

ENVIRONMENTAL PROTECTION AGENCY

[OPPTS-00293; FRL-6591-2]

National Advisory Committee for Acute Exposure Guideline Levels (AEGs) for Hazardous Substances; Proposed AEG Values**AGENCY:** Environmental Protection Agency (EPA).**ACTION:** Notice.

SUMMARY: The National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) is developing AEGs on an ongoing basis to provide Federal, State, and local agencies with information on short-term exposures to hazardous chemicals. This notice provides AEG values and Executive Summaries for 14 chemicals for public review and comment. Comments are welcome on both the AEG values in this notice and the Technical Support Documents placed in the public version of the official docket for these 14 chemicals.

DATES: Comments, identified by the docket control number OPPTS-00293, must be received by EPA on or before July 24, 2000.

ADDRESSES: Comments may be submitted by mail, electronically, or in person. Please follow the detailed instructions for each method as provided in Unit I. of the "SUPPLEMENTARY INFORMATION." To ensure proper receipt by EPA, it is imperative that you identify docket control number OPPTS-00293 in the subject line on the first page of your response.

FOR FURTHER INFORMATION CONTACT: For general information contact: Barbara Cunningham, Director, Office of Program Management and Evaluation, Office of Pollution Prevention and Toxics (7401), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 554-1404; e-mail address: TSCA-Hotline@epa.gov.

For technical information contact: Paul S. Tobin, Designated Federal Officer (DFO), Office of Prevention, Pesticides and Toxic Substances (7406), 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 260-1736; e-mail address: tobin.paul@epa.gov.

SUPPLEMENTARY INFORMATION:**I. General Information****A. Does this Action Apply to Me?**

This action is directed to the general public to provide an opportunity for

review and comment on "Proposed" AEG values and their supporting scientific rationale. This action may be of particular interest to anyone who may be affected if the AEG values are adopted by government agencies for emergency planning, prevention, or response programs, such as EPA's Risk Management Program under the Clean Air Act (CAA) and Amendments Section 112r. It is possible that other Federal agencies besides EPA, as well as State and Local agencies and private organizations, may adopt the AEG values for their programs. As such, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, consult the technical person listed under "FOR FURTHER INFORMATION CONTACT."

B. How Can I Get Additional Information, Including Copies of this Document or Other Related Documents?

1. *Electronically.* You may obtain electronic copies of this document, and certain other related documents that might be available electronically, from the EPA Internet Home Page at <http://www.epa.gov/>. To access this document, on the Home Page select "Laws and Regulations" and then look up the entry for this document under the "Federal Register—Environmental Documents." You can also go directly to the **Federal Register** listings at <http://www.epa.gov/fedrgstr/>.

2. *In person.* The Agency has established an official record for this action under docket control number OPPTS-00293. The official record consists of the documents specifically referenced in this action, any public comments received during an applicable comment period, and other information related to this action, including any information claimed as Confidential Business Information (CBI). This official record includes the documents that are physically located in the docket, as well as the documents that are referenced in those documents. The public version of the official record does not include any information claimed as CBI. The public version of the official record, which includes printed, paper versions of any electronic comments submitted during an applicable comment period, is available for inspection in the TSCA Nonconfidential Information Center, North East Mall Rm. B-607, Waterside Mall, 401 M St., SW., Washington, DC. The Center is open from noon to 4 p.m., Monday through Friday, excluding legal holidays. The telephone number of the Center is (202) 260-7099.

3. *Fax-on-Demand.* You may request to receive a faxed copy of the document(s) by using a faxphone to call (202) 401-0527 and select the item number 4800 for an index of the items available by fax-on-demand in this category, or select the item number for the document related to the chemical(s) identified in this document as listed in the chemical table in Unit III. You may also follow the automated menu.

C. How and to Whom Do I Submit Comments?

You may submit comments through the mail, in person, or electronically. To ensure proper receipt by EPA, it is imperative that you identify docket control number OPPTS-00293 in the subject line on the first page of your response.

1. *By mail.* Submit your comments to: OPPT Document Control Office (7407), Office of Pollution Prevention and Toxics (OPPT), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460. For express delivery, use the address in Unit I.C.2.

2. *In person or by courier.* Deliver your comments to: OPPT Document Control Office (DCO) in East Tower Rm. G-099, Waterside Mall, 401 M St., SW., Washington, DC. The DCO is open from 8 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The telephone number for the DCO is (202) 260-7093.

3. *Electronically.* You may submit your comments electronically by e-mail to: "oppt.ncic@epa.gov," or mail your computer disk to the address identified above. Do not submit any information electronically that you consider to be CBI. Electronic comments must be submitted as an ASCII file avoiding the use of special characters and any form of encryption. Comments and data will also be accepted on standard disks in WordPerfect 6.1/8.0 or ASCII file format. All comments in electronic form must be identified by docket control numbers OPPTS-00293. Electronic comments may also be filed online at many Federal Depository Libraries.

D. How Should I Handle CBI that I Want to Submit to the Agency?

Do not submit any information electronically that you consider to be CBI. You may claim information that you submit to EPA in response to this document as CBI by marking any part or all of that information as CBI. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. In addition to one complete version of the comment that includes any

information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public version of the official record. Information not marked confidential will be included in the public version of the official record without official notice. If you have any questions about CBI or the procedures for claiming CBI, please consult the technical person listed under "FOR FURTHER INFORMATION CONTACT."

E. What Should I Consider as I Prepare My Comments for EPA?

You may find the following suggestions helpful for preparing your comments:

1. Explain your views as clearly as possible.
2. Describe any assumptions that you used.
3. Provide copies of any technical information and/or data that you used that support your views.
4. If you estimate potential burden or costs, explain how you arrived at the estimate that you provide.
5. Provide specific examples to illustrate your concerns.
6. Offer alternative ways to improve the proposed notice.
7. Make sure to submit your comments by the deadline in this document.
8. To ensure proper receipt by EPA, be sure to identify the docket control number assigned to this action in the subject line on the first page of your response. You may also provide the name, date, and **Federal Register** citation.

II. Background

A. Introduction

EPA's Office of Prevention, Pesticides and Toxic Substances (OPPTS) provided notice in the **Federal Register** of October 31, 1995 (60 FR 55376) (FRL-4987-3) of the establishment of the NAC/AEGL Committee with the stated charter objective as "the efficient and effective development of Acute Exposure Guideline Levels (AEGLs) and the preparation of supplementary qualitative information on the hazardous substances for federal, state, and local agencies and organizations in the private sector concerned with [chemical] emergency planning, prevention, and response." The NAC/AEGL Committee is a discretionary Federal advisory committee formed with the intent to develop AEGLs for chemicals through the combined efforts of stakeholder members from both the public and private sectors in a cost-

effective approach that avoids duplication of efforts and provides uniform values, while employing the most scientifically sound methods available. An initial priority list of 85 chemicals for AEGL development was published in the **Federal Register** of May 21, 1997 (62 FR 27734) (FRL-5718-9). This list is intended for expansion and modification as priorities of the stakeholder member organizations are further developed. While the development of AEGLs for chemicals are currently not statutorily based, at least one rulemaking references their planned adoption. The CAA and Amendments Section 112(r) Risk Management Program states, "EPA recognizes potential limitations associated with the Emergency Response Planning Guidelines and Level of Concern and is working with other agencies to develop AEGLs. When these values have been developed and peer-reviewed, EPA intends to adopt them, through rulemaking, as the toxic endpoint for substances under this rule (see 61 FR 31685)." It is believed that other Federal and State agencies and private organizations will also adopt AEGLs for chemical emergency programs in the future.

B. Characterization of the AEGLs

The AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 mins. to 8 hrs. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 mins., 1 hr., 4 hrs., and 8 hrs.) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive and susceptible. The AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million (ppm) or milligrams/meter cubed (mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious,

long-lasting adverse health effects or impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain non-symptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

C. Development of the AEGLs

The NAC/AEGL Committee develops the AEGL values on a chemical-by-chemical basis. Relevant data and information are gathered from all known sources including published scientific literature, State and Federal agency publications, private industry, public databases and individual experts in both the public and private sectors. All key data and information are summarized for the NAC/AEGL Committee in draft form by Oak Ridge National Laboratories together with "draft" AEGL values prepared in conjunction with NAC/AEGL Committee members. Both the "draft" AEGLs and "draft" Technical Support Documents are reviewed and revised as necessary by the NAC/AEGL Committee members prior to formal NAC/AEGL Committee meetings. Following deliberations on the AEGL values and the relevant data and information for each chemical, the NAC/AEGL Committee attempts to reach a consensus. Once the NAC/AEGL Committee reaches a consensus, the values are considered "Proposed" AEGLs. The Proposed AEGL values and the accompanying scientific rationale for their development are the subject of this notice.

In this document the NAC/AEGL Committee is publishing proposed AEGL values and the accompanying scientific rationale for their development for 14 hazardous substances. These values represent the third set of exposure levels proposed and published by the NAC/AEGL

Committee. EPA published the first "Proposed" AEGLs for 12 chemicals from the initial priority list in the **Federal Register** of October 30, 1997 (62 FR 58840-58851) (FRL-5737-3) and for 10 chemicals in the **Federal Register** of March 15, 2000 (65 FR 14186-14196) (FRL-6492-4) in order to provide an opportunity for public review and comment. In developing the proposed AEGL values, the NAC/AEGL Committee has followed the methodology guidance Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances, published by the National Research Council of the National Academy of Sciences (NSC/NAS) in 1993. The term Community Emergency Exposure Levels (CEELs) is synonymous with AEGLs in every way. The NAC/AEGL Committee has adopted the term

Acute Exposure Guideline Levels to better connote the broad application of the values to the population defined by the NAS and addressed by the NAC/AEGL Committee. The NAC/AEGL Committee invites public comment on the proposed AEGL values and the scientific rationale used as the basis for their development.

Following public review and comment, the NAC/AEGL Committee will reconvene to consider relevant comments, data, and information that may have an impact on the NAC/AEGL Committee's position and will again seek consensus for the establishment of interim AEGL values. Although the interim AEGL values will be available to Federal, State, and local agencies and to organizations in the private sector as biological reference values, it is intended to have them reviewed by a

subcommittee of the NAS. The NAS subcommittee will serve as a peer review of the interim AEGLs and as the final arbiter in the resolution of issues regarding the AEGL values, and the data and basic methodology used for setting AEGLs. Following concurrence, "Final" AEGL values will be published under the auspices of the NAS.

III. Fax-On-Demand Item Number for Chemicals Listed in this Document

On behalf of the NAC/AEGL Committee, EPA is providing an opportunity for public comment on the AEGLs for the 14 chemicals identified in the following table. This table also provides the fax-on-demand item number for the chemical specific documents, which may be obtained as described in Unit ?????.

| CAS No. | Chemical name | Fax-On-Demand Item No. |
|--------------------------|-------------------------------------------------------------------------|------------------------|
| 75-78-5 | Dimethyldichlorosilane | 4867 |
| 75-79-6 | Methyltrichlorosilane | 4868 |
| 91-08-7 and 584-84-9 | 2,4- and 2,6-Toluene diisocyanate | 4873 |
| 107-11-9 | Allylamine | 4876 |
| 107-15-3 | Ethylenediamine | 4878 |
| 108-91-8 | Cyclohexylamine | 4883 |
| 123-73-9 (4170- 30-3) | <i>trans</i> -Crotonaldehyde (<i>cis/trans</i> Crotonaldehyde mixture) | 4903 |
| 624-83-9 | Methyl isocyanate | 4898 |
| 7647-01-0 | Hydrogen chloride | 4907 |
| 7803-51-2 | Phosphine | 4923 |
| 13463-39-3 | Nickel carbonyl | 4929 |
| 13463-40-6 | Iron pentacarbonyl | 4930 |

IV. Executive Summaries

The following are executive summaries from the chemical specific Technical Support Documents (which may be obtained as described in Unit I.B.1 and III.) that support the NAC/AEGL Committee's development of AEGL values for each chemical substance. This information provides the following information: A general description of each chemical, including its properties and principle uses; a summary of the rationale supporting the AEGL-1, 2, and 3 concentration levels; a summary table of the AEGL values; and a listing of key references that were used to develop the AEGL values. More extensive toxicological information and additional references for each chemical may be found in the complete Technical Support Documents. Risk managers may be interested to review the complete Technical Support Document for a chemical when deciding issues related to use of the AEGL values within various programs.

A. Dimethyldichlorosilane

1. Description.

Dimethyldichlorosilane is an alkyl-substituted silicon tetrahydride existing as a clear liquid with a sharp acrid odor that is similar to hydrogen chloride (HCl) (HSDB, 1996). Dimethyldichlorosilane is used as a high-purity derivation reagent for gas chromatography (HSDB, 1996) and as an intermediate in the production of silicones that are used as lubricating fluids, resins, and plastic copolymers (Bisesi, 1994). It reacts vigorously with water and decomposes to form HCl and other hydrolysis products (AIHA, 1996). Complete hydrolysis of one mole of dimethyldichlorosilane would yield a maximum of two moles of HCl. Hydrogen chloride is a known respiratory irritant. Data on dimethyldichlorosilane are limited to LC₅₀ studies in rats.

In the absence of appropriate chemical-specific data for dimethyldichlorosilane, a modification

of the AEGL-1 values for HCl was utilized to derive AEGL-1 values for dimethyldichlorosilane. The use of HCl as a surrogate for dimethyldichlorosilane was deemed appropriate since it is believed that it is the hydrolysis product, HCl, that is responsible for the adverse effect. The HCl AEGL-1 values were based on a no-adverse-effect-level (NOAEL) in exercising asthmatics (Stevens et al., 1992). Since two moles of HCl are produced for every mole of dimethyldichlorosilane hydrolyzed, a modifying factor of 2 was applied to the HCl AEGL-1 values to approximate AEGL-1 values for dimethyldichlorosilane. The AEGL-1 values were held constant for all specified exposure periods since mild irritant effects represent threshold effects and generally do not vary over time.

The AEGL-2 was based on corneal opacity, and grey spots on the lungs of rats exposed to 1,309 ppm dimethyldichlorosilane for 1 hr. (Dow

Corning, 1997a). This level was considered to be the threshold for impairment of escape and the onset of serious long-term effects. An uncertainty factor of 10 was applied to account for interspecies variability since data for dimethyldichlorosilane were available for only one species and an uncertainty factor of 3 was applied to account for sensitive human subpopulations since the irritant effects observed are not likely to vary greatly among individuals. A modifying factor of 3 was applied to account for the sparse database for effects as defined by AEGL-2. Thus, the total uncertainty/modifying factor is 100. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases

may be described by $C^n \times t = k$, where the exponent, n , ranges from 0.8 to 3.5 (Ten Berge et al., 1986). Much of the acute toxicity of dimethyldichlorosilane appears to be due to HCl and the value of n reported for HCl is 1 (Ten Berge et al., 1986). Therefore, the exponent $n = 1$ was used for scaling of the AEGL values for dimethyldichlorosilane across time.

The AEGL-3 was based on the calculated LC_{01} of 1,590 ppm in rats exposed to dimethyldichlorosilane for 1 hr. (Dow Corning, 1997a). An uncertainty factor of 10 was applied to account for interspecies variability since data for dimethyldichlorosilane were available for only one species and an uncertainty factor of 3 was applied to account for sensitive human

subpopulations since the irritant effects observed are not likely to vary greatly among individuals. Thus, the total uncertainty factor is 30. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n , ranges from 0.8 to 3.5 (Ten Berge et al., 1986). Much of the acute toxicity of dimethyldichlorosilane appears to be due to HCl, the dimethyldichlorosilane hydrolysis product, and the value of n for HCl is 1 (Ten Berge et al., 1986). Therefore, the exponent $n = 1$ was used for scaling of the AEGL values for dimethyldichlorosilane across time.

The calculated values are listed in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR DIMETHYLDICHLOROSILANE [PPM (MG/M³)]

| Classification | 10 mins. | 30 mins. | 1 hr. | 4 hrs. | 8 hrs. | Endpoint (Reference) |
|------------------------|------------|------------|------------|------------|------------|-------------------------------------------------------------------|
| AEGL-1 (Non disabling) | 0.90 (4.8) | 0.90 (4.8) | 0.90 (4.8) | 0.90 (4.8) | 0.90 (4.8) | Modification of HCl AEGL-1 values (USEPA, 1997) |
| AEGL-2 (Disabling) | 78 (410) | 26 (140) | 13 (69) | 3.3 (17) | 1.6 (8.5) | Corneal opacity, gray spots on lungs in rats (Dow Corning, 1997a) |
| AEGL-3 (Lethality) | 320 (1700) | 110 (560) | 53 (280) | 13 (69) | 6.6 (35) | 1 hr. LC_{01} in rats (Dow Corning, 1997a) |

2. *References*—i. AIHA (American Industrial Hygiene Association). 1996. Emergency Response Planning Guidelines. Dimethyldichlorosilane. AIHA, Fairfax, VA.

ii. Bisesi, M.S. 1994. Organic Silicon Esters. *Patty's Industrial Hygiene and Toxicology*. Fourth Ed. Vol. II, Part D. G.D. Clayton and F.E. Clayton, Eds. pp. 3096–3101.

iii. Dow Corning. 1997a. An acute whole body inhalation toxicity study of dimethyldichlorosilane in Fischer 344 rats. Report No. 1997-10000-43381. Study No. 8487. *Dow Corning Corporation. Health and Environmental Sciences*. Midland, MI.

iv. HSDB (Hazardous Substances Data Bank). 1996. Dimethyldichlorosilane. Retrieved online 7-22-96.

v. Stevens, B., Koenig, J.Q., Rebolledo, V., Hanley, Q.S., and Covert, D.S. 1992. Respiratory effects from the inhalation of hydrogen chloride in young adult asthmatics. *Journal of Occupational Medicine*. 34:923–929.

vi. Ten Berge, W.F., Zwart, A., and Appleman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *Journal of Hazardous Materials*. 13:301–309.

vii. USEPA (United States Environmental Protection Agency). 1997. Acute exposure guideline levels (AEGLs) for hydrogen chloride (NAC/PRO Draft 3:7/97).

B. Methyltrichlorosilane

1. *Description*. Methyltrichlorosilane is an alkyl-substituted silicon tetrahydride existing as a clear liquid with a sharp acrid odor that is similar to HCl (HSDB, 1997).

Methyltrichlorosilane is used as an intermediate in the production of silicones that are used as lubricating fluids, resins, and plastic copolymers (Bisesi, 1994). It reacts vigorously with water and may decompose to form three moles of HCl for every mole of methyltrichlorosilane (AIHA, 1996). Hydrogen chloride is a known respiratory irritant. Data on methyltrichlorosilane are limited to 1-hr. and 4-hr. LC_{50} studies in rats.

In the absence of relevant chemical-specific data for methyltrichlorosilane, AEGL a modification of the AEGL-1 values for HCl was utilized to derive AEGL-1 values for methyltrichlorosilane. The use of HCl as a surrogate for methyltrichlorosilane was deemed appropriate since it is believed that it is the hydrolysis product, HCl, that is responsible for the adverse effect. The HCl AEGL-1 values were based on a NOAEL in exercising asthmatics (Stevens et al., 1992). Since three moles of HCl are produced for every mole of methyltrichlorosilane hydrolyzed, a modifying factor of 3 was applied to the HCl AEGL-1 values to approximate AEGL-1 values for

methyltrichlorosilane. The AEGL-1 values were held constant for all specified exposure periods since mild irritant effects represent threshold effects and generally do not vary over time.

The AEGL-2 was based on ocular opacity, clear fluid around the eyes, nose, and mouth, nasal staining, and hunched posture observed in rats exposed to 622 ppm methyltrichlorosilane for 1 hr. (Dow Corning, 1997a). This level was considered to be the threshold for impairment of escape and the onset of serious long-term effects. An uncertainty factor of 10 was applied to these data to account for interspecies variability since data for methyltrichlorosilane were available for only one species and an uncertainty factor of 3 was applied to account for sensitive human subpopulations since the irritant effects observed are not likely to vary greatly among individuals. A modifying factor of 3 was applied to account for the sparse database for effects as defined by AEGL-2. Thus, the total uncertainty/modifying factor is 100. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n , ranges from 0.8 to 3.5 (Ten Berge et al., 1986). Much of the acute toxicity of methyltrichlorosilane appears to be due to HCl and the value

of n reported for HCl is 1 (Ten Berge et al., 1986). Therefore, the exponent $n = 1$ was used for scaling of the AEGL values for methyltrichlorosilane across time.

The AEGL-3 was based on the calculated LC₀₁ of 844 ppm in rats exposed to methyltrichlorosilane for 1 hr. (Dow Corning, 1997a). An uncertainty factor of 10 was applied to account for interspecies variability since

data were available for only one species and an uncertainty factor of 3 was applied to account for sensitive human subpopulations since the irritant effects observed are not likely to vary greatly among individuals. Thus, the total uncertainty/modifying factor is 30. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where

the exponent, n , ranges from 0.8 to 3.5 (Ten Berge et al., 1986). Much of the acute toxicity of methyltrichlorosilane appears to be due to HCl and the value of n reported for HCl is 1 (Ten Berge et al., 1986). Therefore, the exponent $n = 1$ was used for scaling of the AEGL values for methyltrichlorosilane across time.

The calculated values are listed in the following table.

PROPOSED AEGL VALUES FOR METHYLTRICHLOROSILANE [PPM (MG/M³)]

| Classification | 10 mins. | 30 mins. | 1 hr. | 4 hrs. | 8 hrs. | Endpoint (Reference) |
|-----------------------|------------|------------|------------|------------|------------|-----------------------------------------------------------------------------|
| AEGL-1 (Nondisabling) | 0.60 (3.7) | 0.60 (3.7) | 0.60 (3.7) | 0.60 (3.7) | 0.60 (3.7) | Modification of HCl AEGL-1 values (USEPA, 1997) |
| AEGL-2 (Disabling) | 37 (230) | 12 (73) | 6.2 (38) | 1.6 (9.8) | 0.78 (4.8) | Ocular opacity, irritation and hunched posture in rats (Dow Corning, 1997a) |
| AEGL-3 (Lethality) | 170 (1000) | 56 (340) | 28 (170) | 7.0 (43) | 3.5 (21) | 1 hr. LC ₀₁ in rats (Dow Corning, 1997a) |

2. References—i. AIHA. 1996.

Emergency Response Planning Guidelines. Methyltrichlorosilane. AIHA, Fairfax, VA,

ii. Bisesi, M.S. 1994. Organic Silicon Esters. *Patty's Industrial Hygiene and Toxicology*. Fourth Ed. Vol II, Part D. G.D. Clayton and F.E. Clayton, Eds. pp. 3096–3101.

iii. Dow Corning. 1997a. An acute whole body inhalation toxicity study of methyltrichlorosilane in Fischer 344 rats. Report No. 1997-10000-43537. Study No. 8602. Dow Corning Corporation. *Health and Environmental Sciences*. Midland, MI.

iv. HSDB. 1997. Methyltrichlorosilane. Retrieved online 10-10-97.

v. Stevens, B., Koenig, J.Q., Rebollo, V., Hanley, Q.S., Covert, D.S. 1992. Respiratory effects from the inhalation of hydrogen chloride in young adult asthmatics. *Journal of Occupational Medicine*. 34:923–929.

vi. Ten Berge, W.F. et al. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *Journal of Hazardous Materials*. 13:301–309.

vii. USEPA. 1997. Acute exposure guideline levels (AEGLs) for hydrogen chloride (NAC/PRO Draft 3:7/97).

C. and D. 2,4- and 2,6-Toluene Diisocyanate (TDI)

1. *Description*. Toluene diisocyanate (TDI) is among a group of chemicals, the isocyanates, that are highly reactive compounds containing an -NCO group. Toluene diisocyanate exists as both the 2,4- and 2,6- isomers which are available commercially usually in ratios of 65:35 or 80:20 (Karol, 1986; WHO, 1987). Toluene diisocyanate is used extensively in the manufacture of

polyurethane foam products as well as paints, varnishes, elastomers, and coatings (WHO, 1987).

Toxicological effects from inhaled TDI consist of irritation and sensitization of the respiratory tract. Sensitization may occur from either repeated exposure over a relatively long period of time (i.e., years), or, it may consist of an induction phase precipitated by a relatively high concentration followed by a challenge phase in which sensitized individuals react to a low concentration of TDI. Because repeated exposures are required for sensitization, only irritation effects were considered in establishing AEGL values.

Human data were available for derivation of AEGL-1 and -2. Asthmatics were exposed to 0.01 ppm (0.071 mg/m³) TDI for 1 hr., then after a rest of 45 mins., to 0.02 ppm (0.142 mg/m³) TDI for 1 hr. Controls were exposed to 0.02 ppm (0.142 mg/m³) TDI for 2 hrs. (Baur, 1985). Although no statistically significant differences in lung function parameters were observed among asthmatics during or after exposure, non-pathological bronchial obstruction was indicated in several individuals. In the control group, there was a significant increase in airway resistance immediately and 30 mins. after the beginning of exposure but none of the subjects developed bronchial obstruction. Both groups reported symptoms of eye and throat irritation, cough, chest tightness, rhinitis, dyspnea, and/or headache but time to onset of symptoms was not given. There was also no indication whether the effects were worse in asthmatics with 0.01 or 0.02 ppm. Therefore, the concentration of 0.02 ppm (0.142 mg/m³) was chosen as the basis for the 10-mins., 30-mins., and 1-hr. AEGL-1

values and the concentration of 0.01 ppm (0.071 mg/m³) was chosen as the 4- and 8-hr. AEGL-1 values.

Extrapolations were not performed.

Derivation of AEGL-2 was based on human data. Exposure of volunteers to 0.5 ppm (3.56 mg/m³) for 30 mins. resulted in severe eye and throat irritation and lacrimation (Henschler et al., 1962). A higher-exposure concentration was intolerable. Extrapolations were made using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (Ten Berge et al., 1986). In the absence of an empirically derived, chemical-specific exponent, to obtain conservative and protective AEGL-2 values, scaling was performed using $n = 3$ for extrapolating to the 10-min. time point and $n = 1$ for the 1- and 4-hr. time points. The 4-hr. value is also proposed for the 8-hr. value since extrapolation to 8 hrs. resulted in a concentration similar to that shown to be tolerated for >7 hrs. with only mild effects. An uncertainty factor of 3 was applied to account for sensitive individuals because the mechanism of action of an irritant gas is not expected to differ among individuals.

No human data were available for derivation of AEGL-3 values. Reports of human fatalities occurred under unusual circumstances and exposure concentrations were not measured. Deaths were attributed to chemical pneumonitis. Therefore, animal data were used to derive AEGL-3 values. Based on LC₅₀ values, the mouse is the most sensitive species to the effects of TDI. The 4-hr. mouse LC₅₀ of 9.7 ppm (69.1 mg/m³) (Duncan et al., 1962) was divided by 3 to estimate a threshold of lethality. This estimated 4-hr. lethality threshold was used to extrapolate to the 30-min. and 1- and 8-hr. AEGL-3 time

points. Values were scaled using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (Ten Berge et al., 1986). In the absence of an empirically derived, chemical-specific exponent, to obtain conservative and protective AEGL-2 values, scaling was performed using $n = 3$ for extrapolating to the 30-min. and 1-hr. time points and $n = 1$ for the 8-hr. time point. A total uncertainty factor of 10 was applied which includes 3 to account for sensitive individuals and 3 for interspecies extrapolation (the

mechanism of action of an irritant gas is not expected to vary greatly between or among species). The 10-min. values were not extrapolated from 4 hrs. because the NAC/AEGL Committee determined that extrapolating from greater than or equal to 4 hrs. to 10 mins. is associated with unacceptably large inherent uncertainty, and the 30-min. values were adopted for 10 min. to be protective of human health. Therefore, the 10-min. AEGL-3 value was flatlined from the 30-min. value.

The NAC/AEGL Committee recognizes that individuals pre-sensitized to TDI may exist in the general population, but that this rate of sensitization cannot be predicted. If the rate of sensitization to TDI in the general population were quantifiable, the NAC/AEGL Committee might have considered lower values for AEGL-3. At the proposed AEGL-3 levels, there may be individuals who have a strong reaction to TDI and these individuals may not be protected.

SUMMARY OF PROPOSED AEGL VALUES FOR 2,4-/2,6-TOLUENE DIISOCYANATE [PPM (MG/M³)]

| Classification | 10 mins. | 30 mins. | 1 hr. | 4 hrs. | 8 hrs. | Endpoint (Reference) |
|-----------------------|-----------------|-----------------|-----------------|-----------------|-----------------|------------------------------------------------------------------------|
| AEGL-1 (Nondisabling) | 0.020 (0.14) | 0.020 (0.14) | 0.020 (0.14) | 0.010 (0.07) | 0.010 (0.07) | Chest tightness, eye and throat irritation (Baur, 1985) |
| AEGL-2 (Disabling) | 0.24 (1.71) | 0.17 (1.21) | 0.083 (0.59) | 0.021 (0.15) | 0.021 (0.15) | Severe eye and throat irritation, lacrimation (Henschler et al., 1962) |
| AEGL-3 (Lethal) | 0.65 (4.6) | 0.65 (4.6) | 0.51 (3.6) | 0.32 (2.3) | 0.16 (0.93) | 4-hrs. LC ₅₀ in the mouse (Duncan et al., 1962) |

2. References—i. Baur, X. 1985.

Isocyanate hypersensitivity. Final Report to the International Isocyanate Institute. III File No. 10349; III Project: E-AB-19.

ii. Duncan, B., Scheel, L.D., Fairchild, E.J., Killens, R., and Graham, S. 1962. Toluene diisocyanate inhalation toxicity: Pathology and mortality. *American Industry Hygiene Association Journal*. 23:447-456.

iii. Henschler, D., Assman, W., and Meyer, K. O. 1962. On the Toxicology of Toluenediisocyanate [in German]. *Archiv fur Toxikologie* 19:364-387.

iv. Karol, M.H. 1986. Respiratory effects of inhaled isocyanates. *CRC Critical Reviews in Toxicology*. Vol. 16. CRC Press.

v. Ten Berge, W.F., Zwart, A., and Appelman, L. M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *Journal of Hazardous Materials*. 13:301-309.

vi. WHO (World Health Organization). 1987. Toluene diisocyanates. *Environmental Health Criteria* 75. WHO, Geneva. pp.72.

E. Allylamine

1. *Description*. Allylamine is a colorless or yellowish volatile liquid with a very sharp ammonia-like odor that is irritating to mucous membranes. It is highly flammable and moderately reactive with oxidizing materials. Industrially, it is used in the vulcanization of rubber and in the synthesis of pharmaceuticals. In addition to being a severe respiratory, eye, and skin irritant, allylamine is a

cardiovascular toxin when administered at high doses orally, by injection or by inhalation. Allylamine cardiotoxicity is proposed to be related to its metabolism to acrolein and hydrogen peroxide. Allylamine acute inhalation toxicity has been studied in rats and mice; the response in human volunteers briefly exposed to irritating levels has been reported.

AEGL-1 values were based on an occupational study in which exposure to 0.2 ppm allylamine for 3-4 hrs. a day was not associated with worker detection or complaints, but exposure to higher but undefined concentrations caused mucous membrane irritation (Shell Oil Co., 1992). The same AEGL-1 value is proposed for 10 mins. to 8 hrs. (i.e., "flat-line") because 0.2 ppm is expected to produce no or mild irritation, which does not generally vary greatly with time. No uncertainty factors were applied because 0.2 ppm was a no-effect-level (NOEL) for mucous membrane irritation in humans exposed repeatedly.

The AEGL-2 was based on a rat study in which exposure to 60 ppm for 14 hrs. caused heart lesions including scattered myofibril fragments with loss of striation, perivascular edema, and cellular infiltration (Guzman et al., 1961). Extrapolation to 30, 60, 240, and 480 mins. was performed using the equation $C^n \times t = k$, where $n = 1.71$ (calculated from a linear regression of rat cardiotoxicity data of Guzman et al., 1961). The 10-min. value was not extrapolated from 16 hrs. because the NAC has determined that extrapolating from 4 hrs. to 10 mins. is associated

with unacceptably large inherent uncertainty, and the 30-min. value was adopted for 10 mins. to be protective of human health. An interspecies uncertainty factor of 10 was applied to account for the lack of acute toxicity studies and toxicokinetic and metabolism data from other species. An intraspecies uncertainty factor of 10 was applied because significant intraspecies variation occurred in the rat cardiotoxic responses in the key study, and there were no data to determine the human variability of allylamine-induced cardiotoxicity.

The AEGL-3 values were derived from a rat inhalation LC₅₀ study where exposure was for 1, 4, or 8 hrs. (Hine et al., 1960). The threshold for lethality, as represented by LC₀₁ values calculated using probit analysis, was the AEGL-3 toxicity endpoint. The 1, 4, and 8-hr. AEGL-3 values were based on their respective LC₀₁ values, and the 10- and 30-min. AEGL-3 values were extrapolated from the 1-hr. LC₀₁ using the equation $C^n \times t = k$, where $n = 0.8458$ (calculated from a linear regression of the Hine et al., 1960 data). An uncertainty factor of 30 was applied: 10 to account for interspecies variability (to account for the lack of acute toxicity studies and toxicokinetic and metabolism data from other species) and 3 for human variability (lethality, as an endpoint associated with severe pulmonary edema, is not likely to vary greatly among humans). Similar AEGL-3 values were obtained from other rat studies that used fewer animals and exposure concentrations.

SUMMARY OF PROPOSED AEGL VALUES FOR ALLYLAMINE [PPM (MG/M³)]

| Classification | 10 mins. | 30 mins. | 1 hr. | 4 hrs. | 8 hrs. | Endpoint (Reference) |
|----------------|------------|------------|------------|------------|------------|------------------------------------------------------------------|
| AEGL-1 | 0.2 (0.47) | 0.2 (0.47) | 0.2 (0.47) | 0.2 (0.47) | 0.2 (0.47) | NOAEL for human mucous membrane irritation (Shell Oil Co., 1992) |
| AEGL-2 | 4.2 (9.8) | 4.2 (9.8) | 2.8 (6.5) | 1.2 (2.8) | 0.83 (1.9) | Heart lesions in rats (Guzman et al., 1961) |
| AEGL-3 | 140 (330) | 40 (94) | 18 (42) | 3.5 (8.1) | 2.3 (5.4) | Lethality threshold in rats (Hine et al., 1960) |

2. *References*—i. Guzman, R.J., Loquvam, G.S., Kodama, J.K., and Hine, C.H. 1961. Myocarditis produced by allylamines. *Archives of Environmental Health*. 2:62–73.

ii. Hine, C.H., Kodama, J.K., Guzman, R.J., and Loquvam, G.S. 1960. The toxicity of allylamines. *Archives of Environmental Health*. 1:343–352.

iii. Shell Oil Co. 1992. Initial submission: Letter submitting enclosed information on exposure of workers to mono-allylamine, di-allylamine, and tri-allylamine. EPA/OTS Doc. #88–920002051.

iv. Ten Berge, W.F., Zwart, A., and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapors and gases. *Journal of Hazardous Materials*. 13:302–309.

F. Ethylenediamine (EDA)

1. *Description*. Ethylenediamine (EDA) is a basic, hygroscopic, flammable liquid that is an eye, mucous membrane, and respiratory irritant and a known respiratory and skin sensitizer. Occupational inhalation exposure has resulted in an asthmatic response including rhinitis, coughing, wheezing, shortness of breath, and bronchospasm. EDA is used to stabilize rubber latex, as an inhibitor in antifreeze solutions, and in the preparation of dyes, insecticides, and fungicides.

The values developed for AEGL-2 and AEGL-3 level were based on studies in which toxicity endpoints

occurred that were within the scope of the definition for that level. However, persons previously sensitized to EDA may experience more severe effects, the extent of which cannot be predicted from the available information. No data were available to determine the concentration-time relationship for EDA toxic effects. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (Ten Berge et al., 1986). To obtain conservative and protective AEGL-2 and AEGL-3 values, scaling across time was performed using $n = 3$ to extrapolate to exposure times <8 hrs., except for the 10-min. values. The NAC determined that extrapolating from 4 hrs. to 10 mins. is associated with unacceptably large inherent uncertainty, and the 30-min. values were adopted for 10 mins. to be protective of human health. AEGL-1 values were not recommended due to insufficient data.

AEGL-2 values were based on a study in which rats and guinea pigs (6/group) exposed for 8 hrs. to ≥ 484 ppm EDA (1,000 ppm nominal) had bronchiolar edema of unspecified severity and “light cloudy swelling of the kidney” but none died (Carpenter et al., 1948). An uncertainty factor of 100 was used: 10 for intraspecies variability (mechanism of toxicity and variability of the toxic response among humans is uncertain) and 10 for interspecies variability (key study tested only one EDA

concentration and reported few experimental details, not providing a clear picture of species variability). The derived AEGL-2 values are supported by a study in which rats (15/sex) exposed to 132 ppm 7 hours/day for 30 days had a slight increase in the incidence (i.e., 1/26 vs. 0/27 for controls) of unspecified “major” histopathological lesions (Pozzani and Carpenter, 1954).

The AEGL-3 values were derived from a range-finding test in which 0/6 rats died from exposure for 8 hrs. to ~1,000 ppm (2,000 ppm nominal) but 6/6 died from 8-hr. exposure to ~2,000 ppm (4,000 ppm nominal) (Smyth et al., 1951). Toxic effects (other than death) were not described; 1,000 ppm was considered to be the estimated lethality threshold. An uncertainty factor of 100 was applied: 10 for intraspecies variability (cause of death was not defined in key study and variability of the toxic response among humans cannot be predicted) and 10 for interspecies extrapolation (only one EDA concentration was tested, the cause of death was not defined in the key study, and there were no data from other species). The AEGL-3 values are supported by a study in which rats (15/sex) exposed to 225 ppm 7 hours/day for 30 days had fractional mortality (first two deaths were on exposure day 4), and most rats had cloudy swelling of the liver and kidney convoluted tubules (Pozzani and Carpenter, 1954).

SUMMARY OF AEGL VALUES FOR ETHYLENEDIAMINE [PPM (MG/M³)]

| Classification | 10 mins. | 30 min. | 1 hr. | 4 hrs. | 8 hrs. | Endpoint (Reference) |
|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-------------------------------------------------------------------|
| AEGL-1 | Not recommended | Not recommended | Not recommended | Not recommended | Not recommended | Not recommended |
| AEGL-2 | 12 (30) | 12 (30) | 9.7 (24) | 6.1 (19) | 4.8 (13) | Bronchiolar edema, kidney swelling (Carpenter et al., 1948) |
| AEGL-3 | 25 (62) | 25 (62) | 20 (49) | 13 (31) | 10 (26) | Lethality threshold; no stated toxic effects (Smyth et al., 1951) |

2. *References*—i. Carpenter, C.P., Smyth, Jr., H.F., and Shaffer, C.B. 1948. The acute toxicity of ethylene imine to small animals. *Journal of Industrial Hygiene and Toxicology*. 30:2–6.

ii. Pozzani, U.C. and Carpenter, C.P. 1954. Response of rats to repeated inhalation of ethylenediamine vapors. *AMA Archives of Industrial Hygiene and Occupational Medicine*. 9:223–226.

iii. Smyth, H.F., C.P. Carpenter, and C.S. Weil. 1951. Range-finding toxicity data: List IV. *AMA Archives of Industrial Hygiene and Occupational Medicine*. 4:119–122.

iv. Ten Berge, W.F., Zwart, A., and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapors and gases. *Journal of Hazardous Materials*. 13:302-309.

G. Cyclohexylamine

1. *Description*. Cyclohexylamine is a respiratory, eye, and skin irritant, as well as a strong base ($pK_a = 10.7$) with a fishy, amine odor that has only recently been found naturally. It is used primarily for boiler water treatment (corrosion inhibition) as well as organic synthesis of rubber and agricultural chemicals. Occupational exposures to cyclohexylamine caused headache, nausea, dizziness, vomiting, eye, nose and throat irritation, and rapid and irregular heartbeats in some individuals. Acute exposure in animals resulted in extreme mucous membrane irritation, gasping, CNS effects (tremors, clonic muscular spasms), lung hemorrhage, opaque corneas, vascular lesions, and hemolysis.

No data were available to determine the concentration-time relationship for cyclohexylamine toxicity. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (Ten Berge et al., 1986). To obtain conservative and protective AEGL-2 and AEGL-3 values, scaling across time was performed using $n = 3$

to extrapolate to shorter exposure times and $n = 1$ to extrapolate to longer exposure times for 30 min. through 8-hr. values (scaling was not performed for AEGL-1 derivation). The 10-min. values were not extrapolated from 4 hrs. because the NAC determined that extrapolating from 4 hrs. to 10 mins. is associated with unacceptably large inherent uncertainty, and the 30-min. values were adopted for 10 mins. to be protective of human health.

AEGL-1, AEGL-2, and AEGL-3 values were derived from a study in which Sprague-Dawley rats (5/sex/dose) were exposed for 4 hrs. to 54.2 ppm or 567 ppm cyclohexylamine vapor, or to a vapor/aerosol combination containing 542 ppm vapor and 612 mg/m³ aerosol (Bio/dynamics, Inc., 1990). At 54.2 ppm, rats had labored breathing, partially closed eyes, and red nasal discharge; rats exposed to the two higher doses additionally had rales, gasping, dried red facial material, tremors, weight loss, irreversible ocular lesions, and two rats exposed to the aerosol-containing atmosphere died. AEGL-1 values were obtained by dividing the lowest-observed-adverse-effect-level (LOAEL) of 54.2 ppm by 3 to estimate a NOAEL, which may be associated with mild or no respiratory and ocular irritation. An uncertainty factor of 10 was applied: 3 to account for sensitive humans and 3 for interspecies variability, because mild sensory irritation from a surface-contact,

basic irritant gas is not likely to vary greatly among humans or animals. The same AEGL value was adopted for 10 mins., 30 mins., 1, 4, and 8 hrs.; flat-lining across time was considered appropriate since mild irritant effects generally do not vary greatly over time.

AEGL-2 values were based on exposure for 4 hrs. to 54.2 ppm, at which concentration the rats had moderate respiratory effects and ocular irritation, and which was a NOAEL for irreversible ocular lesions. An uncertainty factor of 10 was used: 3 for interspecies variability and 3 for intraspecies variability (moderate respiratory and ocular irritation from a surface-contact, basic irritant gas is not likely to vary greatly among humans or animals).

The AEGL-3 values were based on exposure for 4 hrs. to 567 ppm, which caused severe respiratory effects and irreversible ocular lesions and was regarded as an estimate of the lethality threshold because 2/10 animals died at the next higher concentration tested. An uncertainty factor of 30 was applied: 3 to account for intraspecies variability (lethality response resulting from a basic irritant gas is not likely to vary greatly among humans) and 10 for extrapolation from animals to humans (significant variation was seen among species for the exposure causing lethality, and the data were insufficient to determine that rats were the most sensitive species).

SUMMARY OF PROPOSED AEGL VALUES FOR CYCLOHEXYLAMINE [PPM(MG/M³)]

| Classification | 10 mins. | 30 mins. | 1 hr. | 4 hrs. | 8 hrs. | Endpoint (Reference) |
|----------------|-----------|-----------|-----------|-----------|-----------|--------------------------------------------------------------------------------------------------------------------|
| AEGL-1 | 1.8 (7.3) | 1.8 (7.3) | 1.8 (7.3) | 1.8 (7.3) | 1.8 (7.3) | NOAEL for respiratory and ocular irritation; may cause mild or no sensory irritation (Bio/dynamics, Inc., 1990) |
| AEGL-2 | 11 (44) | 11 (44) | 8.6 (35) | 5.4 (22) | 2.7 (11) | Moderate respiratory effects, ocular irritation; NOAEL for irreversible ocular lesions (Bio/dynamics, Inc., 1990). |
| AEGL-3 | 38 (150) | 38 (150) | 30 (120) | 19 (77) | 9.4 (38) | Lethality threshold, severe respiratory effects, and irreversible ocular lesions (Bio/dynamics, Inc., 1990). |

2. *References*—i. Bio/dynamics, Inc. 1990. An acute inhalation toxicity study of C-1388 in the rat. Final Report. Project No. 89-8214. December 4, 1990.

ii. Ten Berge, W.F., Zwart, A., and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapors and gases. *Journal of Hazardous Materials*. 13:302-309.

H. and I. Cis- and Trans-Crotonaldehyde

1. *Description*. Crotonaldehyde is a colorless, flammable liquid and an extreme eye, skin, and respiratory

irritant. It causes a burning sensation in the nasal and upper respiratory tract, lacrimation, coughing, bronchoconstriction, pulmonary edema, and deep lung damage. Crotonaldehyde is used primarily for the manufacture of sorbic acid and other organic chemicals. It is found in tobacco smoke and is a combustion product of diesel engines and wood, but also occurs naturally in meat, fish, and many fruits and vegetables.

Crotonaldehyde can exist as either the *cis* or the *trans* isomer; commercial crotonaldehyde is a mixture of the two isomers consisting of >95% *trans*

isomer. Because virtually no physical or chemical data or in vivo exposure studies were located for the *cis* or *trans* isomers individually (information was for the commercial mixture), and because OSHA, NIOSH, and the ACGIH have adopted the same occupational exposure limits for both isomers, the AEGL values prepared in this report will apply to both *trans*-crotonaldehyde (123-73-9) and to the *cis/trans* mixture (4170-30-3), which contains predominantly the *trans* isomer.

AEGL-1 values were derived from a Health Hazard Evaluation conducted by NIOSH where workers exposed to about

0.56 ppm crotonaldehyde for >8 hrs. reported occasional minor eye irritation (Fannick, 1982). Exponential scaling across time was not performed because results from another study suggested that the concentration-time relationship determined from the rat LC₅₀ study of Rinehart (1967) was not appropriate for predicting human sensory irritation (i.e., irritation was much greater for shorter exposure durations than for longer exposure durations yielding comparable concentration x time (Ct) values. An uncertainty factor of 3 was applied to account for sensitive humans; a greater uncertainty factor is not needed because the endpoint of mild eye irritation is not expected to vary greatly among humans.

AEGL-2 values were based on a study in which rats exposed to 8,000 ppm-min crotonaldehyde had about a 20–40% reduction in pulmonary function (manifested as a decrease in carbon monoxide and ether uptake rates compared to pre-exposure values). The animals had proliferative lesions of the respiratory bronchioles but there was

little or no evidence of alveolar edema (Rinehart, 1967). The individual experimental concentrations and exposure times were not given, but exposure was stated to be for 5–240 mins. AEGL-2 values were calculated by dividing 8,000 ppm-min by 10, 30, 60, 240, or 480 mins. (concentration and time appeared to be equally important for toxicity). An uncertainty factor of 30 was used: 3 to account for sensitive humans (crotonaldehyde acts primarily as a surface-contact irritant and the irritation response is not expected to vary greatly among humans) and 10 for extrapolation from animals to humans (based on the lack of actual concentration and time data, and the stated variability in the animal responses, and the absence of supporting animal or human studies).

The AEGL-3 was based on a LC₅₀ study in which Wistar rats were exposed to crotonaldehyde vapor for 5 mins. to 4 hrs. (Rinehart, 1967). The 10-min., 30-min., 1-hr., and 4-hr. AEGLs were obtained using the respective LC₀₁

values (268, 138, and 26 ppm, respectively; calculated by probit analysis from mortality data). The 8-hr. AEGLs were derived from the 4-hr. LC₀₁; scaling across time was performed using the exponential relationship $C^n \times t = k$, where $n = 1.2$ was derived by Ten Berge et al. (1986) from this study LC₅₀ data. During exposure, all animals gasped and had a lowered breathing rate; those exposed to >1,000 ppm had an excitatory stage. Rats lost up to 25% of their body weight by 1–3 days post-exposure, after which time they began to recover their weight. Most rats died by 4 days after exposure and had clear or slightly blood-tinged nasal exudate; all animals that died within 1 day also had terminal convulsions. An uncertainty factor of 10 was applied: 3 to account for extrapolation of rats to humans, and 3 to account for sensitive humans. Similar or higher AEGL-3 values were obtained from LC₅₀ studies in rats, mice, and guinea pigs.

SUMMARY OF PROPOSED AEGL VALUES FOR CROTONALDEHYDE [PPM(MG/M³)]

| Classification | 10 mins. | 30 mins. | 1 hr. | 4 hrs. | 8 hrs. | Endpoint (Reference) |
|-----------------------|-------------|-------------|-------------|-------------|-------------|------------------------------------------------------------------------|
| AEGL-1 (Nondisabling) | 0.19 (0.53) | 0.19 (0.53) | 0.19 (0.53) | 0.19 (0.53) | 0.19 (0.53) | Human mild eye irritation (Fannick, 1982) |
| AEGL-2 (Disabling) | 27 (76) | 8.9 (25) | 4.4 (13) | 1.1 (3.2) | 0.56 (1.6) | Rat impaired pulmonary function, bronchiole lesions (Rinehart, 1967) |
| AEGL-3 (Lethal) | 44 (130) | 27 (76) | 14 (40) | 2.6 (7.4) | 1.5 (4.2) | Rat lethality threshold using LC ₁ values (Rinehart, 1967). |

2. *References*—i. Fannick, N. 1982. Sandoz Colors and Chemicals, East Hanover, New Jersey (Health Hazard Evaluation Report, No. HETA-81-102-1244), Cincinnati, OH. United States National Institute for Occupational Safety and Health, Hazard Evaluations and Technical Assistance Branch.

ii. Rinehart, W. 1967. The effect on rats of single exposures to crotonaldehyde vapor. *American Industrial Hygiene Association Journal*. 28:561–566.

iii. Ten Berge, W.F., Zwart, A., and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapors and gases. *Journal of Hazardous Materials*. 13:302–309.

J. Methyl Isocyanate (MIC)

1. *Description*. Methyl isocyanate (MIC) is one of the most reactive of all isocyanates and is rapidly degraded in aqueous medium (Varma and Guest, 1993). Because of its reactivity, MIC is used as an intermediate in the synthesis of N-methylcarbamate and N-methylurea insecticides and herbicides (Hartung, 1994). During the night of

December 2/3, 1984, an estimated 30 tons of MIC was released from a chemical plant in Bhopal, India, resulting in one of the worst industrial accidents in history (Karlsson et al., 1985).

Signs of severe irritation to the respiratory tract were reported for victims of the Bhopal disaster and autopsies revealed the cause of death to be pulmonary edema (Weill, 1988). Long-term pulmonary and ocular effects have been documented in survivors. The spontaneous abortion rate (Arbuckle and Sever, 1998) and the infant death rate (Varma, 1987) among women who were pregnant at the time of the release were significantly increased in the months following the disaster. Numerous animal studies corroborate the epidemiological findings in humans. A compilation of case reports in industrial workers consistently noted skin and respiratory irritation in MIC exposed workers but no definitive case of sensitization (Ketcham, 1973). The mechanism of action for the pulmonary, skin, and eye effects is irritation, but the mechanism

of action for the systemic effects is unknown.

AEGL-1 values were not derived. Although human and animal data were available for irritation levels, the irritation threshold for MIC may be above the level of concern for systemic effects such as embryo and fetal lethality.

Systemic and developmental toxicity data from rats and mice were used for derivation of AEGL-2. An increase in cardiac arrhythmias occurred in rats 4 months after a 2-hr. exposure to 3 ppm (Tepper et al., 1987). Pregnant Swiss-Webster mice were exposed to analytically monitored concentrations of 0, 2, 6, 9, and 15 ppm MIC for 3 hrs. on gestation day 8 (Varma, 1987). Placental weights and fetal body weights were significantly reduced at all concentrations. Exposures to concentrations of 9 and 15 ppm resulted in deaths of two dams in each group, a significant increase in complete litter resorption among surviving dams, and fetuses with significant reductions in the lengths of the mandible and long bones. The concentration of 2 ppm for 3 hrs. was an experimentally derived

lowest-observed effect level for decreased fetal body weights. Values scaled for the derivation of the 10- and 30-min., and 1-, 4-, and 8-hr. time points were calculated from the equation $C^n \times t = k$, where $n = 1$. The value of n was empirically derived from regression analysis of lethality data for rats. Identical AEGL-2 values are derived based on the exposures of 3 ppm for 2 hrs. and 2 ppm for 3 hrs. The experimental concentrations were reduced by a factor of 3 to estimate a threshold for effects on cardiac arrhythmias or fetal body weights. A total uncertainty factor of 30 was applied including 3 for interspecies variation because similar developmental toxicity results have been obtained in both rats and mice and 10 for intraspecies variation since the

mechanism of action for systemic effects is unknown.

The neonatal survival study with mice by Schwetz et al. (1987) was used for derivation of AEGL-3 values. Pregnant mice were exposed to 0, 1, or 3 ppm for 6 hours/day on gestation days 14–17. Dams were allowed to litter for evaluation of neonatal survival. A concentration-related increase in the number of dead fetuses at birth was observed in both exposure groups and an increase in pup mortality during lactation was observed in the 3 ppm group. No differences in pup body weights occurred during lactation between the treated and control groups. The 6-hr. exposure to 1 ppm was used to derive AEGL-3 values and is considered a NOEL for pup survival during lactation. Values scaled for the

derivation of the 10- and 30-min., and 1-, 4-, and 8-hr. time points were calculated from the equation $C^n \times t = k$, where $n = 1$. The value of n was empirically derived from regression analysis of lethality data for rats. A total uncertainty factor of 30 was applied including 3 for interspecies variation because similar developmental toxicity results have been obtained in both rats and mice and 10 for intraspecies variation since the mechanism of action for systemic effects is unknown. However, because n was derived from exposures ranging from 7.5 to 240 mins., it is felt that extrapolation from 6 hrs. to the 10-min. AEGL-3 value is valid.

The proposed values for the three AEGL classifications for the five time periods are listed in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR METHYL ISOCYANATE [PPM (MG/M³)]

| Classification | 10 mins. | 30 mins. | 1 hr. | 4 hrs. | 8 hrs. | Endpoint (Reference) |
|-----------------------|----------------|----------------|-----------------|---------------|----------------|---------------------------------------------------------------------------------------|
| AEGL-1 (Nondisabling) | NA | NA | NA | NA | NA | NA |
| AEGL-2 (Disabling) | 0.40 (0.94) | 0.13 (0.32) | 0.067 (0.16) | 0.017 (0.034) | 0.0083 (0.019) | Decreased fetal body weights (Varma, 1987); cardiac arrhythmias (Tepper et al., 1987) |
| AEGL-3 (Lethal) | 1.2 (2.8) | 0.40 (0.95) | 0.20 (0.47) | 0.050 (0.12) | 0.025 (0.059) | Decreased pup survival during lactation (Schwetz et al., 1987) |

NA: Not assigned, since AEGL-1 effects would occur at concentration levels higher than AEGL-2 levels.

2. *References*—i. Arbuckle, T.E. and Sever, L.E. . 1998. Pesticide exposures and fetal death: a review of the epidemiologic literature. *Critical Reviews in Toxicology* . 28:229–270.

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K. Hydrogen Chloride (HCl)

1. *Description*. Hydrogen chloride (HCl) is a colorless gas with a pungent suffocating odor. It is used in the manufacture of organic and inorganic chemicals, oil well acidizing, steel pickling, food processing, and processing of minerals and metals. A large amount of HCl is released from solid rocket fuel exhaust. It is an upper respiratory irritant at relatively low concentrations and may cause damage to the lower respiratory tract at higher concentrations. Hydrogen chloride is very soluble in water, and the aqueous solution is highly corrosive.

The AEGL-1 values are based on a 45 min. NOAEL in exercising adult

asthmatics (Stevens et al., 1992). No uncertainty factors were applied for inter- or intraspecies variability since the study population consisted of sensitive humans. Additionally, the same value was applied across the 10- and 30-min., and 1-, 4-, and 8-hr. exposure time points since mild irritancy is a threshold effect and generally does not vary greatly over time. Thus, prolonged exposure will not result in an enhanced effect.

The AEGL-2 for the 30-min., 1-, 4-, and 8-hr. time points was based on severe nasal or pulmonary histopathology in rats exposed to 1,300 ppm HCl for 30 mins. (Stavert et al., 1991). An uncertainty factor of 3 was applied for interspecies variability because the test species (rodents) is 2–3 times more sensitive to the effects of HCl than primates. An uncertainty factor of 3 was applied for intraspecies extrapolation since the mechanism of action is direct irritation and the subsequent effect or response is not expected to vary greatly among individuals. An additional modifying factor of 3 was applied to account for the sparse database of effects defined by AEGL-2 and since the effects observed at the concentration used to derive AEGL-2 values were somewhat severe. Thus, the total uncertainty and

modifying factor adjustment is 30-fold. It was then time-scaled to the, and 1-, 4-, and 8-hr. AEGL exposure periods using the $C^n \times t = k$ relationship, where $n = 1$ based on regression analysis of combined rat and mouse LC₅₀ data (1 min. to 100 min.) as reported by Ten Berge et al., 1986. The 10-min. AEGL-2 value was derived by dividing the mouse RD₅₀ of 309 ppm by a factor of 3 to obtain a concentration causing irritation (Barrow et al., 1977). One-third of the mouse RD₅₀ for HCl corresponds to an approximate decrease

in respiratory rate of 30%, and decreases in the range of 20 to 50% correspond to moderate irritation (ASTM, 1991).

The AEGL-3 was based on an estimated NOEL for death of one-third of a 1-hr. LC₅₀ reported for rats (Vernot et al., 1977; Wohlslagel et al., 1976). An uncertainty factor of 3 was applied for interspecies variability because the test species (rodents) is 2-3 times more sensitive to the effects of HCl than primates. An uncertainty factor of 3 was applied for intraspecies extrapolation

since the mechanism of action is direct irritation and the subsequent effect or response is not expected to vary greatly among individuals. Thus, the total uncertainty factor is 10. It was then time-scaled to the specified 10- and 30-min., and 1-, 4-, and 8-hr. AEGL exposure periods using the $C^n \times t = k$ relationship, where $n = 1$ based on regression analysis of combined rat and mouse LC₅₀ data (1 min. to 100 mins.) as reported by Ten Berge et al., 1986.

The calculated values are listed in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR HYDROGEN CHLORIDE [PPM (MG/M³)]

| Classification | 10 mins. | 30 mins. | 1 hr. | 4 hrs. | 8 hrs. | Endpoint (Reference) |
|-----------------------|-----------|-----------|-----------|-----------|-----------|---------------------------------------------------------------------------------------------------------|
| AEGL-1 (Nondisabling) | 1.8 (2.7) | 1.8 (2.7) | 1.8 (2.7) | 1.8 (2.7) | 1.8 (2.7) | NOAEL in exercising human asthmatics (Stevens et al., 1992) |
| AEGL-2 (Disabling) | 100 (160) | 43 (65) | 22 (33) | 5.4 (8.1) | 2.7 (4.1) | Mouse RD ₅₀ (Barrow et al., 1977); Histopathology in rats (Stavert et al., 1991) |
| AEGL-3 (Lethality) | 620 (940) | 210 (310) | 100 (160) | 26 (39) | 13 (19) | Estimated NOEL for death from 1-hr. rat LC ₅₀ (Wohlslagel et al., 1976; Vernot et al., 1977) |

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and alumina on rodents. *Journal of Combustion Toxicology*. 3:61–70.

L. Phosphine

1. *Description*. Phosphine is a colorless gas used as a fumigant against insects and rodents in stored grain. The pesticide is usually applied as a metal phosphide and reacts with moisture to liberate phosphine gas. Phosphine is also used in the semiconductor industry. Information concerning human exposure to phosphine is of limited use in derivation of AEGL values since exposure durations and concentrations are not precisely reported. Appropriate animal data are more abundant; however, data consistent with the definition of AEGL-1 values are not available. Therefore, due to insufficient data, AEGL-1 values were not derived.

The AEGL-2 was based on a NOEL for renal, cardiac, and liver histopathology in mice exposed to 5 ppm phosphine 6 hours/day for 4 days (Morgan et al., 1995). Values were derived assuming a single 6 hr. exposure. An uncertainty factor of 3 was applied to account for interspecies variability since lethality data from rats, mice, rabbits, and guinea pigs suggest little species variability. An uncertainty factor of 10 was applied to account for intraspecies variability since the human data suggest that children may be more sensitive than adults when exposed to presumably similar phosphine concentrations (total UF = 30). The concentration-exposure time relationship for many irritant and

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

The AEGL-3 was based on a NOEL for lethality (18 ppm phosphine) in Sprague Dawley rats exposed to phosphine for 6 hrs. (Newton, 1991). An uncertainty factor of 3 was applied to account for interspecies variability since lethality data from rats, mice, rabbits, and guinea pigs suggest little species variability. An uncertainty factor of 10 was applied to account for intraspecies variability since the human data suggest that children may be more sensitive than adults when exposed to presumably similar phosphine concentrations (total UF = 30). The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n , ranges from 0.8 to 3.5 (Ten Berge, 1986). To obtain conservative and protective AEGL values for the 30-min., 1-, 4-, and 8-hr.

time points in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points and

$n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation. The 30-min AEGL-3 value was also adopted as the 10-min. value due to the fact that reliable data are limited to durations 4

hrs., and it is considered inappropriate to extrapolate back to 10-mins.

The calculated values are listed in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR PHOSPHINE [PPM(MG/M³)]

| Classification | 10 mins. | 30 mins. | 1 hr. | 4 hrs. | 8 hrs. | Endpoint (Reference) |
|-----------------------|-------------|-------------|-------------|-------------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AEGL-1 (Nondisabling) | | | | | | Appropriate data not available |
| AEGL-2 (Disabling) | 0.38 (0.54) | 0.38 (0.54) | 0.30 (0.42) | 0.19 (0.27) | 0.13 (0.18) | NOEL for histopathology in mice exposed to 5 ppm phosphine 6 hours/day for 4 days. Values were calculated assuming a single 6 hr exposure (Morgan et al., 1995) |
| AEGL-3 (Lethality) | 1.4 (1.9) | 1.4 (1.9) | 1.1 (1.6) | 0.69 (0.97) | 0.45 (0.63) | NOEL for lethality in rats exposed to 18 ppm phosphine for 6 hrs. (Newton, 1991) |

2. *References*—i. Newton, P.E. 1991. Acute Inhalation exposures of rats to phosphine. Bio/Dynamics, Inc. East Millstone, NJ. Project No. 90-8271.

ii. Morgan, D.L., Moorman, M.P., Elwell, M.R., Wilson, R.E., Ward, S.M., Thompson, M.B., O'Connor, R.W., and Price, H.C. 1995. Inhalation toxicity of phosphine for Fischer 344 rats and B6C3F1 mice. *Inhalation Toxicology*. 7: 225-238.

iii. Ten Berge, W.F. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *Journal of Hazardous Materials*. 13:301-309.

M. Nickel Carbonyl

1. *Description*. Nickel carbonyl, formed by the reaction of carbon monoxide with metallic nickel, is used in nickel refining, in the synthesis of acrylic and methacrylic esters, and for other organic synthesis. In air, nickel carbonyl rapidly decomposes to nickel and carbon monoxide with a 50% decomposition at room temperature and total decomposition at 150-200°C.

Human data are limited to case reports, primarily of nickel workers, that affirm the extreme toxicity of the compound. However, definitive exposure terms are lacking in these reports. Significant signs and symptoms of toxicity are known to occur in the absence of recognizable odor. Human case studies have shown that a latency period of 10 occurs between initial signs of toxicity and subsequent serious effects that may progress to death. The primary target of nickel carbonyl-induced acute toxicity appears to be the lungs, although extrapulmonary involvement has also been reported. The specific mechanism of toxicity is unclear but appears to involve damage to pulmonary tissue.

Animal data are limited to lethality and developmental toxicity. Lethality values (LC₅₀) are available for rats, mice, cats, and rabbits. Thirty-minute LC₅₀

values for these species range from 33.6 to 266 ppm. These lethality data indicate notable species variability in the lethal response to inhaled nickel carbonyl; smaller species are generally more sensitive. Developmental toxicity has been demonstrated in rats and hamsters following single 30-min. (11.2-42 ppm, rats) or 15-min. (8.4 ppm, hamsters) exposures of dams during gestation.

Limited data in rats have provided equivocal evidence of pulmonary carcinogenicity following acute or long-term exposure to nickel carbonyl. Studies of respiratory tract cancer in nickel workers suggest that nickel dusts and nickel sulfides may be more relevant than nickel carbonyl. Data are unavailable for a quantitative assessment of the carcinogenic potential of nickel carbonyl in humans or animals.

Exposure-response data over multiple time periods are unavailable for nickel carbonyl and, empirical derivation of a scaling factor (n) was not possible. The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n , ranges from 0.8 to 3.5. In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation.

Neither human nor animal data are available for deriving AEGL-1 values. Both human and animal data affirm the extreme toxicity of nickel carbonyl, and human exposures indicate that signs and symptoms of toxicity may occur in the absence of detection. Therefore, AEGL-1 values are not recommended.

With the exception of teratogenicity and fetotoxicity data in rats and hamsters, neither human nor animal

data are available that identify effects consistent with AEGL-2. The developmental effects are notable (ocular malformations, fetotoxicity, and neonate lethality) and the exposures producing these effects approach those known to cause lethality in animal species. The AEGL-2 values were based upon significantly increased incidences of malformations in the offspring of Syrian hamsters which had been exposed to 8.4 ppm nickel carbonyl for 15 mins. per day on gestation days 4 or 5 (Sunderman et al., 1980). As previously noted, time scaling was accomplished by the use of linear $C^1 \times t = k$ extrapolation for 30-min., 1-hr. and 4-hr. AEGL-2 time points and exponential extrapolation $C^3 \times t = k$ for the 10-min. AEGL-2 values. A total uncertainty factor adjustment of 100 (10 for interspecies variability and 10 for intraspecies variability) was applied. The interspecies uncertainty factor adjustment is justified by the absence of human data and only limited data in animal species with which to assess species variability in the toxic responses to nickel carbonyl. The uncertainty factor for individual variability accounted for lack of data with which to identify sensitive subpopulations or to determine individual variability in the toxic responses to nickel carbonyl.

AEGL-3 values were derived based upon an estimated lethality threshold in mice (3.17 ppm) exposed to nickel carbonyl for 30 mins. (Kincaid et al., 1953). Lethality data were available for several species (rats, mice, rabbits, and cats). A total uncertainty adjustment of 10 was applied (each uncertainty factor of 3 is the approximate logarithmic mean of 10 which is 3.16; hence, $3.16 \times 3.16 = 10$). Analysis of the available data indicated that the mouse was the most sensitive species and larger species tended to be somewhat less sensitive. Therefore the uncertainty factor adjustment for interspecies variability

was limited to 3. An additional factor of 3 was applied to account for uncertainties regarding individual variability in the lethal response due to direct contact pulmonary damage by nickel carbonyl.

There are limited, equivocal data showing the development of pulmonary tumors in rats exposed chronically to nickel carbonyl and equivocal data suggestive of a tumorigenic response following a single massive exposure of

rats to nickel carbonyl. However, a quantitative cancer assessment was not feasible.

SUMMARY OF PROPOSED AEGL VALUES FOR NICKEL CARBONYL [PPM MG/M³]

| Classification | 10 mins. | 30 mins. | 1 hr. | 4 hrs. | 8 hrs. | Endpoint (Reference) |
|-----------------------|-----------------|-------------|-----------------|-------------------|--------|-----------------------------------------------------------------------------------------------------------|
| AEGL-1 (Nondisabling) | NR | NR | NR | NR | NR | Not recommended |
| AEGL-2 (Disabling) | 0.096 (0.66) | .042 (0.29) | 0.021 (0.14) | 0.0053 (0.037) | NA | Developmental toxicity in hamsters; gestational exposure (15 mins., 8.4 ppm) |
| AEGL-3 (Lethal) | 0.46 (3.2) | 0.32 (2.2) | 0.16 (1.1) | 0.040 (0.27) | NA | Estimated lethality threshold (LC ₀₁ of 3.17 ppm); mouse lethality data (Kincaid et al., 1953) |

NR: Not recommended. Numeric values for AEGL-1 are not recommended because:

1. The lack of available data,
2. An inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2, or
3. The derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

NA: Not appropriate. AEGL values for 8 hrs. were not developed due to the rapid decomposition of nickel carbonyl under ambient atmospheric conditions.

2. *References*—i. Kincaid, J.F., Strong, J.S., and Sunderman, F.W. 1953. Nickel poisoning. Experimental study of the effects of acute and subacute exposure to nickel carbonyl. *Archives of Industrial Hygiene and Occupational Medicine*. 8:48–60.

ii. Sunderman, F.W., Jr., Shen, S.K., Reid, M.C., and Alpist, P.R. 1980. Teratogenicity and embryotoxicity of nickel carbonyl in Syrian hamsters. *Teratogenicity Carcinogenicity Mutagenicity*. 1:223–233.

N. Iron Pentacarbonyl

1. *Description*. Iron pentacarbonyl is one of several iron carbonyls. It is formed by the interaction of carbon monoxide with finely divided iron. Iron pentacarbonyl is used in the manufacture of powdered iron cores for electronic components, as a catalyst and reagent in organic reactions, and as an anti-knock agent in gasoline. Iron pentacarbonyl is pyrophoric in air (–15°C flashpoint), burning to ferric oxide.

Quantitative toxicity data and odor detection data for humans are unavailable. Qualitative descriptions of the signs and symptoms of iron pentacarbonyl exposure include giddiness and headache, and occasionally dyspnea and vomiting. With the exception of dyspnea, these signs and symptoms are alleviated upon removal from exposure but fever, cyanosis, and coughing may occur at 12 to 36 hrs. after exposure. This information could not be validated and additional details were unavailable.

Animal data are limited to lethality findings in rats, mice, and rabbits. Based upon the limited data available, the rat appears to be the most sensitive species

as determined by the 30-min. LC₅₀ of 118 ppm and a 4-hr LC₅₀ of 10 ppm relative to the 30-min. LC₅₀ of 285 ppm for the mouse. A steep exposure-response relationship is suggested by data showing 50% lethality in rats following only two 6-hr exposures to 3 ppm. For mice, a 1.35-fold increase in the LC₅₀ results in near 100% mortality for the same exposure duration, suggesting a steep exposure-response relationship for this species as well. Similarly, a 2.8-fold increase in exposure concentration (86–244 ppm) results in a mortality rate in rats of 4/12 to 11/12. No reproductive/developmental toxicity, genotoxicity, or carcinogenicity data are available for iron pentacarbonyl.

Although exposure-response data for the same toxicity endpoint over multiple time periods were limited to several LC₅₀ values, these data suggested a near-linear relationship. Therefore, the value of *n* was set at unity for the exponential temporal scaling equation, Cⁿ×t=k AEGL values were developed for 10 mins., 30 mins., 1 hr., and 4 hrs. only. AEGL values were not developed for the 8-hr. time point due to the rapid decomposition of iron pentacarbonyl under ambient atmospheric conditions.

Data consistent with AEGL-1 effects were limited to labored breathing and signs of irritation in rats exposed to 5.2 ppm for 4 hrs. and no observable effects in rats exposed for 6 hours/day to 1 ppm for 28 days. However, analysis of the overall data set for iron pentacarbonyl indicated a very steep exposure-response curve with little margin between exposures producing no observable effects and those resulting in lethality. Therefore, it was the

consensus of the NAC/AEGL Committee on AEGLs to recommend no AEGL-1 values.

Limited data in rats revealed that there is only a small margin between exposures causing little or no toxicity and those causing more severe effects and death. No effect was observed following exposure of rats to 1 ppm, 6 hours/day for up to 28 days while a single exposure to 2.91 ppm for 6 hours/day caused notable signs of toxicity with a 10% mortality. The occurrence of deaths in laboratory species several days following cessation of exposure is also a factor to consider in the derivation of AEGL-2 values showed. In the absence of exposure-response data for serious and/or possibly irreversible effects, AEGL-2 value were developed by a three-fold reduction in the AEGL-3 values. This 3-fold reduction was justified by the apparently steep exposure-response relationship in rats where there appears to be about a three-fold difference between exposures that produce no lethality and those resulting in 50–100% lethality. The AEGL-2 values also reflect the application of uncertainty factors of 10 for interspecies variability and 3 for intraspecies variability as described for the development of AEGL-3 values.

Animal data consistent with AEGL-3 were limited to 30-min. LC₅₀ values for rats (118 ppm) and mice (285 ppm), a 45.5-min. LC₁₀ value for rabbits (250 ppm), and 4-hr. LC₅₀ in rats (10 ppm). In addition to a 4-hr. LC₅₀ value for rats, Biodynamics (1988) also provided 4-hr. LC₁₆ estimate of 6.99 ppm and an estimated lethality threshold (4 hrs) of 5.2 ppm for male and female rats. Data from a study by BASF (1995), however,

showed that a single 6-hr exposure to 2.91 ppm resulted in 10% (1 of 10 rats) mortality and that a second exposure resulted in 50% mortality. Remaining rats, however, survived an additional 26 6-hr. exposures. A total uncertainty factor of 30 was applied. An uncertainty factor of 10 was applied to account for interspecies variability and justified due to the absence of definitive quantitative lethality data in humans and the uncertainties regarding the mechanism

of iron pentacarbonyl-induced lethality. An additional factor of 3 was applied to account for uncertainties regarding individual variability in the toxic response to iron pentacarbonyl. The adjustment for this area of uncertainty was limited to 3 because the available data did not indicate a high level of variability among test species and because the mechanism of action for the observed toxic responses appears to be a port-of-entry effect mediated by

contact irritation and destruction of pulmonary epithelium. The AEGL values for iron pentacarbonyl are presented in the table below.

Neither quantitative nor qualitative data are available regarding the potential carcinogenicity of iron pentacarbonyl by any route of exposure. Therefore, a quantitative assessment of potential risk is not possible. Genotoxicity tests in several strains of *Salmonella typhimurium* were negative.

SUMMARY OF PROPOSED AEGL VALUES FOR IRON PENTACARBONYL [PPM (MG/M³)]

| Classification | 10 mins. | 30 mins. | 1 hr. | 4 hrs. | 8 hrs. | Endpoint (Reference) |
|-----------------------|-----------|------------|------------|--------------|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AEGL-1 (Nondisabling) | NR | NR | NR | NR | NR | Not recommended; insufficient data |
| AEGL-2 (Disabling) | 1.2 (9.6) | 0.40 (3.2) | 0.19 (1.5) | 0.050 (0.40) | NA | Based upon a three-fold reduction in the AEGL-3 values |
| AEGL-3 (Lethal) | 3.5 (28) | 1.2 (9.6) | 0.58 (4.6) | 0.15 (1.2) | NA | Estimated lethality threshold in rats (6-hr. exposure to 2.91 ppm) (BASF, 1995). n = 1; UF = 30 (10 for interspecies variability, 3 for individual variability) |

NR: Not recommended. Numeric values for AEGL-1 are not recommended because:

1. The lack of available data,
2. An inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2, or
3. The derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

NA: Not appropriate; AEGL values for 8 hr. were not developed due to the rapid decomposition of iron pentacarbonyl under ambient atmospheric conditions.

2. *References* —i. BASF (Badische Anilin & Soda Fabrik). 1995. Study on the inhalation toxicity of eisenpentacarbonyl as a vapor in rats—28 day test. BASF Department of Toxicology. Environmental Protection Agency/Office of Toxic Substances, Document #89-950000244.

ii. Biodynamics. 1988. An acute inhalation toxicity study of iron pentacarbonyl in the rat. Final Report. Environmental Protection Agency/Office of Toxic Substances, Document #88-920001300.

V. Next Steps

The NAC/AEGL Committee plans to publish "Proposed" AEGL values for five-exposure periods for other chemicals on the priority list of 85 in groups of approximately 10 to 20 chemicals in future **Federal Register** notices during the calendar year 2000.

The NAC/AEGL Committee will review and consider all public comments received on this notice, with revisions to the "Proposed" AEGL values as appropriate. The resulting AEGL values will be established as "Interim" AEGLs and will be forwarded to the NRC/NAS, for review and

comment. The "Final" AEGLs will be published under the auspices of the NRC/NAS following concurrence on the values and the scientific rationale used in their development.

List of Subjects

Environmental protection, Hazardous substances.

Dated: June 16, 2000.

Susan H. Wayland,
Acting Assistant Administrator for
Prevention, Pesticides and Toxic Substances.
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