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Acute Exposure Guideline Levels for Selected Airborne Chemicals

Subcommittee on Acute Exposure Guideline Levels,
Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

National Research Council
Original Committee Members

- Daniel Krewski (Chair), University of Ottawa, Ottawa, Ontario, Canada
- Edward C. Bishop, Parsons Engineering Science, Inc., Fairfax, Virginia
- James V. Bruckner, University of Georgia, Athens, Georgia
- John Doull, University of Kansas Medical Centre, Kansas City, Kansas
- Donald E. Gardner, Inhalation Toxicology Associates, Inc., Raleigh, North Carolina
- David W. Gaylor, U.S. Food and Drug Administration, Jefferson, Arkansas
- Harihara Mehendal, University of Louisiana, Monroe, Louisiana
- Florence K. Kinotshita, Hercules Incorporated, Monroe, Louisiana
- Stephen U. Lester, Center for Health, Environment and Justice, Falls Church, Virginia
- Richard B. Schlesinger, New York University School of Medicine, Tuxedo, New York
- Calvin C. Willhite, State of California, Berkely, California
### Range of Chemical Agents

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<th>Volume 1</th>
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<th>Volume 3</th>
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Acute Exposure Guideline Levels for Selected Airborne Chemicals:
Volume 15 (2013)

Authors
Committee on Acute Exposure Guideline Levels; Committee on Toxicology; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies; National Research Council

Description
Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 15 identifies, reviews, and interprets relevant toxicologic and other scientific data for ethyl mercaptan, methyl mercaptan, phenyl mercaptan, tert-octyl mercaptan, Lewisite, methyl isothiocyanate, and selected monoisocyanates in order to develop acute exposure guideline levels (AEGLS) for these high-priority, acutely toxic chemicals.

http://www.nap.edu/catalog.php?record_id=18449
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C. Glossary
D. Technical Support Document (TSD)
E. TSD Summary
F. TSD Derivation of AEGL Values
G. TS Time-Scaling Calculations
H. TSD Carcinogenicity Assessment
I. TSD AEGL Derivation Summary
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Introduction

• Hazardous substances may be released in a variety of ways:
  – Chemical spills, industrial explosions, fires, transportation accidents, terrorist attacks
• Resulting exposure to workers and the general population may range from low to dangerously high levels, with a wide variety of exposure durations
• Health risks from such exposures range from mild irritation that immediately subsides to acute reversible effects, to long-term irreversible effects
Acute Exposure Guideline Levels

• **AEGLs** provide estimates of airborne concentrations for a range of exposure durations to hazardous substances

• These guidelines are useful in estimating the risks and magnitude of health effects resulting from exposures to accidental or terrorist events

• Workplace exposure limits do exist, however, these limits are not easily translatable to emergency situations or exposures of high concentration and short duration
The National Advisory Committee (NAC) for Acute Exposure to Guideline Levels for Hazardous substances was established in the USA in 1995.

The Committee was mandated to identify, review, and utilize scientific data to develop AEGLs for high priority hazardous substances.

In 1999, the AEGL program was expanded internationally to included participation of several OECD member-countries.
Non-published, Non-peer Reviewed Industry Data

Published Literature Search

Other Data/Information Sources

Special Toxicity Studies

AEGL Development Team – ORNL Scientist Chemical Manager, Chemical Reviewers

Technical Support Documents (TSDs)

Distribute Draft or Proposed TSDs/AEGLs to Committee Members

NAC/AEGL Committee Meeting to Discuss Draft or Proposed AEGLs

NAC/AEGL Committee Consensus on Proposed AEGLs

YES

NO
AELGs Development Process (2/2)

- Major Changes
  - NAC/AEGL Committee Consensus on Revisions to Proposed AEGLs
    - YES
    - NO
      - Interim AEGLs

- Minor Changes
  - NAS-NRC AEGL Subcommittee
  - NAC/AEGL Committee
    - NO
      - NAS-NRC AEGL Subcommittee Concurrence
    - YES
      - NAS-NRC Publication of Final AEGLs

FR Publication

Major Comments/Issues?

Concurrence
AEGLs

- There are three AEGLs that represent increasing severities of adverse health effects: AEGL-1, AEGL-2, AEGL-3

- Each AEGL is derived for five exposure durations: 10min, 30min, 1h, 4h, and 8h

- AEGLs are airborne concentrations expressed in ppm or mg/m³
• **AEGL-1** is the level of a substance which it is predicted that the general population, including susceptible individuals, could experience discomfort, irritation, although these effects are not disabling and are reversible upon cessation of exposure.
• **AEGL-2** is the concentration of a substance above which it is predicted that the general public, and susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape exposure.
• *AEGL-3* is the concentration of a substance that the general population and susceptible individuals could experience life-threatening health effects or death.
AEGL Summary

**AEGL-1** – Irritation and other reversible effects

**AEGL-2** – Irreversible or disabling effects

**AEGL-3** – Lethal effects
Initially the establishment of an AEGL for a specific chemical involves the collection and review of all relevant published and unpublished information on a chemical.

Evidence evaluated includes:
- Chemical-physical relationship, structure-activity relationship, in vitro toxicity, animal toxicity, controlled human studies, observations of humans involved in accidental exposures, epidemiologic studies.

Toxicity data from human studies are preferred over animal studies, and data from inhalation studies are the most appropriate route of exposure.
When human toxicity data are not available or information is inadequate, data from animal studies are then extrapolated to estimate potential toxicity in humans.

- Extrapolation involves complete utilization of available data as well as expert scientific judgment.
- Uncertainty factors are employed to account for lack of knowledge when extrapolations are required.

Data from most sensitive animal species are usually used to set AEGLs, and all endpoints are evaluated.
Step-wise Development of AEGLs

• **AEGL-1 endpoints**
  – Are not recommended when the value exceeds the AEGL-2 value

• **AEGL-2 endpoints**
  – The highest experimental exposure levels that did not cause a significant decrease in parameters such as, hematocit, kidney pathology, behavioral change, CNS effects are used for setting AEGL-2 levels

• **AEGL-3 endpoints**
  – Highest exposure levels that did not cause life-threatening effects or death are used to set AEGL-3 levels
Extrapolation from animals to human responses is complex.

The quantitative relationship between airborne concentrations and the delivered dose to the target tissue for humans and the animal species are not usually known.

Exposure concentrations are used without any dosimetric corrections when extrapolating from animals to humans.

- When valid data and models exist to correct for this, the correction is ensured to be protective.
Indicators of Risk

• No Observable Adverse Effect Level (NOAEL)

• Lowest Observable Adverse Effect Level (LOAEL)

• Benchmark Dose (BMD) – dose associated with a 10% increase in risk
Traditionally, a NOAEL is selected to set acceptable levels of exposure to potentially toxic agents.

The NOAEL/LOAEL approach has several limitations:
- Does not consider the shape of the dose-response curve
- Restricted to concentrations used in the experiments
- The power of the experiment to detect adverse health effects generally is not considered.
A Signal-to-Noise Crossover Dose as the Point of Departure for Health Risk Assessment

Salomon Sand, Christopher J. Portier, Daniel Krewski

http://dx.doi.org/10.1289/ehp.1003327

Online 3 August 2011
Signal-to-Noise Crossover Dose (SNCD)
Uncertainty Factors

- AEGLs based on PoD derived from animal data are divided by an uncertainty factor to allow for the possibility that humans may be more susceptible than animals.
- Uncertainty factors are usually assigned a default value of 10.
- Uncertainty factors exist for both intra and interspecies extrapolations.
- The total uncertainty factor consists of the multiplication of $U_A \times U_H$. 
AEGLs are established for six exposure durations in order to meet a wide range of needs for government and private agencies – 10min, 30min, 1h, 2h, 4h, 8h

Experimental data do not generally include these specific exposure durations, thus extrapolation is required

The relationship between concentration and duration exposure, with a specific response is a function of its physical, chemical, toxicological, and pharmacological properties
Time Scaling

- ten Berge’s equation: $C^n t = k$
  - $C =$ concentration and $t =$ exposure duration
  - Haber’s rule a special case with $n = 1$
- Range of $n$ is from 1 to 3
- The default value of $n$ is 1, when extrapolating from an AEGL with a shorter exposure duration to a longer exposure duration
- When extrapolating from an AEGL with a longer exposure duration to a shorter duration of exposure $n = 3$
Categorical Regression

- A new methodology not yet routinely used by the NAC in the development of AEGLs
- Developed by the Environmental Protection Agency (US) to conduct a meta-analysis of concentration-exposure duration data with a variety of responses in multiple species
- The approach provides estimates of the proportion of animals in an AEGL category for various concentrations and durations of exposure
- Categorical regression is limited by the difficulty in assigning severity categories to various health effects
AN EXPOSURE-RESPONSE CURVE FOR COPPER EXCESS AND DEFICIENCY

Andrea Chambers¹, Daniel Krewski¹, Nicholas Birkett¹,², Laura Plunkett³, Richard Hertzberg⁴, Ruth Danzeisen⁵, Peter J. Aggett⁶, Thomas B. Starr⁷, Scott Baker⁵, Michael Dourson⁸, Paul Jones⁹, Carl L. Keen¹⁰, Bette Meek¹¹, Rita Schoeny¹², Wout Slob¹³

¹Institute of Population Health, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada
²McLaughlin Centre for Population Health Risk Assessment and Department of Epidemiology and Community Medicine, University of Ottawa, 451 Smyth Rd., Ottawa, Ontario, Canada
³Integrated Biostatistics, LLC, Houston, Texas, USA
⁴Department of Environmental and Occupational Health, Emory University, 1518 Clifton Rd., Atlanta, Georgia, USA
⁵Environment Program, International Copper Association, Ltd., New York, New York, USA
⁶School of Medicine and Health, Lancaster University, Lancaster, United Kingdom
⁷TBS Associates, Raleigh, North Carolina, USA
⁸Toxicology Excellence for Risk Assessment, Cincinnati, Ohio, USA
⁹Waltham Center for Pet Nutrition, Waltham on the Wolds, Leicestershire, United Kingdom
¹⁰Department of Nutrition, University of California at Davis, Davis, California, USA
¹¹McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada
¹²U.S. Environmental Protection Agency, Washington, DC, USA
¹³Dutch National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
Dose-response relationships for essential trace elements are complex.
Severity scores can be assigned

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<tr>
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<tr>
<td>5</td>
<td>Irreversible Gross Excess</td>
</tr>
<tr>
<td>4</td>
<td>Reversible Gross Excess</td>
</tr>
<tr>
<td>3</td>
<td>Metabolic Perturbation</td>
</tr>
<tr>
<td>2</td>
<td>Early Biological Indicators Altered Cu Metabolism</td>
</tr>
<tr>
<td>1</td>
<td>Homeostatic Adaptation to High Intakes</td>
</tr>
<tr>
<td>0</td>
<td>No change compare to controls</td>
</tr>
<tr>
<td>1</td>
<td>Homeostatic Adaptations to Low Intakes</td>
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<td>2</td>
<td>Early Biological Indicators of Def Cu Levels</td>
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<td>Irreversible Gross Deficiency</td>
</tr>
<tr>
<td>6</td>
<td>Death</td>
</tr>
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</table>
ED10 Dose - Duration Curves for Severity Level 3 for Toxicity due to Copper Excess

The graph shows the ED10 dose-duration curves for severity level 3 toxicity due to copper excess for humans, mice, and rats. The x-axis represents duration in days, ranging from 0 to 150, and the y-axis represents dose in mg/kg bw/day, ranging from 0.0001 to 10000.

The curves for human, mouse, and rat toxicity are distinguished by different symbols and line styles: humans are represented by circles, mice by black circles with a plus sign, and rats by triangles.

The data points indicate the effect of different dose levels over varying durations on the severity of copper toxicity in these species.
Dose-Response Curves for Copper Deficiency and Excess

McLaughlin Centre for Population Health Risk Assessment
Short-term Exposure to Carcinogens

- **AEGL-2** corresponds to irreversible or serious long lasting health effects, such as cancer.
- 400 chemicals have been reported to produce tumors in animals after a single exposure.
  - Only a few of the studies have used inhalation as the exposure route.
- No **AEGL-2** levels have yet been based solely on carcinogenicity.
- No official procedures have been adopted by regulatory agencies for estimating cancer risks by short-term exposures to carcinogens.
Example: Nerve Agent GB (Sarin)

Development of acute exposure guideline levels for airborne exposures to hazardous substances

Daniel Krewski, a,* Kulbir Bakshi, b Roger Garrett, c Ernest Falke, c George Rusch, d and David Gaylor e

a University of Ottawa, Ottawa, Ont., Canada
b U.S. National Research Council, Washington, DC, USA
c U.S. Environmental Protection Agency, Washington, DC, USA
d Honeywell International, Inc., Morristown, NJ, USA
e Sciences International, Inc., Little Rock, AR, USA
Sarin

• Toxic ester derivative of phosphonic acid containing a fluoride substituent group.
  • Used by terrorist in the 1995 terrorist attack in the Tokyo subway system
  • Acts as an anticholinesterase properties

• Exposure to acutely toxic concentrations can result in:
  • Excessive secretions and sweating, miosis, bronchospasm, intestinal hypermotility, bradycardia, muscle fasciculations, twitching, weakness, paralysis, loss of consciousness, convulsions, depression of respiratory system, and death
# Sarin AEGLs (ppm)

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<th>Classification</th>
<th>10-min</th>
<th>30-min</th>
<th>1-h</th>
<th>4-h</th>
<th>8-h</th>
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<tr>
<td>AEGL-1</td>
<td>0.0012</td>
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<td>AEGL-2</td>
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<td>0.0085</td>
<td>0.0060</td>
<td>0.0029</td>
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<td>AEGL-3</td>
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<tr>
<td>Classification</td>
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<td>1-h</td>
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<td>AEGL-1</td>
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<td>0.0028</td>
<td>0.0014</td>
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<td>AEGL-2</td>
<td>0.087</td>
<td>0.50</td>
<td>0.035</td>
<td>0.017</td>
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<tr>
<td>AEGL-3</td>
<td>0.38</td>
<td>0.19</td>
<td>0.13</td>
<td>0.070</td>
<td>0.051</td>
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AEGLs Endpoints for Sarin

**AEGL-1**
EC$_{50}$ for miosis observed in adult female rats (Mioduszewski et al 2002b)

**AEGL-2**
Miosis, dyspnea, RBC-ChE inhibition, changes in human volunteers (Baker and Sedgewick 1996)

**AEGL-3**
Based on experimental SD rat lethality data (LC$_{01}$ and LC$_{50}$); whole-body dynamic concentrations (Mioduszewski et al. 2000, 2001, 2002a)
Derivation of AEGL-1 for Sarin

• Toxic endpoint: EC$_{50}$ for miosis observed in adult female SD rats

• Time Scaling $C^{nxt} = k; n = 1.93$
  – Based on the LC$_{01}$ data of SD rats

• Uncertainty Factors
  – Interspecies UF = 1 (miosis response to GB vapor is similar across mammal species)
  – Intraspecies UF = 10 (adjustment for possible susceptible individuals)

• Key Study – Mioduszewski et al. (2002b)
Derivation of AEGL-2 for Sarin

- Toxic endpoint: Observed effects include miosis in eight of eight subjects, dyspnea and photophobia in some individuals, inhibition of RBC-ChE to approximately 60% of individual baseline, and small changes in single fibre electromyography.
- Time Scaling $C^{nxt} = k; n = 2$
- Uncertainty Factors
  - Interspecies UF = 1 (human data were used)
  - Intraspecies UF = 10 (for possible susceptible individuals)
- Key Study – Baker and Sedgwick (1996)
Derivation of AEGL-3 for Sarin

- Toxic endpoint: Fourteen-day acute lethal toxicity of GB to female SD rats. Female rats were more sensitive to GB vapor toxicity than males.
- Time Scaling $C^{\text{next}} = k; n = 2$
- Uncertainty Factors
  - Interspecies UF = 3 (female rat data); full default value of 10 not considered appropriate since the mechanism of toxicity in rats and human is the same; (ChE inhibition)
  - Intraspecies UF = 10 (for possible susceptible individuals)
- Key Study – Mioduszewski et al. (2000, 2001, 2002a)
Summary

- Systematic approach to setting short-term exposure guidelines for highly hazardous substances
- Useful for both emergency response and emergency planning
- Collaborative process involving the U.S. EPA, the U.S. NRC, the National Advisory Council, Oak Ridge National Laboratory, and the European Union
- Risk assessment methodology made explicit in the Standing Operating Procedures
- Fifteen volumes of AEGGLs published to date
- Becoming de facto international standards, meeting a need for guidance on acute exposure levels for hazardous substances