 2 - 5 - 10 - 20 -..)*

limited precision of other input data
limited precision of analytical devices
limitations toxicological database

- *All numbers in mg/m^3*
- *Nomenclature:*

AEGL-1 = Communication Guidance Level
AEGL-2 = Alarm Threshold Level
AEGL-3 = Life-Threatening Level

Slide 9

Present developments

- *Emergency numbers list is being updated*

improve quality
add 30 chemicals
improve nationwide acceptance

- *Program 'adopted' by Ministry of Environment*
- *Draft S.O.P. available*
- *Problematic endpoints:*

carcinogenicity
reproductive and developmental toxicity