Texas Commission on Environmental Quality (TCEQ) Response to Public Comments Received on the Proposed Development Support Document for Xylenes January 30, 2009

The public comment period for the proposed Development Support Document (DSD) for the xylenes ended on January 30, 2009. Total Petrochemicals, the Texas Chemical Council combined with the American Chemistry Council, and ExxonMobil Refining & Supply Co. submitted comments. The Toxicology Division (TD) of the TCEQ appreciates the effort put forth to provide technical comments on the proposed DSD for the xylenes. The goal of the TD and TCEQ is to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD), and evaluation of these comments furthers that goal. A summary of the Total Petrochemicals, the Texas Chemical Council combined with the American Chemistry Council, and the ExxonMobil comments are provided below, followed by TCEQ responses. TCEQ indicates what changes, if any, were made to the DSD in response to the comments. The full comments from Total Petrochemicals, the Texas Chemical Council combined with the American Chemistry Council, and ExxonMobil are in Appendices 1, 2, and 3, respectively.

Total Petrochemicals (TPI)
Comments Regarding the TCEQ DSD for Xylene ESL Values

1.0 TPI believes that the total uncertainty factor used to develop both the acute Reference Value (ReV) and the chronic ReV for xylenes in the DSD is too high.

Conversely, the hazard quotients used to derive ESLs from the ReVs are too low. Taken together, these figures produce acute and chronic ESLs that TPI believes are too conservative.

TCEQ Response: The DSD was not revised based on the above comment. Applying a lower uncertainty factor may be appropriate for "emergency-type" guidelines such as Acute Exposure Guideline Levels (AEGLs), which are Public Emergency Response Guidelines intended for emergency exposure periods ranging from 10 minutes to 8 hours. It is important to note that, "Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asyptomatic, non-sensory effects".

Conversely, "ESLs are chemical-specific air concentrations set to protect human health and welfare. Exposure to an air concentration at or below the ESL is not likely to cause an adverse health effect in the general public, including sensitive subgroups such as children, the elderly, pregnant women, and people with preexisting health conditions." Furthermore, ESLs are meant to be protective of intermittent, acute exposure or repeated chemical exposure over the course of a lifetime. Therefore, applying a higher uncertainty factor is appropriate and considered more protective for developing xylenes' short and long-term ESLs.

Regarding the Hazard Quotient, same response as provided to the Texas Chemical Council combined with the American Chemistry Council Comment 1.0.

2.0 The odor-based ESL for xylenes should be reevaluated because the Commission has not developed a scientifically sound basis for establishing a criterion for xylene's odor properties.

The DSD fails to demonstrate an adverse effect on public health from odor properties. The lack of correlation between odor and health risks is well understood and has been summarized by the US EPA in its 1992 publication *Reference Guide to Odor Thresholds for Hazardous Air Pollutants Listed in the Clean Air Act Amendments of 1990.*

TCEQ Response: The DSD was not revised based on the above comment. Development of xylene's proposed odor-based ESL is based on directives from Sections 382.0518 and 382.085 of the Texas Health and Safety Code (THSC) that specifically mandate the Texas Commission on Environmental Quality (TCEQ) to "conduct air permit reviews of all new and modified facilities to ensure that the operation of a proposed facility will not cause or contribute to a condition of air pollution." In addition, Section 382.003 of the THSC defines air pollution as "air contaminants that: (a) are or may tend to be injurious to or adversely affect human health or welfare, animal life, vegetation, or property; or (b) interfere with the normal use and enjoyment of animal life, vegetation, or property." Furthermore, according to Section 382.002 of the THSC, the powers of the Commission, including the issuance of air permits, are used for "controlling or abating air pollution and emissions of air contaminants, consistent with the protection of public health, general welfare, and physical property, including the esthetic enjoyment of air resources by the public and the maintenance of adequate visibility." In response to the THSC mandate, TCEQ has historically considered odor, and its potential to create a condition of odor nuisance, in the development of short-term ESLs (< 1 hour).

Regarding the scientific basis for xylene's odor-based ESL comment: Xylene's proposed odor-based ESL adheres to TCEQ's 2006 regulatory guidance document, *Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors* (RG-442), that underwent external scientific peer review and two rounds of public comment. Furthermore, development of xylene's odor-based ESL included a comprehensive literature search, consideration of all available xylene odor studies, and selection of the lowest 50% odor detection threshold among the studies that meet the American Industrial Hygiene Association and USEPA odor evaluation criteria.

Please note that ESLs, including odor-based ESLs, are intended to be guidelines and not strict standards. For example, when applying the odor-based ESL in an air permit application review, consideration of the nature of the odor, the surrounding land use, the frequency of odor-based ESL exceedance, and the odor complaint history at the site, all play a role in allowing off-site concentrations that exceed the odor-based ESL. Xylene is odorous at a concentration much lower than at a concentration which could cause an adverse health effect. Because of this, if the permit applicant's predicted or monitored xylene concentrations are allowable from an odor perspective, they are also allowable from a health perspective as well.

Although TCEQ's TD recognizes that the body of data and information surrounding available odor threshold values are not very robust for some chemicals, xylene's odor-based ESL is considered a useful tool in the air permit review process, and addresses the Commission's mandate to protect public welfare and public enjoyment of air resources.

Texas Chemical Council combined with the American Chemistry Council Comments Regarding the TCEQ DSD for Xylene ESL Values

1.0 The Panel Urges TCEQ to Consider a Hazard Quotient (HQ) of 1.0 in Developing an Acute ESL for Xylenes

TCEQ Response: The DSD was not revised based on the above comment. In order to adequately consider the potential for cumulative and aggregate exposures, TCEQ's TD believes that it is prudent to apply an HQ of less than 1 for chemical effects known or assumed to be nonlinear, which is consistent with Section 5.130 of Subchapter D of the Texas Water Code which states: "The Commission shall develop and implement policies, by specific environmental media, to protect the public from cumulative risk in areas of concentrated operations".

Furthermore, applying an HQ of less than 1, or as in this case 0.3, is consistent with Section 1.4 of TCEQ's Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors, October 2006, RG-442, which states: "In consideration of cumulative and aggregate exposure, the Toxicology Section (TS) uses an HQ of 0.3 to calculate short-term and long-term ESLs for chemicals with nonlinear dose-response assessment".

2.0 TCEQ to Reconsider the Appropriateness of Using 50% Odor Detection Thresholds in the Development of ESLs

TCEQ Response: The DSD was not revised based on the above comment. Same response as provided to TPI Comment 2.0. In addition, the Ruth (1986) and Amoore and Hautala (1983) studies which were cited as support by the Texas Chemical Council and American Chemical Council for not developing odor-based ESLs are not studies that meet the American Industrial Hygiene Association and USEPA odor evaluation criteria.

3.0 The Panel has concerns with TCEQ's Selection of the Ernstgard (2002) Study As the Key Study For Developing A Health-Based Acute ReV and ESL For Xylenes

TCEQ Response: The DSD was not revised based on the above comment. The Ernstgard Study (2002) is well conducted and reported, and is peer reviewed. Furthermore, the key study selection follows guidance in the Select Key Studies Section 2.3.3 of TCEQ's Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors, October 2006, RG-442. In addition, ATSDR (2007) also chose this study to develop an acute toxicity value.

Regarding the comment for the "use of an intraspecies variability uncertainty factor of less than 10", see the response as provided to TPI Comment 1.0.

4.0 The Panel Urges TCEQ to Consider A Hazard Quotient of 1.0 In Developing A Health-Based Chronic ESL For Xylenes

TCEQ Response: The DSD was not revised based on the above comment. Same response as provided in TPI Comment 1.0.

ExxonMobil Refining & Supply Company
Comment Regarding the TCEQ Development Support Document for Xylene ESL Values

1.0 ExxonMobil Urges TCEQ to Consider Using a 3-fold Intra-species Uncertainty Factor to Account for Human Variability

ExxonMobil requests that TCEQ consider using a 3-fold intra-species uncertainty factor rather than a 10-fold factor to account for human variability for respiratory irritation. The 10-fold factor is used to derive both the acute and chronic ESL. To support this recommendation, we reference the Standard Operation Procedures used for Developing Acute Exposure Guideline Levels (AGELs) for Hazardous Chemicals, published by the National Research Council.

TCEQ Response: Please note that AGELs are **Public Emergency Response Guidelines**, and are applied to emergency exposure periods ranging from 10 minutes to 8 hours. Furthermore, "Airborne concentrations below the AGEL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asyptomatic, non-sensory effects". Therefore, applying a 3-fold uncertainty factor for human variability may be appropriate for "emergency-type" guidelines.

However, "ESLs are chemical-specific air concentrations set to protect human health and welfare. Exposure to an air concentration at or below the ESL is not likely to cause an adverse health effect in the general public, including sensitive subgroups such as children, the elderly, pregnant women, and people with preexisting health conditions." ESLs are meant to be protective of repeated chemical exposure over the course of a lifetime. Thus, applying a 10-fold uncertainty factor for human variability is considered appropriate for developing xylenes' short and long-term ESLs.

Appendix 1

Total Petrochemicals
Comments Regarding the Xylenes Effects Screening Level DSD

TOTAL PETROCHEMICALS

Via Electronic Mail: tox@tceq.state.tx.us

January 26, 2009

Toxicology Section, MC 168
Texas Commission on Environmental Quality
P.O. Box 13087
Austin, TX 78711-3087

RE: Comments Regarding the Xylenes Effects Screening Level Development Support Document

Dear Sir or Madam:

Total Petrochemicals, USA, Inc. (TPI) submits these comments in response to the Texas Commission on Environmental Quality's (Commission) request for public comment on its Effects Screening Level (ESL) Development Support Document (DSD) concerning xylenes.

TPI believes that the total uncertainty factor used to develop both the acute Reference Value (ReV) and the chronic ReV for xylenes in the DSD is too high. Conversely, the hazard quotients used to derive ESL's from the ReV's are too low. Taken together, these figures produce acute and chronic ESL's that TPI believes are too conservative.

The odor-based ESL for xylenes should be reevaluated because the Commission has not developed a scientifically sound basis for establishing a criterion for xylene's odor properties. The DSD fails to demonstrate an adverse effect on public health from xylene odors. The lack of correlation between odor and health risks is well understood and has been summarized by the US EPA in its 1992 publication *Reference Guide to Odor Thresholds for Hazardous Air Pollutants Listed in the Clean Air Act Amendments of 1990*.

TPI appreciates the opportunity to participate in the development of ESL's and the TCEQ's efforts to protect public health. If you have any questions regarding these comments, please contact me at 713-483-5056.

Sincerely,

Jason D. Frederick
Senior Environmental Coordinator

TOTAL PETROCHEMICALS USA, INC.
P.O. Box 674411, Houston, Texas, 77267-4411
1201 Louisiana Street, Suite 1800, Houston, Texas 77002
Tel: 713.483.5000

Appendix 2

Texas Chemical Council combined with the American Chemistry Council Comments Regarding the Xylenes Effects Screening Level DSD

TCEQ Toxicology Section:

The Texas Chemical Council and the American Chemistry Council's Toluene and Xylenes Panel appreciate the opportunity to comment in response to the Texas Commission on Environmental Quality's (TCEQ) request for public comments on its Effects Screening Level (ESL) Development Support Document concerning xylenes. We understand the importance of ESLs in providing TCEQ with guidance to protect human health and welfare.

Please let me know if you have any questions or require additional information.

Sincerely,

Mike McMullen

Director of Regulatory Affairs

Texas Chemical Council

1402 Nueces Street

Austin, TX 78701

512/646-6404

MMcMullen@txchemcouncil.org

TEXAS CHEMICAL COUNCIL

1402 Nueces Street • Austin, Texas 78701-1586 • (512) 646-6400 • Fax (512) 646-6420

January 26, 2009

Toxicology Section, MC 168
Texas Commission on Environmental Quality
P.O. Box 13087
Austin, TX 78711-3087

Re: Comments Regarding the Xylenes Effects Screening Level Development Support Document

Dear Sir or Madam:

On behalf of the Texas Chemical Council and the American Chemistry Council's Toluene and Xylenes Panel[1] (The Panel), these comments are submitted in response to the Texas Commission on Environmental Quality's (TCEQ) request for public comments on its Effects Screening Level (ESL) Development Support Document concerning xylenes.

The Panel understands the importance of ESLs in providing TCEQ with guidance to protect human health and welfare. The Panel considers the Draft Development Support Document (DSD) for xylenes to be scientifically sound on several issues and demonstrates the diligence of TCEQ's effort to develop supportable values. However, TCEQ was overly conservative on a few key scientific issues which affect the acute ReV and ESLs for xylenes. The Panel offers the comments below for TCEQ's consideration.

1. **The Panel Urges TCEQ to Consider A Hazard Quotient of 1.0 In Developing An Acute ESL For Xylenes**

The Panel has strong reservations concerning the use of a hazard quotient (HQ) of less than 1.0 for non-carcinogenic effects for any purpose, including consideration of cumulative and aggregate exposures. In deriving the acute ReV for xylenes, TCEQ incorporates an uncertainty factor of 30. Health protective assumptions have been considered and built into the derivation of the acute ReV for xylenes, such that the available evidence does not support the need for additional factors for health protection. Based on available data, a short-term ESL of 1700 ppb should be appropriate to address any potential acute effects of short-term xylenes exposure.

[1] The T&X panel members are Sunoco, Inc., CITGO Petroleum Corporation, ExxonMobil Chemical Company, Chevron Phillips Chemical Company LP, Total Petrochemicals USA, Inc., Shell Chemical LP, Flint Hills Resources, Marathon Petroleum Company LLC and BP.

2. TCEQ to Reconsider the Appropriateness of Using 50% Odor Detection Thresholds in the Development of ESLs

The Panel believes it is inappropriate to use odor thresholds in the development of ESLs. Published odor thresholds for a given material can vary dramatically. This variability has been attributed to a number of factors including but not limited to reliance on different test methods, trained versus untrained test subjects, purity of the test sample, differences in test environment conditions and human variability. The test methods and conditions are often not reported in detail making it difficult to choose the most reliable value. In the case of xylenes, TCEQ provides two references (Nagata 2003 o-, m-, p-xylene = 380, 41, and 58 ppb, respectively and Hellman1974 mixed xylenes 80 ppb) for 50% odor threshold values. The report by Nagata does not appear to be from a peer reviewed publication. It should also be noted that while the report by Nagata was released in 2003, the actual studies were carried out from 1976-1988. Furthermore, Ruth (1986) reported a range of odor thresholds for xylene from 348 ppb to 174000 ppb while Amoore and Hautala (1983) reported an odor threshold value of 1100 ppb for m-xylene. The differences in reported values clearly demonstrate the lack of precision involved in the estimation of odor threshold and thus the lack of reliability for using reported odor threshold values in the calculation of ESLs. Simply relying on the lowest values without further justification may result in an unnecessarily low and overly conservative ESL value. TCEQ should not rely on odor thresholds in the development of ESLs for xylenes. However, if TCEQ continues to rely on odor thresholds as a basis for ESLs TCEQ must indicate that these values are not based on anticipated health effects but rather simply represent a very conservative estimate of an odor recognition level.

3. The Panel has concerns with TCEQ's Selection of the Ernstgard (2002) Study As the Key Study For Developing A Health-Based Acute ReV and ESL For Xylenes

The study by Ernstgard et al. appears to be well reported and peer reviewed. The Panel believes the results are of limited value in deriving an ESL. The only positive findings in this study were based on subjective results from a questionnaire. There were no significant changes in any of the analytical or "measured" values with the exception of changes in pulmonary function values in females and these effects were even found to change throughout the day in control subjects. The authors of this study referred to these findings as "doubtful". The primary problem in relying on results from this questionnaire is that the test subjects were not "blinded" to exposure. As a result, the subjects could easily detect the odor of the test material and therefore could differentiate between control and exposed tests.

The Panel believes that if the TCEQ continues to rely on the Ernstgard study TCEQ should consider an UF of less than 10 for intraspecies variability given that the POD was based solely on subjective findings in non-blinded test subjects, that the effects

were minimal in nature and that other references cited by TCEQ indicate NOAEL of greater than or equal to 100 ppm.

4. **The Panel Urges TCEQ to Consider A Hazard Quotient of 1.0 In Developing A Health-Based Chronic ESL For Xylenes**

As stated previously in these comments, the Panel continues to have strong reservations concerning the use of a hazard quotient (HQ) of less than 1.0 for non-carcinogenic effects for any purpose, including consideration of cumulative and aggregate exposures. In deriving the chronic ReV for xylenes, TCEQ uses an uncertainty factor of 100. Health protective assumptions have been considered and built into the derivation of the chronic ReV for xylenes, and thus the weight of the evidence supports a HQ of 1.0 for the derivation of the chronic ESL for xylenes.

The Panel appreciates the opportunity to comment on this important document and looks forward to future discussions with TCEQ. If further information is needed with respect to these comments, please feel free to contact me.

Sincerely,

Mike McMullen
Director of Regulatory Affairs
Texas Chemical Council
(512) 646-6404

CC: Leslie Berry, ACC Toluene and Xylene Panel

References

Amoore, J.E. and Hautala, E. (1983). Odor as an Aid to Chemical Safety Odor Thresholds Compared with Threshold Limit Values and Volatilities for 214 Industrial Chemicals in Air and Water Dilution. J. Applied Tox. Vol 3 NO. 6., pp. 272-290.

Ruth, J.H. (1986) Odor Thresholds and Irritation Levels of Several Chemical Substances: A Review. Am Ind. Hyg. Assoc. J. Vol. 47., pp. A142-A151

Appendix 3

ExxonMobil Comments Regarding the Xylenes Effects Screening Level DSD

That's fine. We apprecite the comments. Thanks.
-----Original Message-----
From: "Mike McMullen" <mmcmullen@txchemcouncil.org>
To: Honeycutt, Michael <MHoneycu@tceq.state.tx.us>

Sent: 1/27/2009 10:04:34 AM
Subject: Additional Comments on Xylene

Dr. Honeycutt,

One of our members (Exxon) is going to submit an additional comment today on Xylene if you don't mind accepting it.

Mike

Mike McMullen

Director of Regulatory Affairs

Texas Chemical Council

1402 Nueces Street

Austin, TX 78701

512/646-6404

MMcMullen@txchemcouncil.org

>>> <judy.m.bigon@exxonmobil.com> 1/28/2009 6:21 AM >>>
ExxonMobil appreciates the opportunity to provide these comments (with attachments) on the DSD for the xylenes ESL. Please contact me if you need any additional information. (See attached file: XOM Comments on TCEQ DSD-ESL for Xylenes.doc) (See attached file: XOM Attachment - Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals.htm) (See attached file: XOM Attachment - AEGL Irritants.doc) Judy M. Bigon State Regulatory Advisor Downstream & Chemical SHE ExxonMobil Refining & Supply Company 4582 Kingwood Dr., #328 Kingwood, TX 77345 Phone: 281-360-6598 Cell: 713-725-6162 judy.m.bigon@exxonmobil.com

ExxonMobil
Refining & Supply Company
Downstream and Chemical SH&E
4582 Kingwood Dr., #328
Kingwood, TX 77345

ExxonMobil Refining & Supply

Via Electronic Mail

January 27, 2009

Toxicology Section, MC 168
Texas Commission on Environmental Quality
P.O. Box 13087
Austin, TX 78711-3087

Re: Comments Regarding the Xylenes Effects Screening Level Development Support Document

Dear Sir or Madam:

ExxonMobil Refining & Supply Company (ExxonMobil) submits these comments in response to the Texas Commission on Environmental Quality's (TCEQ) request for public comments on its Effects Screening Level (ESL) Development Support Document (DSD) concerning xylenes.

ExxonMobil understands the importance of ESLs in providing TCEQ with guidance to protect human health and welfare. We consider the DSD for xylenes to be scientifically sound on several issues and it demonstrates the diligence of TCEQ's effort to develop supportable values. ExxonMobil fully supports the comments submitted by the American Chemistry Council's Toluene and Xylenes Panel and offers the additional comments below for your consideration.

ExxonMobil Urges TCEQ to Consider Using a 3-fold Intra-species Uncertainty Factor to Account for Human Variability

ExxonMobil requests that TCEQ consider using a 3-fold intra-species uncertainty factor rather than a 10-fold factor to account for human variability for respiratory irritation. The 10 fold factor is used to derive both the acute and chronic ESL. To support this recommendation, we reference the Standard Operation Procedures used for Developing Acute Exposure Guideline Levels (AEGLs) for Hazardous Chemicals, published by the National Research Council. (Attached to e-mail) In the section of this document that addressed the procedures to consider intra-species uncertainty which appears on page 90, it is stated as follows:

2.5.4.4.4. Response of Normal and Susceptible Individuals to Chemical Exposure is Unlikely to Differ for Mechanistic Reasons

In those cases in which the mode or mechanism of action is such that the response elicited by exposure to the chemical by different subpopulation is unlikely to differ, an intraspecies UF of 3-fold is generally used. Typically, this response involved a direct-acting mechanism of toxicity in which metabolic or physiologic differences are unlikely to play a major role."

This section was based on a review conducted by the EPA AEGL Committee of the literature on common irritants. (Attached to email) The agents included ozone, SO_2, chlorine, and other common pollutants for which there were human clinical data in both healthy subjects and those with certain conditions such as asthma and COPD. The degree of variability in response was far less than 10.

ExxonMobil appreciates the opportunity to comment on this important document and looks forward to future discussions with TCEQ. If further information is needed with respect to these comments, please contact me at (281) 360-6598 or by e-mail at judy.m.bigon@exxonmobil.com.

Sincerely,

Judy M. Bigon
State Regulatory Advisor
Downstream & Chemical SHE

WHITE PAPER

THE RELATIVE SUSCEPTIBILITY OF CHILDHOOD ASTHMATICS AND ADULT ASTHMATICS TO ACUTE EXPOSURES OF IRRITANT CHEMICALS

August 1, 2001

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EXECUTIVE SUMMARY

Variations in the toxicologic response of mammalian species to chemical exposures are well known, and variation among individuals in the human population are also known to occur. As outlined in the Standing Operations Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (SOP Manual), the National Advisory Committee for the Development of Acute Exposure Guideline Levels for Extremely Hazardous Chemicals (NAC/AEGL Committee) applies intraspecies uncertainty factors (UFs) to account for known and unknown variabilities in response.

In the case of chemical irritants, an intraspecies UF of 3-fold is generally applied to account for susceptible individuals, including asthmatics, children and infants, the elderly, and those with other illnesses. Although the mode of action of direct acting irritants is believed to be similar among healthy individuals, some variation in the response severity and the threshold concentration is expected to exist among healthy individuals and to a greater extent among asthmatics or other individuals with compromised pulmonary function. However, this variation or difference is generally not expected to exceed 3-fold. This is supported directly or indirectly by studies with normal healthy individuals and/or asthmatics that indicate a range in variation between healthy individuals and asthmatics of 1- to 5-fold for various chemical irritants (D'Alessandro et al., 1969; Rotman et al., 1983; Sander et al., 1987; Bhambhami et al., 1994, 1996a; Von Nieding et al., 1980; Linn et al., 1985; Hackney et al., 1978; Linn et al., 1994; Horstman et al., 1995; Bedi et al., 1982; Stacey et al., 1981; Utell et al., 1983; Koenig et al., 1993; and Morrow et al., 1994) for responses in the discomfort range of effects. However, substantial variability among asthmatic subjects has been reported (Horstman et al., 1986). There are no data elucidating differences between healthy individuals and asthmatics related to thresholds for disability and mortality.

With respect to chemical irritants, the National Research Council's Subcommittee on Acute Exposure Guideline Levels (NRC/NAS AEGL Subcommittee) has raised the questions as to whether healthy children are more susceptible than healthy adults and asthmatic children more susceptible than asthmatic adults. To answer this question, the NRC/AEGL Subcommittee informally requested the NAC/AEGL Committee to review the scientific literature on the subject and to present their findings and conclusions.

As a prelude to the investigation of possible differences between asthmatic children and asthmatic adults, the existing data were reevaluated to reaffirm that the previously selected UF of 3-fold to account for differences between healthy individuals and asthmatics was adequate to account for differences between healthy individuals and what might be considered adult asthmatics. The NAC/AEGL Committee's original conclusion for a 3-fold UF is generally supported by the limited data available and information provided in this document. Further, it was concluded that any differences for the effects observed in susceptibility between healthy adults and healthy children has been accounted for by the 3-fold UF already being used for asthmatics and other

susceptible subpopulations. Therefore, in response to the questions posed by the NRC/NAS AEGL Committee, the focus of the NAC/AEGL Committee has been on the question of whether asthmatic children are more susceptible to chemical irritants than asthmatic adults.

The NAC/AEGL Committee's search and evaluation effort was directed toward human data that permitted direct or indirect comparisons between asthmatic children and asthmatic adults. The Committee found only a limited amount of useful information and data from which to evaluate the question and draw conclusions.

With respect to anatomical and physiological considerations, the comparison between children and adults is very complex. For example, it is known that children have smaller airways than adults. However, it has been shown that children have less smooth muscle mass within the broncho-pulmonary system (Matsuba and Thurlbeck, 1972) leading to less severe bronchoconstriction for an equivalent stimulus by a chemical irritant. Based on comparative studies with children and adults (de Pee et al., 1991), this factor may offset the many other considerations such as degree of inflammatory airway wall swelling (Bel et al., 1989; James et al., 1989), changes in the geometry and mechanical properties of the airways and parenchyma with lung growth (Thurlbeck, 1975), slow increases in the transpulmonary pressure from childhood to adulthood (De Troyer et al., 1978), and thickness of airway walls in infants (James, 1989). The consideration of dosimetric concentrations was difficult to evaluate. Although children breathe approximately twice the volume of air per kg of body weight per day as adults (Bearer, 1995), other factors, for which data are lacking, such as minute volume to surface area, scrubbing, metabolic rate differences, and overall pulmonary function status of child and adult asthmatics result in an unclear picture that precludes a useful conclusion of their impact.

In terms of epidemiological data, it has been reported by Mannino et al., (1998) that the prevalence or diagnosis of asthma has increased 75 percent between 1980 and 1994 in the United States and was 67 percent higher for children 5 to 14 years of age than adults 35 and older. Also, the death rate for children 19 years and younger increased 78 percent during the same period (CDC, 1998). However, the death rate from asthma decreased in all age groups from 1960 to about 1975 and subsequently began to rise again, although not reaching the 1960 levels as of 1992 (Mannino et al., 1998). Further, it is not known whether these statistics reflect actual increases or improved reporting procedures. Irrespective of this issue, this type of data do not provide credible evidence of greater or lesser severity or susceptibility of asthmatic children to chemical irritants when compared to asthmatic adults.

Numerous other epidemiological studies have been conducted with children and/or adults in an attempt to correlate physiological responses with levels of air pollutants such as sulfur dioxide, acid sulfates, nitrogen dioxide, hydrogen sulfide, ozone, and total suspended particles. However, no reports or data were found providing comparisons of responses between asthmatic children and asthmatic adults.

Data reported on children alone also were not useful, even indirectly, since the studies either did not identify asthmatics as a study population, lacked definitive qualitative and/or quantitative data on the relative contributions of the chemical pollutants in question (eliminating the possibility of comparisons across studies), or failed to demonstrate the threshold required to cause significant decrements in airway function parameters. Excess mortality rates were reported for children during the period of the severe air pollution that occurred in London, England in 1952 (Bates, 1995). However, the excess deaths within each of the three age categories of children (from less than 4 weeks of age to 14 years of age) were significantly less than the excess deaths recorded for each of the three age categories of adults ranging from 45 to 75+ years of age.

No controlled exposure studies using chemical irritants to compare the relative susceptibility (sensitivity) of asthmatic children and asthmatic adults were found in the published scientific literature. However, studies have been reported that directly compared the responses of children and adults to a methacholine challenge covering a broad spectrum of bronchial sensitivity in the normal and asthmatic range (de Pee et al., 1991). The studies were conducted using a range of dose levels of methacholine to determine the sensitivity of airway narrowing and its relationship to the concentration required to reach the maximal responses or plateau levels in airway narrowing as measured by FEV_1 and $MFEV_1$ in both child and adult normal and asthmatic groups. The significance of the approach is based on earlier studies demonstrating that nonspecific airway responsiveness to methacholine or histamine is increased in nearly all asthmatic individuals (Cockcroft et al., 1977; Juniper et al., 1978 and 1981; Townley et al., 1979.) Although, as expected, the data of de Pee et al. (1991) demonstrated differences between healthy and asthmatic groups, no significant differences were observed between children and adults within the healthy or the asthmatic groups. In both child and adult asthmatics the maximal decrease in FEV1 exceeded 50 percent at low levels of methacholine challenge and the maximal response plateau for MFEV1 was elevated over non-asthmatic subjects.

A similar methacholine challenge study using 3 age groupings of 1 to 6, 7 to 11, and 12 to 17 year olds classified as mild, moderate, or severe asthmatics was conducted by Avital et al., (1991). Responses were measured in the two older groups as the provocation concentration of methacholine producing a decrease in FEV1 of 20 percent and in the younger group of lung sounds ("wheezing") detected by stethoscope at the tracheal level. No significant differences in response were found among the three different age groups in each category of degree of severity of asthma. However, there was a significant difference in response between mild and both moderate and severe asthma categories and between the moderate and severe asthma categories for all ages. Both of these controlled exposure studies provide support that child asthmatics are not more sensitive to effects of methacholine challenge than adult asthmatics and, hence, are not likely to be more susceptible to chemical irritants.

In summary, there is very limited data to answer the question as to whether

asthmatic children are more sensitive or susceptible to chemical irritants than adult asthmatics. No data from controlled exposure studies or epidemiological studies have provided evidence of greater sensitivity or susceptibility of asthmatic children to chemical irritants or other bronchial reactive substances than that observed in adult asthmatics. Conversely, there is evidence from controlled studies using methacholine challenges that supports no differences in the sensitivity of child asthmatics to non-specific airway responsiveness as compared to adult asthmatics.

In view of these findings it is concluded that the current approach of the NAC/AEGL Committee of using an uncertainty factor of 3-fold to account for the variability of susceptible populations, including asthmatics, is generally adequate for asthmatic children as well as asthmatic adults. However, the NAC/AEGL Committee will continue to follow the SOP Manual procedures that emphasize the evaluation of newly derived AEGL values with all other supporting data in order to provide a "weight of evidence" approach to the development of the final AEGL values. In instances where the supporting data do not agree with the initial AEGL values derived, appropriate adjustments are made. As a result, the derivation of the AEGL values has been, and will continue to be, chemical-specific. Examples of, and information on, chemical irritants where this approach has been used have been added to the appendices of this document. They include allyl alcohol, chlorine, hydrazine, hydrogen chloride, and hydrogen fluoride and represent a diverse group of chemical irritants.

1 INTRODUCTION

A considerable portion of the chemicals considered for AEGL development are irritants. These chemicals react directly and in a non-discriminative manner with biological tissue. Since this reaction is similar in all individuals there should be little variability within a population. It is known that asthmatics are a susceptible sub population and uncertainty factors have been applied to accommodate this lower threshold. However, a question has been raised as to whether asthmatic children and infants may be more susceptible to irritant exposure than adult asthmatics because of differences in physiology and maturity of the airways. The purpose of this document is to attempt to respond to this question by evaluating relevant data and information and to make a determination as to whether a special consideration should be given to childhood asthmatics. As a basis for reviewing the scientific literature and discussing the findings, it is first necessary to provide a clear picture of the characteristics of asthma in general and identify the differences in responses between asthmatics and non-asthmatics when exposed to the chemicals broadly described as “irritants”. Because of this broad classification, information about differences in the modes or mechanisms of action as they relate to differences in responses by asthmatics and normal individuals will be discussed.

2 DESCRIPTION OF ASTHMA

Asthma has been described by the Second Panel on the Management of Asthma (NIH, 1997) as a “chronic inflammatory disorder of the airways.” This inflammation contributes to airway hyper-responsiveness, airflow limitation, respiratory symptoms, and disease chronicity. Inflammation of the airway contributes to airflow limitation by contributing to bronchoconstriction, edema, mucus plug formation, and airway wall remodeling leading to bronchial obstruction.

Asthma is characterized by episodic symptoms of airflow obstruction which are partially reversible. The asthmatic condition also includes immunohistopathologic features such as denudation of the airway epithelium, collagen deposition beneath the basement membrane, edema, mast cell activation, and inflammatory cell infiltration (neutrophils-especially in sudden fatal asthma exacerbations; eosinophils; and lymphocytes-TH2-like cells). The strongest factor which predisposes an individual to asthma is development of an IgE-mediated response to common air allergens (atopy). In allergen stimulated bronchoconstriction, the mechanism is the IgE dependent release of mediators from the mast cells. These mediators include histamine, tryptase, leukotrienes and prostaglandins which can contract bronchial smooth muscle directly. Mediator release from airway cells can also be caused by nonsteroidal anti-inflammatory drugs such as aspirin - a non-IgE dependent mechanism.

Acute bronchoconstriction can be brought about by exercise and exposure to irritant gases such as SO_2 (Stacey et al., 1981; Linn et al., 1977; Horstman et al., 1986). The intensity of this response seems to be related to the degree of severity of

inflammation in the asthmatic individual but the mechanism is less well understood than for allergen induced bronchoconstriction (Busse et al., 1993)

Typical symptoms of respiratory irritation due to both allergens and chemical irritants can include cough, wheezing, shortness of breath, chest tightness, sputum production, dyspnea (NIH, 1997; Bousquet et al., 2000).

The NIH panel has divided asthmatics into four categories according to the severity of the symptoms and signs (NIH, 1997). They are mild intermittent, mild persistent, moderate persistent, and severe persistent according to Table 2-1 below (from NIH, 1997).

Table 2-1

ASTHMA SEVERITY (NIH, 1997)			
STEP	Symptoms	Nighttime symptoms	Lung function
4 Severe persistent	-Continual symptoms -Limited physical activity -Frequent exacerbations	Frequent	-FEV_1 or PEF $\frac{c}{\lambda}$ 60% predicted -PEF variability > 30%
3 Moderate persistent	-Daily symptoms -Daily use of inhaled short-acting $beta_2$-agonists -Exacerbations affect activity -Exacerbations $\frac{24}{12}$ 2 times a week; may last days.	> 1 time a week	-FEV_1 or PEF > 60% - < 80% predicted -PEF variability >30%
2 Mild persistent	-Symptoms >2 times a week but < 1 time a day -Exacerbations may effect activity	> 2 times a month	-FEV_1 or PEF $\frac{24}{12}$ 80% predicted -PEF variability < 20%
1 Mild intermittent	-Symptoms $\frac{c}{\lambda}$ 2 times a week -Asymptomatic and normal PEF between exacerbations -Exacerbations brief (from a few hours to a few days); intensity may vary	$\frac{c}{\lambda}$ 2 times a month	-FEV_1 or PEF $\frac{24}{12}$ 80% predicted -PEF variability < 20%

Exercise and the bronchoconstrictors, histamine (histamine acid phosphatase) and methacholine (a synthetic analogue of acetylcholine), have been used to induce non-specific bronchial reactivity in the clinical assessment of asthma. Inhalation tests with bronchoconstrictors are a sensitive indicator of bronchial hyperreactivity (Cockcroft et al., 1977). Histamine and methacholine are thought to induce bronchoconstriction through different mechanisms. Histamine is thought to act chiefly as an irritant that

stimulates vagal parasympathetic reflex bronchoconstriction via direct effects on histamine H1 and H2 receptors; there may also be a direct effect on bronchial muscle (Altounyan, 1971; Sellick and Widdicombe, 1971; Juniper et al., 1978). In contrast, methacholine is thought to have no effect on irritant receptors and to exert its effect directly through cholinergic receptors on smooth muscle (Goodman and Gilman, 1975; Juniper et al., 1978). According to Hargreave et al. (1981), there is a strong correlation (r2 = .85) between responsiveness as bronchoconstriction and challenge doses of histamine and methacholine. These authors report that responsiveness to both agents can be reproducibly measured under carefully controlled conditions. The most standardized clinical measurement is the tidal breathing challenge. Responses to challenge doses of histamine or methacholine are represented by the PC_{20} which is the concentration of either agent that produces a 20% fall in peak expiratory flow rate or forced expiratory volume in one second (FEV_1) using the tidal breathing method. A PC_{20} following a challenge dose of <8 mg/mL of aerosol is consistent with the definition of asthma (Cockcroft et al., 1977; Hargreave et al., 1981; Sears, 1993). Exceptions occur as there are a few asthmatics who do not demonstrate bronchial responsiveness to histamine (Warner and Boner, 1988 and others). As noted above, in asthmatic children, there is also a correlation between the response to histamine and the response to exercise (Mellis et al. 1978). The degree of responsiveness of asthmatics to histamine or methacholine relates closely with the presence and severity of asthma which, in turn, correlates with the amount of treatment required to control symptoms (Cockcroft et al., 1977; Hargreave et al., 1981; Murray et al., 1981).

2.1 Cause of Bronchoconstriction by Chemical Irritants

Healthy humans exposed to 4-6 ppm of SO_2 (Nadel et al., 1965) experience an increase in airways resistance and symptoms of irritation (cough, irritation of the pharynx and substernal area). Pretreatment with atropine eliminated the increase in airways resistance response although the symptoms persisted.

Cats were exposed to 4-6 ppm SO_2 which was delivered to the upper airways (mouth to trachea) or lower airways (trachea to lung) (Nadel et al., 1965). Exposure to SO_2 increased airways resistance under both conditions. However, pretreatment with atropine, or blocking nerve impulse conduction in the cervical vagosympathetic nerves (cooling them with cold saline in brass thermodes), eliminated the increase in airways resistance from SO_2 exposure.

The results in humans and cats demonstrate that the initial response to low levels of SO_2 exposure in the upper or lower airways is narrowing of the airways due to the reflex nature of bronchoconstriction via the vagus nerves. The authors state that SO_2 exposure stimulates sensory end organs in the trachea and bronchi. They are thought to arise from the "cough" receptors (Eltman, 1943; Larsell, 1921). Since bronchoconstriction in the lower airways was brought about by vagal nerve stimulation when only the upper airway was exposed to SO_2, these sensory end organs also enervate the upper as well as the lower airways. This study also rules out local stimulation of the smooth muscle by SO_2 exposure at low levels. However, inhalation

of high levels of phosgene and ammonia caused some changes in transpulmonary pressure/ventilatory volume which remained after vagotomy (Banister et al., 1949). The residual effect of bronchoconstriction after vagotomy in this case may be due to direct stimulation of the smooth muscle by SO_2 or a mediator released due to SO_2 exposure.

These results indicates that SO_2 exposure to low levels causes bronchoconstriction by stimulating the vagus nerve, which causes a reflex bronchoconstriction of the airways and a resultant increase in airways resistance. The increase in airways resistance is similar to that seen with asthmatics exposed to SO_2. In both cases the increase in airways resistance upon exposure to an irritant gas is rapid, typically within one minute. Even though the airways resistance effect of the SO_2 exposure disappeared with pretreatment to atropine, the symptoms remained. Thus, SO_2 exposure causes both immediate bronchoconstriction as well as other changes which cause symptoms of discomfort.

3 BIOLOGICAL RESPONSE TO DIFFERENT LEVELS OF IRRITANT EXPOSURE

Asthma has been defined in terms of symptoms, frequency of symptoms, and lung function measures (FEV_1, PEF decrements) by NIH, 1997 (see NIH Table). Much of the literature on the effects of irritant exposure on asthmatic and healthy individuals measure signs e.g. lung function changes such as SRaw (airways resistance times thoracic gas volume-basically the FRC) and FEV_1, and sometimes symptoms. Quantitative measures of lung function can be readily analyzed statistically. However, they do not always correlate well with symptoms of increased airways resistance in healthy and asthmatic people (see discussion above). Although an investigator may measure a change in lung function as the result of exposure to an irritant, the clinical significance is not always clear. However, changes in lung function are the most frequently measured response to irritant exposure. Therefore they are considered along with other signs and symptoms in the development of AEGL values. The signs and symptoms and their relation to irritant exposure will be the major consideration in determining the appropriate selection of uncertainty factors for irritant gases where possible.

Because the NAC/AEGL Committee develops AEGL values for three separate tiers of health effect endpoints, the issue of potential differences in biological response between childhood asthmatics and adult asthmatics, and between asthmatics and healthy individuals must be addressed at different levels of irritant exposure. Therefore, to organize the discussion, different exposure levels are discussed within the context of AEGL-1, AEGL-2, and AEGL-3 effects.

3.1 Acute Exposures to Low Levels of Irritant Gases Which Cause Effects Consistent with AEGL-1 Effects (Discomfort)

As previously discussed, asthma is a chronic inflammatory disorder of the

airways. Initial responses to irritant exposure in experimental studies in healthy and asthmatic individuals are signs and symptoms of airflow obstruction which are reversible with $beta_2$ agonists. For the purposes of the development of uncertainty factors for AEGL values for exposure to irritants, which are for single exposures to a gas, the focus will be on the response by bronchoconstriction and the consequences of these events. Typical asthmatic symptoms such as cough, wheezing, shortness of breath, chest tightness, sputum production, dyspnea can occur in both healthy and asthmatic individuals as a result of irritant exposure. In general, the experimental literature has reported the use of asthmatic subjects that have withdrawn medication during exposure to evaluate exposure levels up to discomfort levels. If the experimental subject becomes severely distressed, exposure is typically discontinued. Thus, the experimental literature on the response of healthy and asthmatic individuals to irritant exposure deals with effects within the AEGL-1, or discomfort, range.

The AEGL-1 is defined as:

> AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter (ppm or mg/m^3)) 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.
>
> Airborne concentrations below the AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and non-disabling odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

There are a number of difficulties in analyzing the experimental data to determine the threshold for response to irritant gases by asthmatic and healthy individuals. There are no good animal models for asthma and limited animal data for AEGL-1 type of effects which deal with discomfort and non-disabling effects. The most useful data that address these effects are a number of human inhalation studies which examine the possible effects of irritant gas exposure using pulmonary function mechanics tests. These studies often measure possible effects of irritating gases on forced vital capacity (FVC), forced expiratory volume in one minute (FEV_1), airway resistance (Raw) and airway conductance (SGaw) (see Glossary for definitions). They may measure statistically significant changes or a specific level of change (e.g. 100% decrease in SRaw). Experimenters do not always record symptoms of irritant exposure such as

cough, sputum production, wheezing, chest tightness, substernal irritation, dyspnea, throat and nasal irritation, and fatigue. Without careful recording of symptoms and their correlation with measured signs it is difficult to assess the biological relevance of the measures when looking for thresholds of asthmatic and healthy individual response to irritant exposure. While airway hyperresponsiveness and symptom severity are related, each can occur in the absence of the other, suggesting that they reflect different aspects of airway abnormality (Woolcock, A.J. 1994. Asthma. in CAHNGE REFERENCES TO REFLECT THIS. Murray JF, Nadel JA, 1994 Volume 2. p. 1298). When airway hyperresponsiveness is associated with symptoms of asthma, it is an important indicator of the severity of the disease. There is a good correlation between FEV1 and symptoms in a population studies (Woolcock, 1994 Murray JF, Nadel JA 1994, p. 1298).

The experimental designs may or may not incorporate exercise and the exercise intensity when measuring responses to irritant exposure, and may or may not conduct the exposure via mouthpiece. These factors may increase the sensitivity to the response. In most experiments, severe asthmatics are not tested, and typically asthmatic subjects are excluded from the study if they used bronchodilators the day of the study. These factors must be considered when evaluating the studies and considering the variability of response between asthmatics and healthy individuals. Other factors that may influence the results of the study in either direction and, therefore, need to be properly evaluated; include temperature, and duration of exposure.

The ratio of the threshold for response to irritant gas exposure between asthmatic and healthy individuals is used to estimate the appropriate uncertainty factor to use with human data or when only animal data are available. As will be seen in the following analyses, these thresholds are often based upon physiological measures which may or may not be of biological or clinical significance. However, their use is necessary because they represent so much of the data collected. This adds another dimension of uncertainty to any conclusions drawn about intraspecies uncertainty factors.

Two of the most frequently used parameters to measure airway resistance, and, hence, adverse effects to chemical irritants in both healthy individuals and asthmatics are the “forced expiratory volume” (FEV) and the airway resistance (R_{AW}). The FEV_1 represents the volume of air expired in one second. Decreases or decrements in the volume of air expired from a baseline following exposure to a chemical irritant are correlated with biological function and clinical significance. In general, a decrement in FEV_1 of 20 percent is required to elicit changes in biological function that are clinically significant and represent the threshold for notable discomfort that characterizes AEGL-1 level effects. The “Airway resistance” (R_{AW}) is generally reported as the “SR_{AW}” in which the value for RAW is multiplied by the thoracic gas volume to attempt to compensate for the effect of lung volume changes on airway resistance. A limited comparison of mean values obtained for the two parameters, FEV_1 and SR_{AW} indicate that a 1 percent

decrement in FEV_1 is equivalent to about a 7-8 percent increase in SR_{AW}. Therefore a reported SR_{AW} value of +100 percent may be equivalent to an FEV_1 decrement of approximately 13-14%, which is below a clinically significant level of airway resistance.

3.1.1 Chemical Specific Human Data

Human experimental data on chemicals for which exposure in both normal and potentially susceptible subjects was reviewed and summarized. Since the available data on some chemicals is rather extensive (e.g., ozone, acid gases), this document should not be viewed as an all encompassing compilation of studies. Rather, the document is intended to provide a reasonable summary of some of the more relevant human experimental data on irritant gases.

Chlorine

D'Alessandro et al. (1996) exposed 5 healthy subjects and 5 subjects with airway hyperreactivity (HR) to 1.0 ppm for 60 minutes. Most of the HR subjects had clinical histories of asthma but only one was being treated regularly with inhaled or systemic corticosteroids. Compared with their baseline values, both the healthy and HR subjects had statistically significant decreases in FEV_1 and FEF_{25-75} and a statistically significant increase in Sraw (all $p<0.05$). When compared with the values for the healthy subjects, the absolute and relative changes in FEV_1 and the absolute change in Sraw of the HR subjects were significantly different ($p<0.05$). Relative changes in FEV_1 for healthy and asthmatic subjects were -4±2% and -16±13%, respectively, and absolute changes in Sraw were +2.1±1.6 (39%) and +7.5±4.9 L cm H_20 L/s (108%), respectively. Two of the HR subjects exposed to 1.0 ppm experienced respiratory symptoms (not described) following exposure. In 5 HR subjects (all with a clinical history of asthma) exposed to 0.4 ppm for 60 minutes, no statistically significant changes in airflow or airway resistance were observed. It was reported that chlorine was not appreciable by smell by any of the subjects at these concentrations.

Rotman et al. (1983) exposed 8 healthy nonsmoking male volunteers aged 19-33 who gave no history of asthma to 1 ppm or 0.5 ppm chlorine. Subjects remained in the chamber for 4 hours, after which time they came out for pulmonary function tests, re-entered the chamber for 4 hours of exposure and then underwent another set of pulmonary function tests. While in the chamber, subjects exercised for 15 minutes to produce a heart rate of 100 beats/minute defined as light-to-moderate exercise by the American Industrial Hygiene Association. Additional pulmonary function tests were performed 24 hours post exposure. A questionnaire was used to record symptomology. Sham exposures were also performed in order to maintain the single blind nature of the investigation. With the sham versus 0.5 ppm exposure, there were trivial changes observed. With the sham versus 1 ppm exposure, there were many statistically significant differences from baseline observed, including decreased FVC, FEV_1, FEF_{25-75}, and PEFR and increased Sraw. For example, Sraw increased from a baseline value of 2.05 to 4.53 L cm H20 L/s at the end of 8 hours.

An additional subject with a history of allergic rhinitis and characterized as atopic by the authors experienced shortness of breath and wheezing during exposure at 1 ppm which caused him to exit the chamber before the full 8-hour exposure. The other subjects did not complain spontaneously of any symptoms after exposure but found that the 1 ppm exposure days were distinguishable from the control or sham days by the occurrence of itchy eyes, runny nose, and a mild burning in the throat, symptoms that were absent on 0.5 ppm and sham exposure days. The single individual with a history of allergic rhinitis also experienced slight changes in pulmonary function (e.g., decreased FEV1, FEV_1, FEF_{25-75} and PERF and increased Sraw) at 0.5 chlorine. His Sraw value approximately doubled during both the 4-hour and 8-hour exposures to 0.5 ppm.

Anglen (1981) conducted a series of studies on healthy male and female subjects exposed to chlorine. Statistically significant changes in pulmonary function and clinical signs of irritation (itching, burning of throat as if the subject had been talking too long) were observed from 8-hour exposures at 1 ppm. A 4-hour exposure at 1 ppm and an 8-hour exposure at 0.5 ppm produced no significant changes in pulmonary function or signs of irritation. Some differences in pulmonary function were seen at the end of 4 hours at 2 ppm, but not at the end of 2 hours at 2 ppm.

Joosting and Verberk (1974) exposed healthy adults aged 28-52 to chlorine for 2 hours at concentrations of 1, 2, and 4 ppm. Pulmonary function measures of response included FVC, FEV, and FIV measurements before and after exposure. Subjective phenomena, recorded with 15 minute interval, included smell, taste, nose, eye, and throat irritation, cough, and other phenomenon (e.g., headache).

D'Alessandro et al. (1996), Rotman et al. (1983), and Anglen (1981) all observed changes in pulmonary function of healthy individuals exposed to 1.0 ppm of chlorine for periods of 60 minutes to 8 hours. Anglen (1981) observed symptoms in healthy individuals exposed to 1.0 ppm for 8 hours and Rotman et al. (1983) found that a healthy individual with a history of allergic rhinitis experienced shortness of breath and wheezing when exposed to 1.0 ppm of chlorine with less than 8 hours of exposure. With the exception of slight changes in the subject with allergic rhinitis, exposure of the subjects to 0.5 ppm did not result in changes in pulmonary function. The threshold for exposures at which healthy individuals begin to respond with changes in pulmonary function to chlorine gas is approximately 1.0 ppm.

Asthmatic individuals exposed to 0.4 ppm of chlorine for 60 minutes did not exhibit any changes in pulmonary function but did exhibit statistically significant changes at 1.0 ppm (D'Alessandro et al. (1996). A "healthy" individual with a history of allergic rhinitis experienced slight changes in pulmonary function at 0.5 ppm chlorine exposure for 8 hours (Rotman et al. (1983). If this person is taken as a susceptible individual, then the threshold for exposures at which susceptible individuals, including asthmatics, begin to respond with changes in pulmonary function to chlorine gas is approximately

0.5 ppm as compared to a reported threshold of 1.0 ppm for healthy individuals.

Formaldehyde

Healthy, nonsmoking subjects were exposed to formaldehyde at 0.5, 2.0, and 3.0 ppm for 3 hr in a controlled environmental chamber (Sauder, et al, 1987). Eye irritation increased linearly from 0.5 to 3.0 ppm HCHO. At 2 ppm, 6/19 subjects reported mild eye irritation and 4/19 moderate eye irritation; at 3 ppm, all 9 subjects experienced eye irritation, 5 as mild, and 4 as moderate. For nose/throat irritation, a mild response was reported by 7/19 of the subjects at 2 ppm and 2/9 at 3 ppm. Exercise produced no significant increase in odor or eye irritation; however, nose/throat irritation increased significantly. The mean increase in nasal flow resistance with at-rest exposure was not significant at 2 ppm formaldehyde but was significant at 3.0 ppm. The relationship of nasal flow resistance in comparison with more traditional measures of pulmonary function (FEV_1, Raw, Vtg, etc.) is unknown. There were no significant decrements in pulmonary function (FEV, FEV_1, and $FEF_{25\%-75\%}$) during a 3-hour exposure and 24 hour post-exposure at 0.5 ppm formaldehyde at rest or at 2.0 ppm with exercise

Nine asthmatic subjects were similarly exposed to formaldehyde at 3 ppm for 3 hours. No significant changes in pulmonary function or airway reactivity were observed. Eye and upper respiratory tract irritation was observed. Therefore, in this study, the irritant response to formaldehyde exposure was similar in non-asthmatic healthy and asthmatic subjects up to the exposure levels tested. It is interesting to note that formaldehyde can induce symptoms of irritation in healthy and asthmatic individuals without any signs of bronchoconstriction at concentrations up to 3.0 ppm.

Hydrogen Chloride

Five male and 5 female 18-25 year old mild asthmatic subjects were exposed to filtered air, 0.80 +/- 0.09 ppm and 1.84 +/- 0.21 ppm HCL while wearing half-face masks, during 3 separate 45 minute experimental sessions involving 15 minute exercises (treadmill walking at 2 mph at an elevation grade of 10%), 15 minute rest, and again 15 minutes of exercise (Stevens et al., 1992). Exposures were separated by at least 1 week. FEV_1, FEV, maximal flow at 50% of expired air, vital capacity, total respiratory resistance and peak flow were measured before and after exposure Subjects also rated the severity of upper and lower respiratory, and other symptoms (excluding eye irritation because of exposure through a half-face mask), before, during, and after exposure. No adverse respiratory effects were found at either 0.80 or 1.84 ppm mean concentration levels. From this limited data set, no conclusions can be drawn about the relative sensitivity of asthmatics to healthy individuals to hydrogen chloride exposure.

Hydrogen Sulfide

Jappinen et al. (1990) exposed a group of ten asthmatics (3 men aged 33-50 and

7 women age 31-61) to 2 ppm hydrogen sulfide for 30 minutes. All subjects complained of an unpleasant odor and nasal pharyngeal dryness at the start of exposure. Three of ten complained of headache after exposure. There were no significant changes on FVC, FEV_1, for FEF following exposure. A slight non statistically significant decrease in S_{raw} was observed; S_{raw} decreased in two and increased in eight subjects, with a range of -57.7% to +30%.

Bhambhani and Singh (1991) exposed 16 healthy male volunteers (age 25.2 +/- 5.5 years) to 0, 0.5, 2.0 or 5.0 ppm hydrogen sulfide during exercise. No effect on heart rate or expired ventilation was observed. There was a tendency for oxygen uptake to increase and carbon dioxide output to decrease with increasing hydrogen sulfide concentration; however, these effects were not statistically significant. There was no discussion of symptoms which might or might not have occurred in the subjects.

Bhambhani et al. (1994; 1996a) exposed 25 healthy volunteers to 0 or 5 ppm hydrogen sulfide for 30 minutes while exercising. No treatment-related effects on oxygen uptake, carbon dioxide production, respiratory exchange ration, heart rate, blood pressure, arterial blood oxygen and carbon dioxide tension or pH, or perceived exertion ratings were reported. In another follow-up study, no changes in pulmonary function (FEV_1, FVC, PEFR, FEF) were observed in healthy volunteers (9 men aged 27.4 +/- 6.4 years, 10 women, age 21.8 +/- 3.0 years) exposed to 0 or 10 ppm hydrogen sulfide for 30 minutes (Bhambhani et al, 1996b). There was no discussion of symptoms which might or might not have occurred in the subjects.

No statistically significant changes were observed when the same pulmonary function tests were performed in non-asthmatic healthy or asthmatic subjects in these studies (FEV_1, FVC, FEF). From these data, it is not possible to determine quantitatively the degree of differential susceptibility to irritation responses in non-asthmatic versus asthmatic subjects, as measured by changes in pulmonary function. Marginal changes in S_{raw} were reported in asthmatics. However, this measure was not assessed in the studies of non-asthmatic healthy individuals. Asthmatic individuals exposed to 2 ppm expressed nasal pharyngeal dryness and some complained of a headache. Unfortunately, the Bhambani papers did not state whether symptoms were observed in healthy individuals exposed to 2 and 5 ppm of hydrogen sulfide. From these studies, symptoms of irritation such as nasal pharyngeal dryness are likely to occur in asthmatics and probably healthy individuals before airways resistance increases due to bronchoconstriction.

Nitrogen Dioxide

Experimental studies with NO_2 in both healthy and asthmatic individuals are inconclusive. A failure to elicit responses of respiratory irritation or pulmonary function decrement have been observed in many studies with exposures up to 4 ppm for 1 hour, however, other studies report positive effects on pulmonary function at lower concentrations. It should be noted that in the studies which found statistically significant

changes with NO_2 exposure, the differences were often of questionable biological or clinical significance even for asthmatics.

Experimental studies with NO_2 in healthy individuals are summarized in the first table below. In several studies, healthy men and/or women were exposed to 0.6 ppm NO_2 for 1-3 hours with intermittent or continuous exercise. No significant effects were observed in any study on pulmonary function, cardiovascular function, metabolism, or symptoms of exposure (Folinsbee et al., 1978; Adams et al., 1987; Frampton et al., 1991; Hazucha et al., 1994). No changes in pulmonary function occurred following exposure to 1.5 ppm for 3 hours or to a baseline of 0.05 ppm with intermittent peaks of 2 ppm, (Frampton et al., 1991). Pulmonary function was not affected in competitive athletes exposed to up to 0.30 ppm for 30 minutes during heavy exercise (Kim et al., 1991) or in healthy adults exposed to 0.3 ppm for 4 hours with intermittent exercise (Smeglin et al., 1985).

No changes in pulmonary function, airway reactivity, or indications of irritation were measured in healthy adults exposed to 1 ppm for 2 hours, 2 ppm for 3 hours (Hackney et al., 1978), 2 ppm for 4 hours (Devlin et al., 1992), 3 ppm for 2 hours (Goings et al., 1989) or to 2.3 ppm for 5 hours (Rasmussen et al., 1992). No statistically significant effects on airway resistance, symptoms, heart rate, skin conductance, or self-reported emotional state were found in healthy volunteers exposed to 4 ppm NO_2 for 1 hour and 15 minutes with intermittent light and heavy exercise (Linn and Hackney, 1983). However, a significant decrease in mean (n = 11) alveolar O_2 partial pressure by 8 mm Hg and a significant increase in mean (n = 11) airway resistance (RAW) from 1.51 to 2.41 cm H_2O/(L/s) occurred in healthy volunteers exposed to 5 ppm for 2 hours with 6/11 individuals responding (von Nieding et al., 1979).

Studies on the effects of NO_2 on pulmonary function in asthmatics are summarized in the second table below. No consistent or clinically significant changes in pulmonary function or reported symptoms have been found in exercising asthmatic adults and adolescents exposed to 0.12 or 0.18 ppm for 40 minutes (Koenig et al., 1987), 0.12 ppm for 1 hour at rest (Koenig et al., 1985), 0.2 ppm for 2 hours with intermittent exercise (Kleinman et al., 1983), 0.3 ppm for 30 minutes (Rubinstein et al., 1990), 1 hour (Vagaggini et al., 1996), or 4 hours (Morrow and Utell, 1989) with exercise, 0.5 ppm for 1 hour at rest (Mohsenin, 1987), up to 0.6 ppm for 75 minutes with intermittent exercise (Roger et al., 1990), and up to 1 ppm for 4 hours (Sackner et al., 1981). No clinically significant changes nor statistically significant differences between control and NO_2 exposure were found for airway resistance, symptoms, heart rate, skin conductance, or self-reported emotional state for asthmatics exposed to 4 ppm for 75 minutes with light exercise (Linn and Hackney, 1984).

In contrast, 7/13 asthmatics experienced slight burning of the eyes, slight headache, and chest tightness or labored breathing with exercise, but no changes in pulmonary function, during exposure to 0.5 ppm for 2 hours (Kerr et al., 1978). Significant group mean reductions in FEV_1 (-17.3% vs -10.0% NO_2 exposure plus

exercise vs air exposure plus exercise) and specific airway conductance (-13.5% vs -8.5%) occurred in asthmatics after exercise during exposure to 0.3 ppm for 4 hours and 1/6 individuals experienced chest tightness and wheezing (Bauer et al., 1985). The onset of effects was delayed when exposures were by oral-nasal inhalation as compared to oral inhalation and may result from scrubbing within the upper airway. In a similar study, asthmatics exposed to 0.3 ppm for 30 minutes at rest followed by 10 minutes of exercise had significantly greater reductions in FEV_1 (10% vs 4% with air) and partial expiratory flow rates at 60% of total lung capacity, but no symptoms were reported (Bauer et al., 1986). In a preliminary study with 13 asthmatics exposed to 0.3 ppm for 110 minutes, slight cough and dry mouth and throat and significantly greater reduction (11% vs 7%) in FEV_1 occurred after exercise, however, in a larger study, no changes in pulmonary function were measured and no symptoms were reported following exposure of 21 asthmatics to concentrations up to 0.6 ppm for 75 minutes (Roger et al., 1990). In general, reductions if FEV_1 of up to 20 percent are not considered to be clinically significant (Gold, W.M. 1994. Pulmonary Function Testing. Volume 1. CHANGE REFERENCES TO REFLECT THIS. Murray and Nadel, 1994a-p871).

The hyperreactivity of asthmatics to an airway challenge following NO_2 exposures has also been highly variable. Methacholine responsiveness in asthmatics was not increased following exposure to 0.25 ppm for 20 minutes at rest plus 10 minutes of exercise (Jörres and Magnussen, 1991) or by exposure to 0.1 ppm for 1 hour at rest (Hazucha et al., 1983). Exposure to 0.1 ppm for 1 hour caused a slight but statistically significant increase in initial specific airway resistance (SRaw from 6.0 to 6.9) and enhanced the bronchoconstrictor effect of carbachol in 13/20 asthmatics, but the remaining 7 subjects were unaffected. However, when the study was repeated in 4 individuals at 0.2 ppm, the results were variable in that two had lesser responses, one had an equal response, and the other had a greater response to carbachol challenge (Orehek et al., 1976). Slight but statistically significant potentiation of airway reactivity (measured as airway resistence) in asthmatics occurred from NO_2 exposures of 0.5 ppm for 1 hour followed by methacholine challenge (Mohsenin, 1987), 0.3 ppm for 40 minutes followed by isocapnic cold air hyperventilation (Bauer et al., 1986), 0.2 ppm for 2 hours followed by methacholine challenge (Kleinman et al., 1983), and 0.25 ppm for 30 minutes followed by isocapnic hyperventilation (Jörres and Magnussen, 1990). A more statistically significant reduction in FEV_1 from challenge with house dust mite antigen was reported for asthmatics as compared to controls (-7.76% vs -2.85%) following exposure to 0.4 ppm for 1 hour (Tunnicliffe et al., 1994), but no statistically significant changes were found in a similar study using a 6-hour exposure (Devalia et al., 1994). A slight response to carbachol challenge was also measured in healthy individuals exposed to 1.5 ppm for 3 hours (Frampton et al., 1991). An increase in airway reactivity to methacholine, but no changes in pulmonary function, was measured in healthy subjects exposed to 2 ppm for 1 hour (Mohsenin, 1988).

Taken together, the data indicate that some asthmatics exposed to 0.3-0.5 ppm NO_2 may respond with either subjective symptoms or slight changes in pulmonary

function of no clinical significance. Also at approximately these same concentrations of NO_2 some asthmatics may show slight hyperreactivity to a bronchial challenge, but the response is not more severe than to NO_2 alone (e.g. while some asthmatics response to a bronchial challenge and to NO_2, the response to the challenge is not additively increased from prior exposure to NO_2). In contrast, some asthmatics did not respond to NO_2 at concentrations of 0.5-4 ppm. The responses of healthy individuals to NO_2 exposures are also variable with some, but not all, responding to 5 ppm. What is most important to recognize is that all reported responses in both asthmatic and healthy subjects at the concentrations discussed were slight and of questionable biological or clinical significance.

Conclusions regarding differences in susceptibility between healthy and asthmatic individuals are difficult to draw from the available data because of the high variability in responses among both classifications of individuals. There is only one study which has studied the responses of both healthy and asthmatic individuals with the same study protocol and experimental setup (Linn and Hackney, 1983). Dose-response patterns are not discernable at these low concentrations and clear thresholds are not apparent. Some individuals reported clinical symptoms in the absence of changes in pulmonary function, while other individuals had measurable changes in pulmonary function tests but no symptoms. Although some individuals may respond at concentrations below which others might show a measurable response, the magnitude of the reported changes was not biologically or clinically significant in either asthmatics or healthy individuals. The data are of questionable value in the assessment of an intraspecies uncertainty factor for irritant gases. Therefore the determination of the relative thresholds for response to NO_2 exposure of healthy and asthmatic has not been made.

Summary of experimental studies in HEALTHY humans exposed to NO_2*			
Exposure	**Subjects**	**Effect**	**Reference**
0.12 ppm	volunteers	odor perceived by 3/9	NRC, 1977
0.22 ppm	volunteers	odor perceived by 8/13	NRC, 1977
0.18 and 0.3 ppm; 30 min	competitive athletes; heavy exercise	no effects	Kim et al., 1991
0.3 ppm; 4 hrs	healthy, exercise	no effects	Smeglin et al., 1985
0.6 ppm; 1-3 hrs	healthy, exercise	no effects	Folinsbee et al., 1978; Adams et al., 1987; Frampton et al., 1991; Hazucha et al., 1994
1.5 ppm; 3 hrs with peaks of 2 ppm	healthy, exercise	no changes in pulmonary function	Frampton et al., 1991
1 ppm; 2 hrs or 2 ppm; 3 hrs	healthy adults	no effects	Hackney et al., 1978
2 ppm; 1 hr	healthy adults	no effects on pulmonary function	Mohsenin, 1988
2 ppm; 4 hrs	healthy adults	no effects	Devlin et al., 1992
3 ppm; 2 hrs	healthy adults	no effects	Goings et al., 1989
2.3 ppm; 5 hrs	healthy adults	no effects	Rasmussen et al., 1992
4 ppm; 1 hr, 15 min	healthy; exercise	no effects	Linn and Hackney, 1983
5 ppm; 2 hrs	healthy	O_2 partial pressure decreased by 8 mm Hg; airway resistence	von Nieding et al.,

		increased from 1.51 to 2.41 cm H_2O/(L/s); 6/11 individuals responded	1979
30 ppm; 6 hrs	healthy	burning sensation in nose and chest, cough, dyspnea, sputum production (only symptoms measured)	Henschler et al., 1960

* Studies listed are to NO_2 exposure only and do not include carbechol or methacholine challenge tests.

Summary of experimental studies in ASTHMATIC humans exposed to NO_2*			
Exposure	**Subjects**	**Effect**	**Reference**
0.12 or 0.18 ppm; 40 min	adults and adolescents; exercising	no effects	Koenig et al., 1987
0.12 ppm; 1 hr	resting	no effects	Koenig et al., 1985
0.2 ppm; 2 hrs	exercise	no effects	Kleinman et al., 1983
0.3 ppm; 0.5, 1 or 4 hrs	exercise	no effects	Rubinstein et al., 1990; Vagaggini et al., 1996; Morrow and Utell, 1989
0.3 ppm; 4 hrs	exercise	1/6 had chest tightness and wheezing; mean reductions in FEV_1 (-17.3% vs -10%) and specific airway conductance (-13.5% vs -8.5%); symptoms delayed when exposure was oral-nasal compared to oral	Bauer et al., 1985
0.3 ppm; 40 min	30 min rest then 10 min exercise	no symptoms; reduced FEV_1 (10% vs 4% with air); partial expiratory flow rate 60% of capacity	Bauer et al., 1986
0.3 ppm; 110 min	exercise	slight cough, dry mouth; reduced FEV_1 (11% vs 7%)	Roger et al., 1990
0.5 ppm; 1 hr	resting	no effects	Mohsenin, 1987
0.5 ppm; 2 hrs	exercise	7/13 had slight burning of eyes, slight headache, chest tightness or labored breathing; no changes in pulmonary function	Kerr et al., 1978
0.6 ppm; 75 min	exercise	no effects	Roger et al., 1990

up to 1 ppm; 4 hrs	no stated	no effects	Sackner et al., 1981
4 ppm; 75 min	exercise	no effects	Linn and Hackney, 1984

* Studies listed are to NO_2 exposure only and do not include carbechol or methacholine challenge tests.

Ozone

Numerous controlled experimental studies have been conducted with ozone, including studies in healthy subjects (young, adult, and elderly), asthmatic subjects (child, adolescent, adult, and elderly), subjects with allergic rhinitis, chronic obstructive pulmonary disease (COPD), and ischemic heart disease. The effect of exercise on response has been evaluated in a large number of studies. Potential gender and ethnic and racial differences , socio-economic status, and impact of environmental factors (e.g., smoking, ambient temperature, and humidity) have been explored to a limited degree. The effects of repeated ozone exposure have also been investigated. Some of the more relevant studies are summarized below. Overall, the data indicate the following:

Responsiveness to ozone is decreased in persons over 50 years of age. Overall, elderly subjects are revealed to be less sensitive to ozone-induced pulmonary function decrements than young healthy subjects.

Recent studies show that asthmatic subjects do no reveal a substantially higher response in pulmonary function compared with health subjects when exposed to 0.12 to 0.4 ppm ozone for less than 3 hours. With prolonged exposure (6.5-7.6 hours) to lower concentrations of ozone (0.12 to 0.16 ppm), asthmatic subjects reveal slightly higher pulmonary function response and symptoms than healthy subjects.

More studies are needed before a conclusion can be drawn regarding the susceptibility of COPD patients to ozone exposure. Most studies on effects of ozone on subjects with COPD do not demonstrate increased pulmonary responsiveness to ozone. However, in one recent study, COPD patients showed a higher FEV_1 loss than healthy subjects from ozone exposure.

Overall, the current literature does not suggest that there is a substantial gender difference in responsiveness to ozone.

Limited results are suggestive of a small (1.5-fold) ethnic difference in ozone pulmonary responses, but more subjects must be studied before final conclusion

can be reached

Limited data indicate that current smoking may blunt responsiveness to ozone exposure.

The results of ozone exposures appear to show an attenuation of symptoms and pulmonary function changes and airway inflammatory responses with repeated low level exposures.

Exercise significantly increases pulmonary responsiveness to ozone.

Ozone Studies in Subjects with Asthma or Allergic Rhinitis

In summary of the U.S. EPA Criteria Document (1996), studies by Linn et al. (1978), Silverman (1979), Koenig et al. (1985, 1987, 1988) have shown that no significant decrements in group pulmonary function could be elicited with ozone exposures ranging from 0.12 to 0.25 ppm for 40 minutes to 2 hours at rest or using light to moderate intermittent exercise protocols in both adults and adolescent asthmatics. Kerit et al (1989) and Eschenbacher et al (1989) used a heavy exercise protocol and ozone exposure at 0.4 ppm for 2-hours. Their data demonstrate that a statistically significant decrease in FVC, FEV_1, ratio of FEV_1 and FVC, and FEF_{25-75} can be elicited in both non-asthmatic and asthmatic subjects. Asthmatic patients were found to have greater decrements in all parameters except FVC and subjective symptoms when compared with non-asthmatic subjects. Bronchial responsiveness as measured by the concentration of methacholine required to increase 100% of airway resistance was also evaluated in these studies. While the asthmatic group had a lower baseline than the non-asthmatic subjects, the percentage increase to bronchial responsiveness after ozone exposure was similar in non-asthmatic and asthmatic subjects. These findings indicate the total inhaled dose (or effective dose) is increased significantly by increasing minute volume during exposure. Mild to moderate asthmatics will respond with a greater obstructive response than will non-asthmatic subjects.

Using a prolonged exposure protocol, Linn et al. (1994) showed that exposure of asthmatic patients (18 to 50 years old, n = 30) to 0.12 ppm ozone for 6.5 hours with exercise (V_E 29 L/min) resulted in a statistically significant decrease in FEV_1 following ozone exposure in asthmatics which was greater than the decrease seen in healthy subjects (-8.6% versus -1.7%).

Horstman et al (1995) compared pulmonary function response and symptoms of asthmatic (19-32 years old, n = 17) and non asthmatic (18-35 years old, n = 13) subjects to ozone. Subjects were exposed to 0.16 ppm ozone or air for 7.6 hours with intermittent light exercise (V_E 30 L/min). In this prolonged exposure study using low ozone concentrations, statistically significant differences in FEV_1 and FEV_1/FVC decrements were observed between asthmatic patients and healthy subjects. However,

the changes were not physiologically or clinically significant for either group. Nine of 17 asthmatics experienced wheezing with ozone, while no healthy subjects experienced wheezing. Six of 17 asthmatics requested inhaled agonist bronchodilator prior to and/or during ozone exposure and experienced some temporary alleviation of decrements. At the end of exposure, asthmatics who were medicated had greater ozone-induced decrements than those who were not medicated. Asthmatic subjects who had the larger ozone-induced FEV_1 decrements had lower baseline FEV_1/FVC and lower baseline % predicted FEV_1.

Jorres et al. (1996) compared ozone-induced pulmonary function changes, symptoms, and responsiveness to allergens among patients with mild stable allergic asthma (21 to 31 years old, n= 24), patients with allergic rhinitis without asthma, and healthy subjects. Subjects were exposed to filtered air or 0.24 ppm ozone for 3-hours during intermittent exercise. The FEV_1 decrease in patients with mild stable allergic asthma or allergic rhinitis without asthma was slightly greater than healthy subjects (12.5% and 14.1% versus 10.2%, respectively) subsequent to ozone exposure While allergen treatment worsened ozone-induced FEV_1 decrement, the responsiveness to methacholine was not altered by ozone exposure and no changes in FEV_1 reported were clinically significant.

Fernandes et al. (1994) investigated the effect of pre-exposure to 0.12 ppm ozone on exercise-induced asthma. Non smoking subjects with mild stable asthma who had exhibited a fall in FEV_1 > 15% after a standard 6 minute treadmill exercise challenge test were exposed to ozone or air for 1-hour at rest. The exposure was followed by a 6 minute exercise challenge; the treadmill speed and inclination were such that patients achieved their maximal exercise. The percent fall in FEV_1 and expiratory flow at 40% of vital capacity were not significantly different following exposure to ozone or air. The effects of exposure on the time course of spirometric response after exercise showed no significant difference between air and ozone exposure. A study conducted by Weymer et al 1(1994), comparing the responses of exercise-induced asthmatic versus non exercise-induced asthmatic patients to ozone reached a similar conclusion. In this study, of 21 asthmatic subjects, none showed exercise-induced asthma positive, and 12 showed exercise-induced asthma negative. Subjects were exposed to 0, 0.1, or 0.25 ppm ozone for 1-hour with intermittent light exercise. Subjects then rested for 1-hour followed by a post exposure standardized exercise challenge in air. No significant changes in FEV_1 or FVC were observed.

In summary, recent studies show that asthmatic subjects do not reveal substantially higher response in pulmonary function compared with healthy subjects when exposed to 0.12 to 0.4 ppm ozone for less than 3-hours. Pre-exposure to ozone (0.1 to 0.25 ppm for 1-hour at rest or with light exercise) does not aggravate exercise-induced asthma. However, asthmatic subjects appear to have a higher responsiveness to allergens than healthy subjects. With prolonged exposure (6.5 to 7.6 hours) to low concentrations of ozone (0.12 to 0.16 ppm), asthmatic subjects reveal higher pulmonary function response and symptoms than healthy subjects. Although it is difficult to set a

bright line for the threshold for asthmatic response to ozone, the above studies are consistent with a hypothesis that asthmatics can begin to respond to ozone at 0.12 ppm for short term exposures of 3 hours or less. This is especially true if the exposure is with exercise and/or prolonged. In a resting state the threshold would probably be higher.

Studies in Subjects With Chronic Obstructive Pulmonary or Ischemic Heart Disease

In studies by Linn et al. (1982a), Linn et al (1983), Solic et al. (1982), Kehrl et al. (1985), no significant changes in pulmonary function or symptoms were detected in COPD patients exposed to ozone. In four of these five studies, patients with mild to moderate COPD where exposed to 0.1 to 0.3 ppm ozone for 1 to 2 hours with intermittent light exercise (V_E 14-28 L/min). No consistent changes of arterial oxygen saturation, pulmonary function or symptoms were observed in these studies.

In a recent study, Gong et al. (1997b) compared the response of ozone exposure between COPD patients and a matched age group of subjects without COPD. Healthy subjects (60-69 years old) and subjects with COPD (59-71 years old) were exposed to air or 0.24 ppm ozone for 4-hours during intermittent light exercise (V_E L/min). COPD subjects had a 19% loss of FEV_1 loss versus 2% in the healthy subjects. There were no significant changes in airway resistance observed in either group. Ozone exposure caused moderate changes in symptoms, and blood oxygenation in COPD patients, but not in healthy subjects.

Drechsler-Parks (1995a) exposed eight elderly healthy subjects with ischemic heart disease (age 56-85) to either air or 0.25 ppm ozone, or 0.6 ppm nitrogen dioxide, or the two in combination, for 90 minutes with intermittent exercise. Exposure to ozone or nitrogen dioxide alone did not significantly modify cardiac output in comparison with air control. A slight exercise-induced increase in cardiac output was observed when subjects were exposed to both pollutants.

In subjects with COPD, the threshold is below 0.24 ppm (Gong et al., 1997b) for longer periods of exposure and undergoing exercise but may be at this level for shorter periods of time (less than 3-4 hours-see 1-2 hour exposure studies at the beginning of this section) and resting if they respond in the same manner as asthmatics.

Influence of Gender, Age, Ethnicity, and Environmental Factors

Frampton et al. (1997) exposed 56 never-smoking and 34 healthy subjects to 0.22 ppm ozone and air for 4-hours with exercise. Both study groups included female subjects. By using multiple logistic regression analysis, the authors found that gender, age and methacholine responsiveness were not predictive of responder status, although pack-year of smoking was associated with decreased ozone responsiveness.

Seal et al. (1996) investigated the effects of gender, age, socio-economic status

and menstrual cycle phase on pulmonary response to ozone exposure. Healthy African American and Caucasian subjects (18 to 35 years old, n = 372) were exposed to air or 0.12, 0.18, 0.24, 0.3, or 0.4 ppm ozone for 2.3 hours with intermittent exercise (V_E 45-55 L/min). Logistic function was used to model the exposure-response relationship, and the significant impact of gender, age, social economic status, and menstrual cycle phase. African American males experienced a significant decrements in FEV_1 following exposure to 0.12 ppm ozone, whereas black women and white men and women did not have significant decrements in FEV_1 at ozone concentrations below 0.18 ppm. No gender related differences or effect of menstrual cycle were observed.

Weinmann et al. (1995b) exposed 24 health non smokers of similar age (12 men, 12 women) to 0.35 ppm ozone and air for 130 minutes with intermittent exercise (V_E 38L/min). No gender related differences in pulmonary function response to ozone were observed.

Bush et al. (1996) found that the absorption distribution of ozone in resting men and women were indistinguishable, although women absorbed ozone at smaller penetration volume than men, and women had smaller dead space volume than men.

Drechsler-Parks (1995b) investigated pulmonary function response in 9 male healthy elderly subjects (56-71 years) following exposure to air and 0.45 ppm ozone for 2-hours. Ozone induced a small, but significant decrement in FVC and FEV_1. When taking into account the effective dose of ozone (concentration x V_E x duration), ozone-induced decrements of pulmonary function in older subjects were much smaller than those typical observed in young males exposure to similar inhaled doses of ozone.

Three studies demonstrate that current smoking may blunt responsiveness to ozone exposure and that smoking cessation for 6 months leads to improved baseline pulmonary function and possibly the re-emergence of ozone responsiveness (Emmons and Foster, 1991; Frampton, 1993; Frampton et al, 1997).

The above studies indicate that responses of smokers and the elderly are less than healthy people to ozone exposure. There is no apparent difference between men and women although African-American men may have a threshold for response at or below 0.12 ppm.

Sulfur Dioxide

A number of factors have been shown to alter the concentration-effect relationship for exposure to SO_2 in humans. These include relative humidity (Linn et al, 1954), ambient temperature (Bethel et al., 1984; Linn et all, 1954), respiratory effort (Linn et al., 1983; Bethel et al., 1983), the presence of aerosol in the inspired air (Koenig et al., 1980), and individual susceptibility (Amdur, 1974; Koenig et al., 1981).

Tables 1 and 2 present effects of SO_2 exposure on healthy human subjects and

subjects with asthma. In studies conducted from 1983 through 1987 with exercising asthmatics, exposures to SO_2 concentrations of 0.25 ppm or less did not induce significant group mean increases in airway resistance in individual asthmatics. On the other hand, exposures to 0.28-0.4 ppm SO_2 or greater (combined with moderate to heavy exercise) induced significant group mean increases in airway resistance in some individual asthmatics. This bronchoconstriction was often associated with wheezing and the perception of respiratory distress. In a few instances it was necessary to discontinue the exposure and provide medication. Some SO_2 -sensitive asthmatics are at risk of experiencing clinically significant (i.e., symptomatic) bronchoconstriction requiring termination of activity and/or medical intervention when exposed to SO_2 concentrations of 0.4 to 0.5 ppm or greater when this exposure is accompanied by at least moderate activity (EPA, 1986).

In healthy adults, no effects were observed at exposures of 0.4 ppm SO_2 for 3 hours during exercise (Bedi et al., 1982). Exposures of 0.75 ppm for 3 hours during exercise produced increased airway resistance in healthy adults (Stacey et al., 1981). In asthmatics, 0.4 ppm SO_2 produced a similar response (Linn et al., 1977). Therefore, the threshold for pulmonary function changes in asthmatics was approximately 2-3-fold less than healthy subjects. However, substantial variability among asthmatic subjects has been reported (Horstman et al., 1986).

Table I

Effects of SO2 Exposure on Healthy Human Subjects

Concentration (ppm)	Duration (min)	Rest or Exercise	Effect
25	360	Resting	Dryness and slight pain in nose, rhinorrhea, conjunctival pain; decreased mucous flow rate, increased airflow resistance, decreased FEV_1 (Anderson, et al. 1974)
16.1	25-30	Resting	Some coughing, slight immutation of the posterior pharynx (Speizer, et al. 1966)
13	10-30	Resting	Coughing, upper airway irritation, increased salivation; increased airflow resistance, increased functional residual capacity (Frank, et al. 1962)
10	10	Resting	7/14 subjects had increased specific airway resistance (Lawther, et al. 1085)
5	360	Resting	Dryness in nose and pharynx; decreased nasal mucous flow rate, increased airflow resistance, decreased FEV_1 (Andersen, I. et al. 1977)
5	10-30	Resting	Coughing, upper airway irritation, increased salivation, increased airway resistance (Frank, N. R. et al. 1962)
4-6	10	Resting	Coughing, some irritation of the pharynx, decreased airway conductance (Nadel, J. A. et al. 1965)
1	360	Resting	No subjective complaints; increased airflow resistance, decreased FEV1(Andersen, I. et al. 1974)
1	10-30	Resting	No effect in 10/11 subjects; 1 subject experienced wheezing and tightness in the chest (Frank, N. R. et al. 1962)
5	1.20	Exercise	Increased tracheobronchial clearance, increased flow resistance (Wolff, D. K. et al. 1975)
0.75	120	Exercise	Increased airway resistance (Stacey, et al. 1981)

0.40	120	Exercise	No effects (Bedi, et al. 1982)

Table 2

Effects of SO2 Exposure on Humans with Asthma

Concentration (ppm)	Duration (min)	Rest or Exercise	Effect
0.28-2.00	10	Exercise	Substantial variability in concentrations required to produce greater than 100% increase in specific airway resistance (Horstman et al., 1986) [(1)]
5	10	Resting resistance	Increased specific airway; some subjects required bronchodilation therapy (Sheppard, et al. 1980)
1	40	Resting / exercise	Changes in pulmonary function (decreased FEV_1, V_{max50} and V_{max75} (Sheppard, D. et al. 1982)
0.75	5	Exercise	Increased specific airway resistance (Linn, et al. 1983)
0.5	3	Exercise	Increased specific airway resistance (cold dry air) (Bethel, R. A. 1984)
0.4	5	Exercise	Increased specific airway resistance, subjective symptoms of discomfort (Linn, et al. 1977)
0.37	120	Resting	No effect on pulmonary function (Bell, et al. 1977)
0.25	75	Exercise	No effect on pulmonary function (Roger, et al. 1985)

[(1)] Note: a 100% increase in specific airway resistance (sR_{AW}) is equivalent to an FEV_1 decrement of approximately 12 to 14%, which is below the threshold for a clinically significant change in pulmonary function.

Sulfuric Acid

Many human studies of the effects of sulfuric acid have been conducted. These studies were reviewed in the Acid Aerosols Issue Paper (U.S. EPA, 1989). A summary of this review appeared in the Air Quality Criteria Document for Particulate Matter (EPA, 1996). The conclusions were as follows:

1. In healthy subjects, no effects on spirometry have been observed after exposure to concentrations of H_2SO_4 less than 500 ug/m^3, and no consistent effects have been observed at levels up to 1,000 ug/m^3 with exposure duration's up to 4 hours. Studies of a variety of other sulfate and nitrate aerosols have similarly demonstrated an absence of spirometric effects on health subjects.

2. Combinations of sulfates with ozone or SO_2 have not demonstrated synergistic or interactive effects.

3. Asthmatic subjects experience modest bronchoconstriction after exposure to approximately 400-1000 ug/m^3 H_2SO_4, and small decrements in spirometry have been observed in adolescent asthmatics at concentrations as low as 100 ug/m^3 for 30 minutes.

4. Some studies suggest that delayed effects may occur in healthy and asthmatic subjects following exposure to H_2SO_4.

5. Effects of sulfate aerosols are related to their acidity, and neutralization by oral ammonia tends to mitigate these effects.

6. Exposure to H_2SO_4 at concentrations as low as 100 ug/m^3 for 60 minutes alters mucocilary clearance.

7. Airway reactivity increases in healthy and asthmatic subjects following exposure to 1,000 ug/m^3 H_2SO_4 for 16 minutes.

8. Differences in estimated respiratory intake explain only a portion of the differences in responses among studies.

Since 1988, ten new human experimental studies on H_2SO_4 have been published. For the most part, these studies confirm the above conclusions. A summary of a few selected studies is presented below. The effective concentration causing responses differs somewhat among the studies. Although the reasons for these inconsistencies remains largely unclear, subject selection and acid neutralization are likely important factors in the differences observed .

Six non-asthmatic and six asthmatic subjects were exposed to 0.10 mg/m^3 of sulfuric acid mist for 2 hours over 2-3 days with intermittent exercise (Avol et al., 1979). There was no change in pulmonary function measurements or findings on symptom questionnaire in either group.

Sixteen non-asthmatic subjects and 17 asthmatics were exposed for 16 minutes to sulfuric acid mist (Utell et al., 1983). At 0.1 mg/m^3, there were no symptoms and no change in airway conductance in either group. At 1.0 mg/m^3, non-asthmatic subjects had significantly increased carbachol sensitivity. At 1.0 mg/m^3, asthmatics had a statistically significant decrease in FEV_1 and airway conductance. Neither group was aware of these breathing changes. Exposure of asthmatics to 0.45 mg/m^3 also showed decreases in FEV_1 and airway conductance (Utell et al., 1983).

Nine asthmatics with exercise-induced bronchospasm (12-18 yrs) were exposed to H_2SO_4 via mouthpiece for 40 minutes, including a 10 minute exercise period (Koenig et al, 1989). The authors concluded that 100 ug/m^3 is close to the threshold concentration that produces pulmonary function changes.

Twelve healthy subjects (20-29 yrs) were exposed to 1,000 ug/m^3 H_2SO_4 for 2 hours including a 1 minute exercise period (Frampton et al., 1992). Four of 12 subjects reported throat irritation . No lung function changes were reported.

Eight healthy and 9 asthmatic subjects (60-76 yrs) were exposed to 74-82 ug/m^3 H_2SO_4 via mouthpiece for 40 minutes including a 10 minute exercise period (Koenig et al., 1993). No significant lung function effects or symptoms were reported.

Seventeen asthmatic subjects (age 20-57) and 17 subjects with COPD (age 52-70) were exposed to 90 ug/m^3 H_2SO_4 or 100 ug/m^3 NaCl for 2 hours including 4 10-minute exercise periods (asthmatics) and 1 minute exercise period (COPD) (Morrow et al., 1994). A slight decrease in FEV_1 was observed in asthmatic but not COPD subjects.

Table 3

Summary of Comparative Irritant Responses In Healthy Versus Potentially Susceptible Subjects

Chemical	Estimated Threshold in Healthy Subjects[1]	Estimated Threshold in Susceptible Subjects[1]	Estimated Differential Response Factor	Susceptible Group
Chlorine	1.0 (P) 1.0 (S)	0.5 (P) 0.5 (S)	2	Asthmatics, history of allergic rhinitis
Formaldehyde	3 (P^3) 2 (S)	>3 (P) <3 (S)	1?	Asthmatics
Hydrogen chloride		>1.8 (P, S)	?	Asthmatics
Hydrogen sulfide	>10 (P)	>2 (P) 2 (S)	?	Asthmatics
Nitrogen dioxide	Conflicting data	Conflicting data	????????	Asthmatics
Ozone	0.25 $(P)^2$	0.12 P^2 <0.24 P >0.25 0.12	1.5 1.0 1.0 1.5 1.0	Asthmatics COPD Ischemic heart dis. African American Gender
Sulfur dioxide	0.75 (P)	0.4 (P)	2-3	Asthmatics; substantial variation in asthmatic group observed
Sulfuric acid	500 ug/m^3	400 ug/m^3 100 ug/m^3 [4]	1.3-5	Adult asthmatics Adolescent asthmatics

[1]The estimated thresholds for responses (expressed in ppm unless otherwise specified) in both healthy and asthmatic subjects are related to pulmonary function indices and symptoms of respiratory distress. The pulmonary function parameters measure airway resistance as FEV_1, SR_{AW}, etc., and although the thresholds included here may vary among the studies reported, they are primarily related to discomfort and below levels of clinical significance. The threshold for symptoms include the onset of coughing, wheezing, shortness of breath, chest tightness, sputum production, and dyspnea. The type of thresholds measured for these parameters are also related to discomfort and at the levels tested may be of questionable clinical significance.

[2]For exposure durations of <3hr
[3]Nasal flow resistance
[4]Exposure was by mouthpiece
P: Pulmonary function
S: Symptoms

3.1.2 Intraspecies Uncertainty Factor for AEGL-1 Values

For a number of irritant chemicals, human experimental data assessing irritant responses in non-asthmatic versus potentially susceptible subjects are available. Some of the more relevant studies were compiled and summarized in order to make general conclusions on the threshold concentrations required to produce an irritant response in non-asthmatic healthy versus potentially susceptible subgroups. This comparison is useful in determining the appropriate uncertainty factor to use when extrapolating from data in healthy subjects to potentially susceptible subgroups.

In a number of studies, the non-asthmatic and potentially susceptible subjects were exposed to the same concentration of irritant gas. This makes assessment of the appropriate UF difficult, since differences in responses at the same concentration cannot be used to directly estimate different thresholds for a response. In addition, differences in study protocols, including differences in the response endpoints measured and the test subjects exposed, make comparisons of effects observed at different concentrations reported from various studies difficult. A number of studies reported effects in both healthy and potentially susceptible subjects exposed to multiple concentrations of irritant gases. These latter data provide the best information for estimating the appropriate intra-species UF for irritant gases.

Another problem with making comparisons between groups is the severity of the endpoint measured often differed. The severities typically measured are often of statistical significance but not necessarily clinically significant. For example, a decrement in FEV_1 of greater than 20% is needed before pulmonary impairment is considered to be mild (Gold, W.M. 1994. Murray and Nadel, 1994a-p871). However, most of the measures of FEV_1 decrement from exposure to irritants is far less than 20%.

A summary of the estimated differences in threshold for irritant responses for non-asthmatic versus potentially susceptible subjects appears in table 3. For some irritant gases (e.g., formaldehyde), no great difference in response is apparent. For other gases (e.g., chlorine, ozone) potentially susceptible subjects such as asthmatics or those with allergic rhinitis respond at a concentration 1 to 3-fold-lower than non-asthmatic healthy subjects. For a few irritants (sulfur dioxide and sulfuric acid), the threshold concentration to which potentially susceptible subjects respond is somewhat lower, on the order of 1-5 fold. Based on this assessment, the original estimate of a 1 to 5-fold difference in the irritant concentrations to which non-asthmatic subjects and

susceptible subjects respond, appears to be a reasonable basis for uncertainty factor selection, in the absence of actual comparative experimental data on the chemical of interest.

3.1.3 Time Scaling for AEGL-1 Values

For AEGL-1 type effects of discomfort including an increase in airway resistance (e.g., an FEV_1 decrement of 20 percent) the concentration required to cause an effect is the same for different exposure durations for chemicals which are highly water soluble and can be scrubbed efficiently in the upper airway passages. For chemicals which penetrate deeply in to the lung (e.g. O_3) time might be a factor which should be considered following the procedures contained in the SOP Guidance Manual (NRC, 2001).

3.2 Acute Exposure to Medium Levels of an Irritant Gas Which Causes Effects Consistent with AEGL-2 Effects (Disabling or Impairment of Escape)

The AEGL-2 is defined as:

> AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.
>
> Airborne concentrations below the AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and non-disabling odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

Information in carefully controlled experiments with exposure levels that may disable an individual can only be found in animal studies. In carefully controlled human studies, exposures are below disabling levels or exposure is typically stopped when subjects complain of notable discomfort. Hence, there are no compelling data on human exposures approaching or exceeding disabling levels of exposure to an irritant which would permit an estimate of the relative sensitivity of asthmatic and healthy individuals. An evaluation of case reports involving mortality or disabling effects from exposure to irritants indicates that pulmonary edema is the most common cause of lethality.

When considering the concentrations of chemicals and the types of adverse effects at the AEGL-2 tier, it appears likely that asthmatics will sustain at least the same level of injury to respiratory tissues as healthy individuals at the same concentration of an irritant. It appears also that, with increasing concentrations, a level of tissue injury may be reached eventually that would be disabling to both asthmatics and healthy individuals. However, the important question is whether there is an irritant concentration below the critical levels described above that will induce responses such as severe bronchoconstriction and inflammatory response in asthmatics that will render them disabled before similar effects are seen in healthy individuals. And, if there is such a concentration, could it be quantitatively more than 3-fold below the threshold concentration for disability in healthy individuals, since this difference represents the basis for selecting an intraspecies uncertainty factor for AEGL-2 effects.

Unfortunately, such data are not available, nor are such data likely to ever be

available from controlled studies with humans. Therefore, the selection of uncertainty factors in deriving AEGL-2 levels for irritants will require a chemical specific analysis of all of the data. This will require careful assessment of the following considerations:

1) Which intraspecies uncertainty factor (1, 3, or 10), when applied to the key study, gives the best fit with all of the other data on the chemical or its analogs? Are the derived AEGL values consistent with the supporting data?

2) If the AEGL value generated by the use of a higher intraspecies uncertainty factor is not reasonable in light of the supporting data, what is the reason?

a) Was an adverse effect used to determine an AEGL-2 level which is far below that expected for an AEGL-2 endpoint. For example, selection of mild coughing as an AEGL-2 endpoint. Why was the endpoint selected conservative or below an AEGL-2 effect level? In this case a lower uncertainty factor may be justified.

b) The use of a higher uncertainty factor drives the AEGL-2 value to a level at or below a level which humans have been shown to tolerate as a result of human exposure or monitoring studies and is not likely to elicit AEGL-2 type effects in asthmatics or other susceptible subpopulations.

c) The use of a higher uncertainty factor would have driven the AEGL-2 value to a level which is not consistent with the supporting data, especially as they relate to the human experience.

d) Are the dose response curves in the animal studies exceptionally steep? For example, if the dose which just initiates a measurable amount of edema is close to the dose which causes death, this may justify a lower uncertainty factor. The irritant chemicals stimulate or injure lung tissue by means of a non-specific chemical reaction with the cells. This reaction should be similar in both asthmatic and healthy individuals. An extremely steep dose response curve described above (from the beginning of lung edema to death) would argue for the conclusion that the difference in concentration between initial reaction with, injury to, and in some cases destruction of, upper and lower respiratory tissue and the concentration that results in death is a very narrow range. One might argue that, although the asthmatic individual might react with pulmonary edema formation and/or inflammatory reaction at the lower end of that range, the range itself is so narrow that the difference between the adverse effects in the asthmatic and the healthy individual is minimal.

e) Other considerations that may be chemical-specific or data-specific that support the conclusions drawn to strengthen the rationale used.

3) Considering interspecies and intraspecies uncertainty factors independently can lead to an overly conservative AEGL value. When the two uncertainty factors are multiplied together the resultant total uncertainty factor generally represents a worst case times a worst case. Therefore the total uncertainty factor must be evaluated and the AEGL values compared with all of the supporting data. If the supporting data do not support the AEGL values it may be necessary to reconsider one or both of the uncertainty factors using the supporting data as a rationale.

4) Give specific data to support the conclusions drawn to strengthen the argument made.

In summary, there is a lack of data to address differences in response thresholds for irritant chemicals between asthmatics and healthy individuals for AEGL-2 level effects. Data indicating differences in responses is available for effects that are more closely aligned with AEGL-1 type of endpoints. In these cases the threshold concentrations to which asthmatic subjects respond range from 1 to 5-fold lower than healthy individuals. In the absence of differential response data between asthmatics and healthy individuals at the AEGL-2 tier, and the existence of human data indicating a 1 to 5-fold range of differences for lesser adverse effects, an intraspecies uncertainty factor of 3 is used and evaluated within the context of other supporting data to further validate the selection. This is supported further by the absence of indirect evidence such as differences in the modes or mechanisms of action of irritants between asthmatics and healthy individuals and the biochemical/physiological details of chemically-induced asthmatic attacks that might provide insight into response differences between asthmatics and healthy individuals at the AEGL-2 tier. In instances where supporting data suggest an intraspecies uncertainty factor of 3 is inadequate, and uncertainty factor of 10 may be used.

Consequently, the NAC/AEGL Committee has generally applied an uncertainty factor of 3 to data from human studies which comprise healthy individuals but no asthmatic test subjects when deriving AEGL-1 values. For many chemical irritants, the same uncertainty factor of 3 has been used to derive AEGL-2 values. The rationale generally has been the fact that the irritants are direct acting and that their effect is not likely to vary among individuals, including susceptible individuals. Further, depending on the type of adverse effect being considered as the endpoint, such as known or suspected tissue injury, and the steepness of the dose-response curve for the effect in question, the conclusion may be reached that any difference in threshold concentration between healthy individuals and asthmatics is not likely to exceed 3-fold. However, in these instances, the derived AEGL-2 value is often evaluated within the context of all other supporting data to further validate the selection. In addition, a substance specific uncertainty factor of less than 3 may be used if available data support a lesser value.

3.2.1 Time Scaling for AEGL-2 Values

Animal data demonstrate that time scaling is necessary for AEGL-2 and AEGL-3

effects where destruction of tissue in the respiratory system is the endpoint (NRC, 2001).

If an AEGL-2 effect is induced by bronchoconstriction it is difficult to draw conclusions about time scaling since this response may represent a threshold effect under certain circumstances and with some irritants may induce late onset bronchoconstriction which does not require a long duration of exposure. In experiments with irritant chemicals with asthmatics which measure decreases in airways resistance the decrease is relatively rapid, within a few minutes. Also, there are data indicating that increased airway resistance may be reversed in instances of extended exposure. There are very little data about time scaling for a bronchoconstriction effect at AEGL-2 levels.

Data in animals clearly indicate that time scaling is appropriate when lung damage is caused by irritating chemicals. This type of damage will also be evidenced in asthmatic individuals. Given what is known about time scaling for destruction of tissue in the respiratory system, time scaling will be used based upon animal data unless there are data on a chemical which indicate that another approach should be taken.

3.3 Acute Exposure to Medium Levels of an Irritant Gas Which Causes Effects Consistent with AEGL-3 Effects (Death)

The AEGL-3 is defined as:

> AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.
>
> Airborne concentrations below the AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and non-disabling odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

As is the case for AEGL-2, no data are available on differences in response thresholds for irritant chemicals between asthmatics and healthy individuals. Consequently, the same conclusions are reached as stated in the AEGL-2 discussion section. Also, the NAC/AEGL Committee's approach is the same for deriving AEGL-3 values.

3.4 Children as a Susceptible Population

In order to answer the question as to whether non-asthmatic children are more susceptible than non-asthmatic adults and/or asthmatic children or adolescents are more susceptible than adult asthmatics to exposure to irritant gasses, a rigorous assessment of this issue is necessary. This requires specific data sets which would allow direct comparisons between healthy children and healthy adults, or between asthmatic children and asthmatic adults, who have been exposed to a range of concentrations of irritants sufficient to determine the respective thresholds for a specific type and severity of response which is physiologically significant.

Initiation and exacerbation of asthma are toxicological endpoints of particular concern in children. Asthma affects more than 15 million Americans, including nearly 5 million children. Asthma prevalence and/or the diagnosis of asthma increased 75% from 1980 to 1994 in the United States (Mannino et al., 1998). Prevalence rate statistics indicate that a significantly higher percentage of children have asthma than adults. In a recent analysis of data from the National Health Interview Survey, the prevalence of diagnosed asthma among children aged 5 – 14 was about 67% higher than for adults aged 35 and above (74.4/1000 vs. 44.6/1000, respectively; Mannino et al., 1998). How much of this increase is due to an actual increase in the prevalence and what proportion is related to improved or more complete records on the diagnosis of asthma is uncertain.

Asthma is the most prevalent chronic disease among children, and can be life-threatening. The death rate for children 19 years and younger from asthma increased by 78% between 1980 and 1993 (CDC, 1998). It is interesting to note however, that the death rate with asthma as the underlying cause decreased in all age groups from 1960 to about 1975 and began to rise again although not reaching the 1960 levels as of 1992 (Mannino et al., 1998). Asthma surveillance data developed by the national Centers for Disease Control and Prevention (CDC) (Mannino et al., 1998), and recent reports on asthma hospitalization by the California Department of Health Services (CDHS, 2000), and King County, Washington, (Solet et al., 2000), indicate that children, especially young children, are impacted by asthma morbidity more than older children or adults. Hospitalization rates for children 0 to 4 years are greater than for all other age groupings (see Table 3.4-1), and is four-fold higher for black children than for white children (CDHS, 2000). The youngest and poorest communities have the highest rates of asthma hospitalization (Solet et al., 2000, Claudio et al., 1999). In Table 3.4-2 the number of asthmatics hospitalized for asthma is estimated for each age group. The data indicate that childhood asthmatics, aged 0-4 are two to three times more likely to be hospitalized than most other groups. It does not appear that the hospitalization rates were simply a reflection of asthma prevalence since the rates for all other age groups were substantially lower. These data could suggest that it represents a more severe manifestation of the disease for 0 to 4 year age group. Further, hospitalization represents a medical decision for admission. This also suggests a concern that may be related to severity and the impact of asthma on very young children. However, there

are a number of medical, social and behavioral factors such as first-time episodic events, initial diagnostic procedures, parental concerns with very young children, experience with established medication with older asthmatics, socioeconomic issues, and other variables that question a direct correlation between hospitalization and degree of severity. In his discussion of the trends in asthma prevalence, Mannino et al. (1998) caution that the reasons for the trends are not clear and it is difficult to differentiate between a true change in asthma rates and an increase in diagnosis by physicians. These possibilities tend to be supported by the more than 60 percent reduction in hospitalization rates for children in the 5 to 14 year old group where many of the aforementioned factors no longer exist. For this reason, the use of hospitalization data as a basis for measuring the differences in severity of asthma between children and adults does not appear scientifically valid.

Another consideration in comparing childhood asthmatics with adult asthmatics are the physiological differences that exists. Children have smaller airways than adults. Since the resistance to airflow is proportional to the fourth power of the airway radius (Levitsky, 1995), bronchoconstriction and increased mucus secretion characteristic of asthma greatly increases airflow resistance in a small child relative to an adult. Thus, breathing difficulty is a common occurrence in young children experiencing an asthma attack. On the other hand young children have less smooth muscle mass (de Pee et al., 1991) which would lead to less pronounced contractions for an equivalent stimulus.

Another issue is the dosimetric consideration that children are subjected to higher doses of chemical irritants when compared to adults on a mg/kg basis. This is a result of breathing approximately twice as much volume of air as adults per day (OEHHA, 2000). However, this is a highly complex area where there are other factors which must be considered when attempting to define dose levels. This includes metabolic rate differences, minute volume to surface area ratios, and scrubbing.

Although children with asthma should be carefully considered with respect to the potential import of irritant chemicals, it is not clear whether children would respond at a quantitatively lower level than other subpopulations that may be sensitive to irritant exposures (e.g., individuals with allergic rhinitis, those with COPD or ischemic heart disease).

In terms of empirical data, it is important to note that there is evidence that this concern may not apply directly to bronchoconstriction. For example, Avital et al. (1991) and de Pee et al. (1991) found no difference between asthmatic adults and asthmatic children when challenged to methacholine (discussed later in this paper). De Pee et al. (1991) commented that the high comparability of the response between adult and child is somewhat surprising because there are a number of physiological factors which are expected to vary between children and adults (e.g. transpulmonary pressure, inflammatory airway wall swelling, parenchymal elastic load, differing airway dimensions, airway wall thickness, smooth muscle mass, etc.). However, as previously stated, up to the age of 9 the comparative amount of smooth muscle in small airways is

relatively small. Apparently all of these factors are balanced between adults and children in a way that results in a similar response between the two groups.

Table 3.4-1. Doctor's Office visits, Emergency Room (ER) Visits, and Hospitalization for Asthma by Age in California for 1995 through 1997

Age (years)	Office per 1000	ER per 1000	Hospital per 10,000
0-4	50.3	120.7	49.7
5-14	51.5	81.3	18.0
15-34	22.8	69.2	10.0
35-64	41.7	64.4	15.2
> 65	44	29.5	25.5

Data from CDHS, 2000

Table 3.4-2. Comparison of Asthma Prevalence and Hospitalization to Estimate the Percent of Asthmatics Hospitalized for Asthma; Based on U.S. data Reported by Mannino et al., 1998 for the Years 1993-1994.

Age (years)	Hospitalizations	Asthma Prevalence	Percent Asthmatics Hospitalized
0-4	97,000	1,024,000	9.5
5-14	67,000	2,004,000	3.3
15-34	78,000	1,876,000	4.2
35-64	139,000	3,982,000	3.5
> 65	85,000	1,480,000	5.7

3.4.1 Studies on Asthmatic Children as a Possible Susceptible Subpopulation of Asthmatics

3.4.1.1 Controlled Exposure Studies

The concentration of methacholine required to reduce the FEV_1 by 20 percent (PC_{20}) was measured in mild, moderate, and severe asthmatics defined by the regimen of medication they were taking (Avital et al., 1991). Age ranges tested were 1-6, 7-11, and 12-17 years old. PC_{20} was determined in children between 7-11 years old. Children from 1-6 years were tested by bronchial provocation with tracheal auscultation (BPTA) to determine the methacholine concentration which causes wheezing (PCW). The PC_{20} and PCW values reported were dependant on asthma severity with significant differences between the mild/moderate and the mild/severe for all age groups, severe

being more methacholine sensitive than moderate who were more methacholine sensitive than mild. There was a significant difference between the moderate/severe for the 1-6 year old age group but not for the 6-11 or 12-17 year age group although the PC20 was lower for the severe asthmatics in these age groups. The small difference between moderate/severe for the older age groups may be a result of the mitigating effects of the steroids being taken in the higher age groups. The only significant response difference among age groups was that observed between the youngest and middle age groups for moderate severity. However the PCW measured in the youngest age group may be an overestimation because the PCW is an end-point concentration whereas the PC_{20} is an interpolated value. When corrections were made for the possible overestimation, the age difference disappeared.

It is well known that in adults increasing sensitivity to methacholine challenge is associated with a higher maximal response (bronchial hyper-responsiveness). As the methacholine challenge concentration increases, the FEV_1 is reduced until it reaches a plateau (de Pee et al., 1991). In an earlier study the authors presented data to show that this plateau occurs at about an 18 percent reduction in a non-asthmatic subject, about a 40 percent reduction in a tested mild asthmatic subject, and did not plateau at about a 55 percent reduction in a moderately asthmatic subject. The purpose of this study was to examine this relationship in children as well and to test the hypothesis that the maximal narrowing of the airways in children is different from adults for similar sensitivities to methacholine challenge.

Subjects were recruited to cover a wide range of bronchial sensitivity in the non-asthmatic and asthmatic range. PD_{20} values for adult and child asthmatics ranged from 0.030-1.2 umole and 0.053-55.8 umole respectively. PD_{20} values for adult and child non-asthmatic subjects ranged from 0.82->59 umole and 1.7->59 umole respectively.

Subjects were tested on 2 separate days within a 2 week period. A complete dose-response curve was obtained in each session if possible. However, if the post saline drop in FEV_1 exceeded 50%, if the subject sustained too much discomfort, or the last dose had been administered no further challenges were made. Maximal response plateau was defined as 2 or more of the last doses falling within a 5% range of each other. The points on the plateau were averaged to obtain the maximal response. When the maximal FEV_1 ($MFEV_1$) response was plotted against the log PD_{20} an inverse relationship was observed which was not different between children and adults. Note that in 10 of 11 asthmatic adults and 5 of 10 asthmatic children, no plateau could be documented (e.g. each increase in dose of methacholine was causing an incremental decrease in FEV_1). In 1 of 9 non-asthmatic children no plateau was reached even though the highest dose had been administered. Two of 8 non-asthmatic adults did not reach a plateau because the test was interrupted due to discomfort. In non-asthmatics 3 of 9 children and 2 of 8 adults did not reach a PD_{20} on at least one occasion.

The inverse relationship between ln PD_{20} and $MFEV_1$ was comparable between adults and children. Maximal response to methacholine challenge as measured by

$MFEV_1$ for given PD_{20}s is similar between adults and children. In both children and adult asthmatics, the maximal decrease in FEV_1 exceeds 50% when the PD_{20} is < 1 umol. In both asthmatic adult and children, the maximal response plateau for FEV_1 is elevated over non-asthmatic subjects and in some there is an unmeasurably high maximal response in the absence of a plateau. It is important to note that both child and adult subjects were selected to represent a broad spectrum of sensitivity to methacholine challenge and that the spectrum of sensitivity of adults and children was similar.

The authors comment that the high comparability of the response between adult and child is not expected because of a number of conditions which might vary between children and adults (e.g. transpulmonary pressure, inflammatory airway wall swelling, parenchymal elastic load, differing airway dimensions, airway wall thickness, etc.). However, until age 9 the relative amount of smooth muscle in small airways is small. Apparently all of these factors in some way balance between adult and child so that the maximal response is similar between the two groups.

3.4.1.2 Epidemiology Studies and Reviews

Bates (1995) reviewed the literature on the effects of airborne pollutants on children. He classified the results by the observed and the pollutant responsible for the outcome. The most serious outcome of pollution exposure was increased mortality in children. In the 1952 London episode the increase in mortality of children in ages <4 weeks to 14 years of age ranged from an increase of 1.3-fold to 2.2-fold over that seen the week before the pollution episode (discussed in more depth later in this section). Evidence was presented that the respiratory mortality of children was greater in more polluted environments. For example, in the Czech Republic the relative increase in respiratory mortality was 3.16, 5.41, and 2.73 in the regions most polluted with TSP (Total Suspended Particulates), SO_2, and NO_2 respectively. He also speculated that the cause of death from respiratory disease in the third world is from the use of biomass fuels with inadequate ventilation.

Bates (1995) discussed studies which demonstrated increased acute respiratory illness in children which was associated with higher levels of pollution. Illness was associated with PM10 (particles less than 10 microns in size) in Utah; ozone and sulfate in Ontario; ozone, sulfate, aerosol hydrogen ion level and PM10 in Toronto; NO2 in Germany; NO_2 and particulates in Switzerland; environmental tobacco smoke. Asthma was aggravated as measured by increases in hospital emergency visits. Increased frequency of emergency room visits were associated with pollution in Philadelphia and were not associated with the ragweed season; when the ozone level exceeded 0.11% in Atlanta; ozone in New Jersey; SO_2 levels in the winter but not summer in Vancouver-the association was observed for people in the 15-60 year age group in the summer; PM10 in Seattle. Increased levels of PM10 was associated with increased medication use among young adult asthmatics in Utah. Increased respiratory symptoms in children, phlegm and cough, were associated with higher pollutant levels of pollutants such as

SO_2, NO_2 and PM10. Decrements of lung function in children have been associated with increased levels of SO_2, particulates, wood smoke, and ozone. Increases in SO_2 levels have been associated with increased school absences in grades 1 to 6 with a greater response in grades 1 to 3.

The Bates (1995) review clearly demonstrates that children and asthmatic children experience increases in death and respiratory illness from increased levels of common pollutants such as SO_2, ozone, NO_2, particulates, and others. However, he presents little data about the difference in frequency of response between age groups (see discussion of the London episode below). More importantly, with regard to the question of the selection of appropriate uncertainty factors to protect children and asthmatic children, there are no data discussed which permit an assessment of the difference in threshold levels of response, or range of response, between adults and children, healthy or asthmatic. Therefore this paper cannot be used address the question of the selection of the appropriate intraspecies uncertainty factor to be used for irritant gasses.

A comprehensive review of the chemical irritants referred to collectively as sulfur oxides was conducted by Schlesinger and Jaspers (1997). Numerous epidemiological studies were cited where children had increased prevalence of cough, wheezing, or bronchitis related to chronic exposure to sulfur oxides. Further, the authors cite responses of various subpopulations ranging from small changes in pulmonary function indices (children), increase in hospital admissions (children), increasing morbidity as a worsening of health status among chronic broncitics (all ages), and mortality (children, elderly, and chronically ill) all related to acute exposure during historical air pollution episodes in the United States and other countries including the London, England episode. However, these studies do not provide data to enable direct comparisons in response between children and adults in either the healthy subpopulation or the asthmatic subpopulation. Further, it is not possible to make valid indirect comparisons across epidemiological studies since definitive data is lacking on the presence or the relative contributions of known pollutants, including the sulfur oxides.

The chamber studies cited earlier deal with AEGL-1 effects in adults and children (e.g. discomfort not great enough to impede escape). There are no human experimental studies dealing with exposure to a serious health effect level or death. However, an assessment of the increase of deaths by age group in the London episode of December 1952 sheds some light on the matter of the relative sensitivity of children to adults when exposed to airborne pollutants. Bates (1995) provided a summary of the increase in mortality in the December 1952 London episode from data in the London Ministry of Health (1954) report. During the week of the episode 2484 people died compared to 945 the week before the episode. Deaths were attributed to exceptionally high concentrations of SO_2 and smoke (Lave and Seskin, 1977). The data (Bates, 1995) are summarized in the table below:

DEATHS IN LONDON ADMINISTRATIVE COUNTY BY AGE							
All	<4 weeks	4 weeks-1 year	1-14 years	15-44 years	45-64 years	65-74 years	75+ years
Week before the episode							
945	16	12	10	61	237	254	335
Week after the episode							
2484	28	26	13	99	652	717	949
Factor by which deaths were increased							
2.6	1.75	2.2	1.3	1.6	2.8	2.8	2.8

The increase in death rate from the pollution episode ranged from 1.3 for 1-14 year old children to 2.8 for 45-75+ years of age. The excess deaths within each of the three age categories of children (from less than 4 weeks of age to 14 years of age) were significantly less than the excess deaths recorded for each of the three age categories of adults ranging from 45 to 75+ years of age. This is particularly significant in view of the likelihood that children tend to spend more time outdoors than adults 45 years of age and older. The greatest increase is for those over 45 years of age with the greatest difference in susceptibility of approximately 2-fold. The exposure was to all age groups, sexes, and individuals of varying degrees of susceptibility and to very similar levels and durations of exposure. The increase in death rate was clearly due to an acute episode. If children represented a particularly sensitive group then their death rate increase should have been much greater than adults. Since this was not the case, these data do not support the possibility that children may be at greater risk of death and therefore more susceptible than adults when exposed to high levels of pollutants.

Numerous other epidemiological studies have been conducted with children and/or adults in an attempt to correlate physiological responses with levels of air pollutants such as sulfur dioxide, acid sulfates, nitrogen dioxide, hydrogen sulfide, ozone, and total suspended particles. However, no reports or data were found providing comparisons of responses between asthmatic children and asthmatic adults. Data reported on children alone also were not useful, even indirectly, since the studies either did not identify asthmatics as a study population, lacked definitive qualitative and/or quantitative data on the relative contributions of the chemical pollutants in question (eliminating the possibility of comparisons across studies), or failed to demonstrate the threshold required to cause significant decrements in airway function parameters.

3.4.1.3 Biological Differences Between Children and Adults

Bearer (1995) discusses physiological, pharmacokinetic, pharmacodynamic, and exposure differences between humans from fetal to adult life. The fetus is susceptible to maternal exposures, especially those which result in storage with subsequent mobilization during pregnancy (PCBs in fat, lead in bone). Infants are closer to the ground and may experience greater exposure to substances in a carpet or grass. Additionally they cannot remove themselves from detrimental exposures such as UV radiation and sunburn. Children have a breathing zone closer to the floor so they will experience a higher exposure to airborne materials denser than air. Greater oxygen consumption in children (approximately 2-fold) per kilogram of body weight can lead to potentially higher exposures. Children consume more food and water than adults on a per kilogram basis which can lead to greater levels of exposure. Behavior can also contribute to increased exposures in children. For example, infants place objects into their mouth and adolescents exercise poor judgement-putting themselves at risk. The impact of different stages in human development on absorption through the placenta, skin, respiratory tract, and gastrointestinal tract is also discussed. Distribution in children may be different. Examples are higher volumes of distribution for drugs in children and greater retention of lead in the infant brain. The impact of metabolism changes during maturation may serve to protect or harm the child depending upon the specific chemical and activity of enzymes which can biotransform chemicals into more toxic metabolites or detoxify them. There is also an impact of development on excretion since the kidney is not mature until 16 months. Target organs in the developing human may be more susceptible to chemical exposures. Children grow by means of cell division, auxelic growth (cells become larger), and accrete non-living structural materials. Other important processes in organ maturation involve cell migration and differentiation. Alveoli are not completely formed until adolescence. Interference with any of these processes through chemical exposure can have permanent consequences with a decrement in organ capacity such as lead toxicity and its impact on intelligence or the induction of cancer in rapidly dividing cells.

The Bearer (1995) review discusses the development of children and the factors that make them other than “little adults”. It presents a number of physiologic differences which could result in children being more susceptible or resistant to chemical exposure. However, with regard to the question of the selection of appropriate uncertainty factors to protect children and asthmatic children, there are no data discussed which permit an assessment of the difference in threshold levels of response, or range of response, between adults and children, healthy or asthmatic. Therefore this paper cannot be used address the question of the selection of the appropriate intraspecies uncertainty factor to be used for irritant gasses.

With respect to anatomical and physiological considerations, the comparison between children and adults is very complex. For example, it is known that children have smaller airways than adults. However, it has been shown that children have less smooth muscle mass within the broncho-pulmonary system (Matsuba and Thurlbeck, 1972) leading to less severe bronchoconstriction for an equivalent stimulus by a chemical irritant. Based on comparative studies with children and adults (de Pee et al.,

1991), this factor may offset the many other considerations such as degree of inflammatory airway wall swelling (Bel et al., 1989; James et al., 1989), changes in the geometry and mechanical properties of the airways and parenchyma with lung growth (Thurlbeck, 1975), slow increases in the transpulmonary pressure from childhood to adulthood (De Troyer et al., 1978), and thickness of airway walls in infants (James, 1989). The consideration of dosimetric concentrations was difficult to evaluate. Although children breathe approximately twice the volume of air per kg of body weight per day as adults (Bearer, 1995), other factors, for which data are lacking, such as minute volume to surface area, scrubbing, metabolic rate differences, and overall pulmonary function status of child and adult asthmatics result in an unclear picture that precludes a useful conclusion of their impact.

3.4.2 Summary and Conclusion

Studies on methacholine sensitivity and reactivity in children, adolescents, and adults from the age of 1-17 (Avital et al., 1991) and 7-47 (de Pee et al., 1991) failed to differentiate between age groups. Avital et al. (1991) determined the PC_{20} (PCW, concentration of methacholine which causes wheezing was measured in 1-6 year olds) in mild, moderate and, severe asthmatic categories in the 1-6, 7-11, and 12-17 year old range. The values for all age groups did not differ significantly within an asthma severity category but did between categories except for the moderate/severe in the 6-11 and 12-17 age group although the PC_{20} was lower for the severe category in these age groups. . De Pee et al. (1991) found that in non-asthmatic and asthmatic adults and children who have been selected for a broad, and overlapping, sensitivity to methacholine challenge, the inverse relationship between PD_{20} and maximal airway narrowing is similar. Thus for direct pharmacologic stimulation of nerve endings, there is evidence that the physiological response in all four categories is similar for comparable sensitivities to methacholine challenge. For this endpoint, adult and child, whether non-asthmatic or asthmatic respond similarly and according to their sensitivity to methacholine. Asthmatics respond to lower doses of methacholine than healthy individuals. However, child asthmatics do not differ from adult asthmatics and non-asthmatic children do not respond differently from non-asthmatic adults when methacholine sensitivity is compared to maximal airway narrowing. This conclusion must be put in the context that there are no data for children under 1 year of age. Although irritant gases at low doses probably do not directly stimulate neuromuscular junctions, the end result of their action is to stimulate these junctions by stimulating the vagus nerve either directly or through an undefined cascade effect (see discussion of Nadel et al., 1965 above who demonstrated that in humans and cats, the initial response to low levels of SO_2 exposure in the upper or lower airways is narrowing of the airways due to the reflex nature of bronchoconstriction via the vagus nerves). Therefore, the methacholine experiments discussed above support the conclusion that childhood asthmatics will respond to similar exposure concentrations with a similar response as adult asthmatics to irritant exposures. The difference in asthmatic severity (mild, moderate, severe) is a more important determinant than age.

Bronchial reactivity as measured by methacholine sensitivity distinguishes between severity groups but is not different between ages within sensitivity groups. Thus, asthmatic children of 1 year of age or older are not more sensitive to methacholine than asthmatic adolescents for given asthma severities.

An evaluation of the December 1952 London episode described by Bates (1995) provided a summary of the increase in mortality in across age groups. The increase in death rate from the pollution episode ranged from 1.3 for 1-14 year old children to 2.8 for 45-75+ years of age. The greatest increase is for those over 45 years of age with the greatest difference in susceptibility of approximately 2-fold. The exposure was to all age groups, sexes, and individuals of varying degrees of susceptibility and to very similar levels and durations of exposure. The increase in death rate was clearly due to an acute episode. If children represented a particularly sensitive group then their death rate increase should have been much greater than adults. Since this was not the case, children do not seem to be at greater risk of death than adults when exposed to high levels of pollutants.

In view of these findings it is concluded that the current approach of the NAC/AEGL Committee of using an uncertainty factor of 3-fold to account for the variability of susceptible populations, including asthmatics, is adequate for asthmatic children as well as asthmatic adults. However, the NAC/AEGL Committee will continue to follow the SOP Manual procedures that emphasize the evaluation of newly derived AEGL values with all other supporting data in order to provide a "weight of evidence" approach to the development of the final AEGL values. In instances where the supporting data do not agree with the initial AEGL values derived, appropriate adjustments are made. As a result, the derivation of the AEGL values has been, and will continue to be, chemical-specific. Examples of, and information on, chemical irritants where this approach has been used have been added to the appendices of this document. They include allyl alcohol, chlorine, hydrazine, hydrogen chloride, and hydrogen fluoride and represent a diverse group of chemical irritants.

4 USE OF KEY AND SUPPORTING DATA TO DERIVE AN INTRASPECIES UNCERTAINTY FACTORS FOR AEGL VALUES

As discussed earlier, the available human data support intraspecies uncertainty factors ranging from 1 to 5 to account for potential differences between healthy individuals and asthmatics for AEGL-1 type of effects. Although no data exist to compare differences between asthmatics and healthy individuals for the more severe effects or lethality that characterize AEGL-2 and AEGL-3, there is a rationale for suggesting that the differences may become less as the concentration of the irritant increases. As the concentrations increase, particularly in the case of highly corrosive irritants, the insult and damage to all respiratory tissues increases in both asthmatics and healthy individuals and may overshadow the typical asthmatic responses. This may be particularly the case for exposure periods beyond 10 minutes because a typical asthmatic response to exposure to an irritant gas often occurs early in this time period.

Given the uncertainties surrounding differences in susceptibility between healthy and asthmatic people for AEGL-2 (serious, irreversible, disabling) and AEGL-3 (death) effects, the use of uncertainty factors in deriving AEGL-2 and AEGL-3 tiers for irritants requires a careful chemical specific analysis of all of the data. This analysis of the supporting data has been used in the selection of appropriate uncertainty factors, and together with the use of sound scientific judgement, is critical in determining the rationale for selection which is made of the most appropriate uncertainty factor.

Appendix B has examples of chemical specific arguments which can be made for data rich and data poor chemicals and should serve as a model of how to select uncertainty factors in the future. The following guidelines have been used to select appropriate intraspecies uncertainty factors.

The selection of uncertainty factors in deriving AEGL-2 and AEGL-3 levels for irritants will require a chemical specific analysis of all of the data. This will require careful assessment of the following considerations:

1) Which intraspecies uncertainty factor (1, 3, or 10), when applied to the key study, gives the best fit with all of the other data on the chemical or its analogs? Are the derived AEGL values consistent with the supporting data?

2) If the AEGL value generated by the use of a higher intraspecies uncertainty factor is not reasonable in light of the supporting data, what is the reason?

a) Was an adverse effect used to determine an AEGL-2 level which is far below that expected for an AEGL-2 endpoint. For example, selection of mild coughing as an AEGL-2 endpoint. Why was the endpoint selected conservative or below an AEGL-2 effect level? In this case a lower uncertainty factor may be justified.

b) The use of a higher uncertainty factor drives the AEGL-2 value to a level at or below a level which humans have been shown to tolerate as a result of human exposure or monitoring studies and is not likely to elicit AEGL-2 type effects in asthmatics or other susceptible subpopulations.

c) The use of a higher uncertainty factor would have driven the AEGL-2 value to a level which is not consistent with the supporting data, especially as they relate to the human experience.

d) Are the dose response curves in the animal studies exceptionally steep? For example, if the dose which just initiates a measurable amount of edema is close to the dose which causes death, this may justify a lower uncertainty factor. The irritant chemicals stimulate or injure lung tissue by means of a non-specific chemical reaction with the cells. This reaction should be similar in both asthmatic and healthy individuals. An extremely

steep dose response curve described above (from the beginning of lung edema to death) would argue for the conclusion that the difference in concentration between initial reaction with, injury to, and in some cases destruction of, upper and lower respiratory tissue and the concentration that results in death is a very narrow range. One might argue that, although the asthmatic individual might react with pulmonary edema formation and/or inflammatory reaction at the lower end of that range, the range itself is so narrow that the difference between the adverse effects in the asthmatic and the healthy individual is minimal.

e) Other considerations that may be chemical-specific or data-specific that support the conclusions drawn to strengthen the rationale used.

3) Considering interspecies and intraspecies uncertainty factors independently can lead to an overly conservative AEGL value. When the two uncertainty factors are multiplied together the resultant total uncertainty factor generally represents a worst case times a worst case. Therefore the total uncertainty factor must be evaluated and the AEGL values compared with all of the supporting data. If the supporting data do not support the AEGL values it may be necessary to reconsider one or both of the uncertainty factors using the supporting data as a rationale.

4) Give specific data to support the conclusions drawn to strengthen the argument made.

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Appendix A-GLOSSARY

CIU=Cumulative inhalation units-used to describe sensitivity to methacholine (Horstman, 1986).

Closing Capacity (CC)=Difference between RV and point where airways begin to collapse. The volume is the closing volume (Levitskly, 1995).

Closing Volume (CV)=Volume of the lung at which airway closure begins (Levitsky, 1995).

Conductance=The reciprocal of resistance (1/Raw). (Nadel et al., 1965).

Expiratory Reserve Volume (ERV)=Volume expelled during a maximal forced expiration that starts at the end of a normal tidal exhalation-about 1.5 liters (Levitsky, 1995).

FEF_{25-75}=Forced expiratory flow 25 to 75% (d'Alessandro et al., 1996).

FEV_1/FVC=Good index of expiratory airways resistance. This ratio is 0.8 in a healthy individual and may be 0.5 in a patient with obstructive airways disease (Levitsky, 1995).

Forced Expiratory Volume (FEV_1)=The volume of air expired during the first second of expiration after a maximal inspiration.

Forced Vital Capacity (FVC)=The volume expelled during a maximal expiratory effort after a maximal inspiration has been made. The point is that a maximum effort is made as opposed to the VC where the subject can exhale at a less than maximal rate. This allows a 1 second measurement to be made. (Levitsky, 1995).

Functional Residual Capacity (FRC)=Volume left at the end of a normal exhalation-about 3 liters (Levitsky, 1995). ERV+RV. What you can forcefully blow out after a normal breath plus the amount left after this forced exhalation which cannot be expelled. The FRC is the volume when no respiratory muscles are contracting and the inward recoil of the lungs is balanced by the outward recoil of the chest.

Inspiratory Capacity (IC)=Volume inhaled during a maximal inspiratory effort begun at the end of a normal tidal exhalation-about 3 liters (Levitsky, 1995).

Inspiratory Reserve Volume (IRV)=Volume inhaled during a maximum forced inspiration starting at the end of a normal inhalation-about 2.5 liters (Levitsky, 1995).

$MFEV_1$=The maximal airway narrowing response observed with a bronchoconstrictor challenge when measured as the maximum decrease in FEV_1 and calculated as the mean response on the plateau of the dose-response curve (de Pee et al.,

1991).

Obstructive lung disease=(Levitsky, 1995 p266) Asthma, chronic bronchitis, emphysema. Interfere with airflow.

PD(MET)="...cumulative dose of methacholine which provided a 100% increase in SRaw over that observed after inhaling normal saline" (Horstman et al., 1986).

PC(SO_2)=Provocative dose of SO_2 or the interpolated concentration of SO_2 which caused an increase in SRaw of 100%.

PC_{20} = Concentration of methacholine required to reduce FEV_1 by 20% (Avital et al., 1991).

PD_{20} = Provocation dose of methacholine required to reduce FEV_1 by 20%. (de Pee et al., 1991)

PEF = Peak expiratory flow (Levitsky, 1995).

Plethysmograph = an airtight chamber. Manometers can be connected to measure changes in pressure within the chamber as the subject's chest cavity expands and contracts during breathing. (DuBois et al., 1956b).

Raw Airway resistance (Raw) (Horstman et al, 1986). Resistance = pressure difference (cmH_2O) / flow (Liters per second) (Levitsky, 1995). Thus for a given pressure difference, the greater the resistance the lower the flow of air. Airway flow in a straight tube is laminar and can be visualized as a series of concentric columns with air in the central columns moving faster than at the periphery. However, this flow only occurs in the smallest airways. Most airflow is turbulent or a combination of both. According to Poiseuille's law the resistance is inversely proportional to the fourth power of the radius of the tube (p36) for laminar flow (true laminar flow probably only occurs in the smallest airways where the linear velocity is low). Therefore, if the radius is cut in half the resistance is multiplied by 16.

The upper airways (down to the larynx) contribute to 25-40 % of the total resistance. Resistance is higher through the nose. In the tracheobronchial tree, the smallest airway provides the greatest resistance. However, the smallest airways are arranged in parallel to their resistances add as the reciprocal of their individual resistances. Thus the greatest resistance under normal conditions is from the medium sized bronchi.

25-40% of the total resistance is in the upper airways (nose, nasal turbinates, oropharynx, nasopharynx, and larynx). Smallest airways are arranged in parallel to their resistance adds as the reciprocal. Therefore their total resistance is

lower during normal breathing. Normally the medium-sized bronchi contribute the greatest resistance to airflow.

Control of bronchial smooth muscle. The smooth muscle of the trachea to the alveolar ducts is controlled by autonomic nervous system efferent fibers. Cholinergic parasympathetic post ganglionic fiber stimulation causes both bronchial smooth muscle constriction and increased glandular mucus secretion. Preganglionic fibers travel in the vagus nerve. Adrenergic sympathetic fiber stimulation causes dilation of the bronchial and bronchiolar smooth muscle and inhibits glandular secretion. Beta$_2$ receptors (adrenergic) mediate dilation and alpha receptor (cholinergic) stimulation mediate bronchoconstriction. Irritants, smoke, histamine cause reflex constriction of the airways. Low CO_2 levels cause local constriction in branches of the bronchi and high CO_2 or low oxygen cause local dilation.

D'Alessandro et al., 1996 exposed healthy and asthmatic individuals to 1 ppm chlorine for 60 minutes and observed an average decrement in the asthmatics of 16% FEV_1 and 108% Raw for a ratio of 6.75.

Residual volume (RV)=Volume of gas left in the lungs after a maximal forced expiration, about 1.5 liters (Levitsky, 1995). Much greater in a diseased state such as emphysema because the inward elastic recoil of the alveoli is diminished.

Restrictive diseases=(Levitsky, 1995) Diseares that restrict lung expansion (e.g. fibrosis).

Spirometer=Device for measuring gas volumes. The residual volume and the total lung capacity cannot be measured. Can also measure FEV_1 and FVC (Levitsky, 1995).

SRaw Raw x Vtg (Horstman et al, 1986). Units are (cmH_2O {measure of pressure difference}/Liters per second) x (Liters). SRaw (Raw X Vtg) was calculated to "compensate approximately for the effect of lung volume changes on resistance" (Linn, et al., 1982).

Tidal volume (V_T)=Volume of air leaving the mouth or nose per breath, about 500 ml resting (Levitsky, 1995). This will increase with exercise.

Total Lung Capacity (TLC)=Volume after a maximal inhalation effort-about 6 liters (Levitsky, 1995). This includes the residual volume

Transmural pressure gradient=Pressure inside (e.g. alveolar pressure) minus pressure outside (intrapleural pressure)

V_E Minute volume

Vtg Thoracic gas volume (Vtg) (Horstman et al, 1986). This is a measure of the Functional Residual Capacity (FRC) (DuBois et al., 1956a).

Vital Capacity (VC)=Volume expelled during a maximum forced expiration following a maximal forced inspiration (Levitsky, 1995).

Appendix B-CHEMICAL SPECIFIC ARGUMENTS FOR THE SELECTION OF UNCERTAINTY FACTORS

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Allyl alcohol

The AEGL values for allyl alcohol were developed using an intraspecies uncertainty factor of 1 for the AEGL-1 values and 3 for the AEGL-2 and AEGL-3 values.

Summary of Proposed AEGL Values for Allyl Alcohol [ppm (mg/m^3)]

Classification	10-minute	30-minutes	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Non-disabling)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	Mean odor detection threshold (AIHA, 1989)
AEGL-2 (Disabling)	9.6 (23)	9.6 (23)	7.7 (19)	4.8 (12)	3.5 (8.5)	Irritation in rats at 40 ppm for 7 hr (Dunlap et al., 1958)
AEGL-3 (Lethality)	36 (87)	25 (61)	20 (48)	10 (24)	7.1 (17)	NOEL for lethality in mice, rats, and rabbits exposed to 200 ppm for 1 hr (Union Carbide, 1951)

Allyl alcohol-rationale for selection of an intraspecies uncertainty factor of 1 for the AEGL-1 tier

Although the human exposures by Dunlap et al. (1958) measured some endpoints consistent with the definition of an AEGL-1, the exposures were of too short a duration to be reliable and the exposure concentrations were most likely nominal concentrations. Therefore, the proposed AEGL-1 values will be based on the mean odor detection threshold value of 1.8 (AIHA). Because odor threshold is not dependent upon the length of exposure, the threshold value is applied to all times.

Allyl alcohol-rationale for selection of an intraspecies uncertainty factor of 3 for the AEGL-2 tier

Although AEGL values are normally based on single-exposure studies, no single-

exposure studies were appropriate for derivation of the allyl alcohol AEGL-2. In a subchronic exposure study, rats repeatedly exposed to 40 ppm for 7 hours/day experienced irritation during the first few exposures that disappeared thereafter (Dunlap et al., 1958). This experiment provides the basis for the AEGL-2 derivation. **The selection of this effect from a multiple exposure study appears to be overly conservative. However, in the same study, 4/10 rats exposed to 150 ppm for 7 hours died during the first exposure and 2/10 died following the first exposure. Although exposure to 40 ppm for 7 hours a day for 60 exposures did not cause a disabling effect, the concentration is within a factor of 4 of a concentration which killed over 50% of the animals in a single exposure. Therefore 40 ppm is a reasonable choice for calculation of AEGL-2 levels**

An uncertainty factor of 3 was applied for species to species extrapolation because there did not appear to be much variation between species: a NOEL for lethality was the same for 3 different species (mice, rats, and rabbits). An uncertainty factor of 3 was also applied for intraspecies extrapolation. Although the traditional approach for uncertainty factors in a case such as this would argue for an uncertainty factor of 10 because of the lack of data addressing interindividual variability, this would result in a composite uncertainty factor of 30. An uncertainty factor of 30 would drive the AEGL-2 values to a level that would be inconsistent with available data (8 hour AEGL-2 of 1.2 ppm): Dunlap et al. (1958) reported that rats exposed for 7 hr/d, 5 days/wk for 60 exposures to 1, 2, or 5 ppm had no observable adverse effects, while rats repeatedly exposed to 20 ppm only exhibited decreased body weight gain, and Torkelson et al. (1959a) reported that no adverse effects were noted when rats, guinea pigs, rabbits, and dogs were exposed to 2 ppm for 7 hr/d, 5 d/wk for 28 exposures, while exposure of rats, guinea pigs, and rabbits exposed to 7 ppm for 7 hr/d, 5 d/wk for 134 exposures exhibited only reversible liver and kidney damage. Therefore, a total uncertainty factor of 10 was applied to the AEGL-2 value.

The experimentally derived exposure value was then scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge, 1986). The value of n was not empirically derived due to the unreliability and inconsistencies of the data; therefore, the default value of n = 1 was used for extrapolating from shorter to longer exposure periods and a value of n = 3 was used to extrapolate from longer to shorter exposure periods. The 10-minute value was set equal to the 30-minute value because it was considered too precarious to extrapolate from the exposure duration of 7 hours to 10 minutes.

The derivation is further supported by the Shell Chemical Corporation (1992) study in which repeated 8-hour exposures of rats to 40 ppm resulted in only moderate lung congestion.

Allyl alcohol-rationale for selection of an intraspecies uncertainty factor of 3 for the AEGL-3 tier

Because the LC_{50} studies were unreliable and the rest of the data did not permit calculation of a dependable concentration-response relationship, a NOEL for lethality in mice, rats, and rabbits of 200 ppm for 1 hour was chosen as the AEGL-3 endpoint (Union Carbide, 1951).

An uncertainty factor of 3 was applied for species to species extrapolation because there did not appear to be much variation between species for lethality. A NOEL for lethality was the same for 3 different species (mice, rats, and rabbits), and this endpoint was used for the AEGL-3 derivation. **The same NOEL for lethality was observed for 3 species. This increases the confidence in that value as a reliable NOEL for lethality.** An uncertainty factor of 3 was also applied for intraspecies extrapolation. Although the traditional approach for uncertainty factors in a case such as this would argue for an uncertainty factor of 10 because of the lack of data addressing interindividual variability, this would result in a composite uncertainty factor of 30. An uncertainty factor of 30 would drive the AEGL-3 values to a level that would be inconsistent with available data (1 hour AEGL-3 of 6.7 ppm): Dunlap et al. (1958) reported that rats exposed for 7 hr/d, 5 days/wk for 60 exposures to 1, 2, or 5 ppm had no observable adverse effects, while rats exposed to 20 ppm only exhibited decreased body weight gain, and Torkelson et al. (1959a) reported that no adverse effects were noted when rats, guinea pigs, rabbits, and dogs were exposed to 2 ppm for 7 hr/d, 5 d/wk for 28 exposures, while exposure of rats, guinea pigs, and rabbits exposed to 7 ppm for 7 hr/d, 5 d/wk for 134 exposures exhibited only reversible liver and kidney damage. Therefore, a total uncertainty factor of 10 was applied to the AEGL-3 value.

The experimentally derived exposure value was then scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge, 1986). The value of n was not empirically derived due to the unreliability and inconsistencies of the data; therefore a default value of n should be used in the temporal scaling of AEGL values across time. If one applies the default value of $n = 1$ for extrapolating from shorter to longer exposure periods and a value of n = 3 to extrapolate from longer to shorter exposure periods, one obtains the values in Table 9.

TABLE 9. AEGL-3 Values For Allyl Alcohol (using a default of n=1 for shorter to longer exposure periods and n=3 for longer to shorter exposure periods)

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-3	36 ppm	25 ppm	20 ppm	5.0 ppm	2.5 ppm

Again, going with a default value results in AEGL values that are inconsistent with the available data. The AEGL-2 data do not support the selection of a value of n=1 for extrapolation to 4 or 8 hours: when using an n=1 (which assumes a "conservative" scenario) to extrapolate from 1 hour to 4 or 8 hours, one obtains a 4-hour AEGL-3 value of 5.0 ppm, which is almost identical to the 4-hour AEGL-2 value of 4.8 ppm, and an 8-hour AEGL-3 value of 2.5 ppm, which is lower than the 8-hour AEGL-2 value of 3.5 ppm. The AEGL-2 values help to serve as a baseline: they are based on a multiple exposure scenario in which rats exposed for 40 ppm for 7 hrs/d exhibited reversible signs of irritation. It is unreasonable to have an AEGL-3 values below the AEGL-2 values. Therefore, in the absence of any further data, an *n* of 2 was selected as a reasonable compromise between the possible values for *n* as reported by ten Berge (1986): it is between the most conservative *n*=1 (which results in unreasonable values) and an *n* of 3, a least conservative value. AEGL-3 values based on an n=3 for extrapolation from 1 hour to 10 and 30 minutes and an n=2 for extrapolation from 1 hour to 4 or 8 hours are presented in Table 10.

TABLE 10. Proposed AEGL-3 Values for Allyl Alcohol

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-3	36 (87)	25 (61)	20 (48)	10 (24)	7.1 (17)

The study in which mice survived a 500 ppm exposure for 0.5 hours produces similar but slightly higher values.

In Figure Allyl alcohol-1 all of the data, including the multiple exposure studies, are plotted by category of AEGL effect along with the AEGL values. The censored category is one in which the animals did not die but experimental observations were not presented in sufficient detail to assign a category to the effect. The AEGL values are certainly protective and reasonable in light of all of the supporting data.

Figure Allyl alcohol-1

Allyl alcohol references:

AIHA (American Industrial Hygiene Association). 1989. Odor Thresholds for Chemicals with Established Occupational Health Standards. AIHA, Fairfax, VA.

Dunlap, M.K., J.K.,Kodama, J.S Wellington, H.H. Anderson, and C.H. Hine. 1958. The toxicity of allyl alcohol. A.M.A. Arch. Ind. Health 18:303-311.

Union Carbide and Carbon Corporation. 1951. Initial submission: Letter from DuPont Chem to USEPA regarding a letter about toxicity studies with allyl alcohol with cover letter dated 10/15/92. Union Carbide and Carbon Corporation, New York, N.Y. Doc. # 88-920009857.

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SUMMARY OF AEGL VALUES FOR CHLORINE					
Classification	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1[a]	1.4 ppm (4.1 mg/m^3)	1.0 ppm (2.9 mg/m^3)	0.5 ppm (1.5 mg/m^3)	0.5 ppm[b] (1.5 mg/m^3)	No to slight changes, pulmonary function - human (Rotman et al., 1983)
AEGL-2	2.8 ppm (8.1 mg/m^3)	2.0 ppm (5.8 mg/m^3)	1.0 ppm (2.9 mg/m^3)	0.71 ppm (2.0 mg/m^3)	Asthmatic-like attack - human (Rotman et al., 1983)
AEGL-3	28 ppm (81 mg/m^3)	20 ppm (58 mg/m^3)	10 ppm (29 mg/m^3)	7.1 ppm (21 mg/m^3)	Lethality - rat (MacEwen and Vernot, 1972; Zwart and Woutersen, 1988)

[a]The distinctive, pungent odor of chlorine will be noticeable to most individuals at these concentrations
[b]Because effects were not increased following an interrupted 8-hour exposure of an atopic individual to 0.5 ppm, the 8-hour AEGL-1 was set equal to 0.5 ppm.

Chlorine-rationale for selection of an intraspecies uncertainty factor of 1 for the AEGL-1 tier

The human studies of Anglen (1981), Rotman et al. (1983), and D'Alessandro et al. (1996) are the only relatively recent studies that addressed sensory irritancy. The Anglen (1981) study did not include sensitive individuals and the D'Alessandro et al. (1996) study did not use control exposures, did not use exercising subjects, and was conducted over a shorter period of time than the Rotman et al. (1983) study. Therefore, the Rotman et al. (1983) study will be used to derive the AEGL-1 and the D'Alessandro et al. (1996) study will be used as a supporting study. Because there was a break midway through the 8-hour exposures in the Rotman et al. (1983) study, possibly allowing for recovery from sensory irritation, only the continuous 4-hour exposure times will be considered.

The 1 ppm concentration for 4 hours resulted in serious symptoms in a sensitive individual but exposure to 0.5 ppm was tolerated for 4 hours (with transient pulmonary function changes - e.g. increase in Raw of 40% which is not clinically significant). Furthermore, the subjects were exercising at a mild level which increased their breathing rate and thus their exposure. Thus, the 0.5 ppm concentration for 4 hours will be used to set the AEGL-1 values. The 0.5 ppm concentration was a no-effect level for sensory irritation in all subjects including a sensitive individual. The sensitive individual was considered representative of the "susceptible" subpopulation; the transient changes in pulmonary function parameters in this individual were not considered adverse effects. The lack of effects in subjects with airway hyperreactivity exposed to 0.4 ppm (D'Alessandro et al., 1996) supports this choice. Because of the longer exposure period, the Rotman et al. (1983) yields a higher NOAEL. Because a sensitive exercising individual characteristic of the susceptible subpopulation (see Section 4.5.1)

did not exhibit adverse effects, there is no need to apply an uncertainty factor for adjustment for differences in human sensitivity.

The 0.5 ppm concentration for the 4-hour exposure was extrapolated to the other time periods using the $C^2 \times t = k$ relationship.

The study conducted by Rotman et al. (1983) actually lasted more than 8 hours if the break after the initial 4-hour session is included. This factor reduces the uncertainty usually associated with scaling from shorter to longer time periods. Because effects were not increased following an interrupted 8 hours of exposure of the sensitive individual to 0.5 ppm, the time-scaled 8-hour AEGL-1 of 0.35 ppm was rounded up to 0.5 ppm.

Further support for the AEGL-1 values comes from Figure Chorine-1 below which is a plot of the human and primate data with the AEGL values. Studies in 5 laboratories on humans show a consistent picture with no or minimal effects at the AEGL-1 levels.

Figure Cholorine-1 Human data

Chlorine-rationale for selection of an intraspecies uncertainty factor of 1 for the AEGL-2 tier

Because human data are available, they should be used to calculate the AEGL-2. In the Rotman et al. (1983) study, the exposure of an exercising sensitive subject to 1 ppm for 4 hours resulted in serious asthmatic-like symptoms and pulmonary function changes which are near the threshold of impairment of escape and which fall under the definition of the AEGL-2 (threshold for irreversible or other serious, long-lasting effects or impaired ability to escape). Because a sensitive individual representative of the susceptible subpopulation (see Section 4.5.1) was tested and his reactions were near the threshold for the definition of the AEGL-2, no uncertainty factor for differences in human sensitivity was applied. Similar changes but without the symptoms in subjects with airway hyperreactivity and or asthma exposed to 1.0 ppm in the D'Alessandro et al. (1996) study support this choice. The 4-hour 1 ppm concentration was scaled to the other time periods using the $C^2 \times t = k$ relationship.

The one-year study in which exposure of Rhesus monkeys to a concentration of 2.3 ppm Cl_2 for 6 hours/day, 5 days/week resulted in mild histopathological changes in the nasal passages and trachea (Klonne et al., 1987) supports the safety of this short-term exposure for humans. The calculated AEGL-2 value for a single 6 hour exposure would be 0.82 ppm which is approximately 3-fold less than an exposure level which caused mild changes below the AEGL-2 definition in a primate which was exposed for 5 days a week over a one year period. The respiratory track of the monkey is an appropriate model for humans.

Chlorine-rationale for selection of an intraspecies uncertainty factor of 3 for the AEGL-3 tier

Because the experimental data with mice appeared to provide an overly conservative estimate of lethality that was not consistent with the overall preponderance of the data, a value less than the concentration that resulted in no deaths in rats but greater than the value that resulted in no deaths in mice was chosen as the basis for the AEGL-3 values. The value of 200 ppm is below the 1-hour highest nonlethal concentration (213 from MacEwen and Vernot, 1972 and 322 ppm from Zwart and Woutersen, 1988) and LC_{01} (288 ppm from Zwart and Woutersen, 1988) in two well-conducted studies with rats and above the 1-hour highest nonlethal concentration in mice, 150 ppm (O'Neil, 1991). The 200 ppm concentration is an LC_{20} for the mouse. An uncertainty factor of 3 was used to extrapolate from rats to humans (the data show that interspecies differences were within a factor of approximately 2 for lethality). In addition, chlorine is a contact-site, direct-acting toxicant; there is no metabolic or pharmacokinetic component to chlorine-induced effects and there is likely to be little difference between species in the response of biological tissues to chlorine exposure. Also, for intraspecies differences, corrosive gases acting at the point of contact would predict low variability in a population; thus an uncertainty factor of 3 is applied to protect sensitive individuals. The relative sensitivity of asthmatics when considering lethality is unknown, but the data from the Rotman et al. (1983) and D'Alessandro et al. (1996) studies showed that doubling a no-effect concentration for irritation and bronchial constriction resulted in potentially serious effects. The data were divided by a combined uncertainty factor of 10 and were scaled to the 30-minute and 4- and 8-hour exposure durations using the $C^2 \times t = k$ relationship which was based on a nuisance level of human irritation.

It should be noted that the proposed 1-hour AEGL-3 of 20 ppm is below an AEGL-3 derived from the 1-hour LC_{01} (the threshold for lethality) of the rat of 28.8 ppm (288/10).

Further support for the total uncertainty factor of 10 comes from Figure Chlorine-2 below which is a plot of the lethality data. The AEGL-3 values are all well below any study which caused lethality in rats, mice, rabbits and dogs.

Figure Chlorine-2 Plot of lethality data

Chlorine references:

Anglen, D.M. 1981. Sensory response of human subjects to chlorine in air. Ph.D. Dissertation, University of Michigan.

D'Alessandro, A., W. Kuschner, H. Wong, H.A. Boushey, and P.D. Blanc. 1996. Exaggerated responses to chlorine inhalation among persons with nonspecific airway hyperreactivity. Chest 109:331-337.

Klonne, D.R., C.E. Ulrich, M.G. Riley, T.E. Hamm Jr., K.T. Morgan, and C.S. Barrow. 1987. One-year inhalation toxicity study of chlorine in rhesus monkeys (Macaca mulatta). Fundam. Applied. Toxicol. 9:557-572.

MacEwen, J.D. and E.H. Vernot. 1972. Toxic Hazards Research Unit Annual Technical Report: 1972. AMRL-TR-72-62, Aerospace Medical Research Laboratory,

Wright-Patterson Air Force Base, OH; National Technical Information Service, Springfield, VA.

O'Neil, C.E. 1991. Immune responsiveness in chlorine exposed rats. PB92-124478, Prepared for National Institute for Occupational Safety and Health, Cincinnati, OH.

Rotman, H.H., M.J. Fliegelman, T. Moore, R.G. Smith, D.M. Anglen, C.J. Kowalski, and J.G. Weg. 1983. Effects of low concentration of chlorine on pulmonary function in humans. Journal of Applied Physiology 54:1120-1124.

Zwart, A. and R.A. Woutersen. 1988. Acute inhalation toxicity of chlorine in rats and mice: time-concentration-mortality relationships and effects on respiration. Journal of Hazardous Materials 19:195 208.

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Hydrazine

The AEGL values for hydrazine were developed using an intrapsecies uncertainty factor of 3 for the AEGL-1,2, and 3 tiers.

SUMMARY OF AEGL VALUES FOR HYDRAZINE

Classification	30-min	1-hour	4-hour	8-hour	Endpoint(Reference)
AEGL-1 (Non-disabling)	0.1 ppm 0.1 mg/m^3	0.1 ppm 0.1 mg/m^3	0.1 ppm 0.1 mg/m^3	0.1 ppm 0.1 mg/m^3	Eye and facial irritation in monkeys (House, 1964)
AEGL-2 (Disabling)	16 ppm 21 mg/m^3	13 ppm 17 mg/m^3	3.1 ppm 4.0 mg/m^3	1.6 ppm 2.1 mg/m^3	Nasal lesions (Latendresse et al., 1995)
AEGL-3 (Lethal)	45 ppm 59 mg/m^3	35 ppm 46 mg/m^3	8.9 ppm 11.6 mg/m^3	4.4 ppm 5.7 mg/m^3	Lethality in rats (HRC, 1993)

Hydrazine-rationale for selection of an intraspecies uncertainty factor of 3 for the AEGL-1 tier

The data from the study by House (1964) in which male monkeys were continuously exposed to hydrazine at 0.52 mg/m^3 (0.4ppm-average concentration for the first 10 days of the 90-day exposure period) resulting in skin flushing and swollen eyes after 24 hours of exposure was used as the basis for the AEGL-1. Based upon the available data, this exposure represents the lowest exposure resulting in a definitive effect that could be considered consistent with the definition of an AEGL-1.

Exponential scaling with the equation $C^n \times t = k$ (ten Berge, 1986) was used to

derive exposure duration-specific values. Data were unavailable for an empirical derivation of *n* in the equation, $C^n \times t = k$. It has been shown that 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 chemical specific data, an *n* of 3 was applied to extrapolate to shorter time periods. The use of exponential scaling rather than linear scaling resulted in AEGL-1 values that are lower (i.e., more protective) for 0.5 and 1 hour durations. These values may, however, be justifiable based upon the steep dose-response for hydrazine (Jacobson et al. (1955) noted the slope of the exposure concentration/lethality curve to be 7.32±1.8 and 3.79±1.6 (±SE) for rats and mice, respectively.) Using an uncertainty factor of 10 and linear scaling (Haber's Law), the resulting AEGL-1 values would be slightly greater (i.e., 2, 1, 0.2, and 0.1 ppm for the 0.5, 1, 4, and 8-hr durations, respectively). Because hydrazine is extremely reactive and irritating at very low concentrations, and because surface contact irritation from hydrazine appears to more dependent upon exposure concentration than exposure duration, the AEGL-1 values were reduced to 0.1 ppm for all AEGL-specific exposure periods. Because hydrazine is extremely reactive and the sensory-irritation effects are considered to be concentration dependent rather than time dependent, the 0.1 ppm AEGL-1 value derived for the 4-hour and 8-hour durations was applied to the 30-minute and 1-hour durations.

A total uncertainty factor of 10 was applied to derive the AEGL-1 values (each uncertainty factor of 3 is actually the geometric mean of 10 [i.e., 3.16], hence; 3.16 x 3.16 = 10). An uncertainty factor of 3 was applied for interspecies variability because the surface contact irritation by the highly reactive hydrazine is not likely to vary greatly among species, and because a nonhuman primate was the test species. An uncertainty factor of 3 was applied for intraspecies variability because the contact irritation from the highly reactive hydrazine is not expected to vary greatly among individuals, including susceptible individuals. **The composite total uncertainty factor of 10 which gives AEGL-1 values of 0.1 ppm for 30 minutes to 8 hours is reasonable in light of more recent single exposure studies which show minimal effects at much higher exposure concentrations. Latendrasse et al. (1995) exposed rats and hamster to 750 ppm of hydrazine for 60 minutes and observed nasal lesions (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, mild apoptosis) 24 hours after exposure. Kulinga (1962) exposed rats and mice to 19 ppm of hydrazine for 2 hours and observed altered conditioned reflex in each species. The value of 0.1 ppm is conservative because time scaling was performed using conservative parameters in the extrapolation equation (see discussion above).**

Hydrazine-rationale for selection of an intraspecies uncertainty factor of 3 for the AEGL-2 tier

The data from the Latendresse et al. (1995) study showing nasal lesions

(minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, mild apoptosis) in rats following a 1-hr exposure to 750 ppm was considered to be appropriate for setting AEGL-2 values. The study protocol and analytical techniques were superior to earlier studies and histopathologic data were available. The toxicity endpoint involved a specific region of the respiratory tract (nasopharyngeal region) and, although toxicologically and physiologically serious, was reversible upon removal from exposure.

An uncertainty factor of 10 for interspecies variability was applied to account for the high degree of variability in the data due to the extreme reactivity of hydrazine that compromised exposure concentration measurements and due to uncertainties regarding. Although the more recent studies such as that by Latendresse et al.(1995) or HRC (1993) appear to have more reliable determinations of hydrazine concentrations, the overall data set for hydrazine is compromised by uncertainties regarding the variability in response among species. Although some of the variability would likely be accounted for by variances in exposure atmosphere measurements, it is still uncertain as to how much variability exists between humans and test species regarding the actual toxic response to inhaled hydrazine. An uncertainty factor of 3 was applied for intraspecies variability because the port-of-entry effect of the extremely reactive hydrazine is due to direct interaction with biological tissues. This contact irritation is not likely to vary considerably among individuals. A modifying factor of 2 was applied to account for data inadequacies regarding exposure-response relationships and identification of toxic responses consistent with AEGL-2 level effects (i.e., serious or irreversible, but nonlethal, effects of acute inhalation exposure to hydrazine). This resulted in a total adjustment of 60-fold for derivation of AEGL-2 values (Table 10).

The total composite uncertainty/modifying factor of 60 gives values which are reasonable yet protective. The methodology used would give a 2 hour AEGL-2 value of 6.2 ppm. However, Kulinga (1962) observed altered conditioned reflex in rats and mice exposed to 19 ppm of hydrazine for 2 hours, a reversible effect. In addition, the endpoint chosen for determining the AEGL-2 values is reversible and below the AEGL-2 threshold.

As previously noted, the data on nonlethal, irreversible effects resulting from acute exposure to hydrazine are limited. The key study (Latendresse et al., 1995) used to derive the AEGL-2 values appears to provide the highest confidence among the data available for AEGL-2 type effects or an estimation of a threshold for such effects.

Hydrazine-rationale for selection of an intraspecies uncertainty factor of 3 for the AEGL-3 tier

Although several inhalation studies are available that provide data showing lethality or life-threatening effects from acute exposure to hydrazine, the quality of the

studies vary considerably. Earlier studies tended to be compromised to varying degrees by analytical deficiencies in determining the hydrazine concentration of the experimental exposures. Several studies were identified for derivation of AEGL-3 values. These included the acute exposure studies by Jacobson (1955), Keller et al. (1988), HRC (1993).

A notable range of values were obtained depending upon the study used. Although AEGL-3 values derived from the embryolethality data reported by Keller et al. (1988) provide the most conservative AEGL-3 values, this study was compromised by the absence of details for experimental protocol and results (see Section 3.4.1). The AEGL-3 values derived from the Jacobson (1955) data were similar although slightly lower.

The AEGL-3 values were derived based upon the data from the HRC study that provided a 1-hr LC_{50} of 4.2 mg/L (approximately 3,192 ppm) in rats for both sexes). Although a 1-hr LC_{01} of 334 ppm was estimated from the HRC data using the method of Litchfield and Wilcoxon (1949), it was considered to be inappropriate for derivation of AEGL-3 values because it was not consistent with the recent data from Latendresse et al. (1995) that showed 1-hr exposure of rats to 750 ppm did not result in any lethalities. It is believed that a 3-fold reduction of the 1-hr LC_{50} (3,192 ppm/3 = 1,064 ppm) provides an estimate of the lethality threshold that is consistent with the available data. For example, the Latendresse et al. (1995) study demonstrated that rats exposed to 750 ppm for 1 hour per week for 10 consecutive weeks did not experience mortality.

Uncertainty factors were applied as described for AEGL-2. An uncertainty factor of 10 for interspecies variability was applied to account for the high degree of variability in the data due to the extreme reactivity of hydrazine that compromised exposure concentration measurements. As previously described in Section 6.3, the more recent studies by Latendresse et al.(1995) and HRC (1993) utilized more sophisticated exposure chambers assuring more reliable hydrazine exposures. However, the overall data set for hydrazine is still somewhat deficient in reliably determining species variability in the toxic response to inhaled hydrazine. Although some of this variability is likely the result of variability in exposure atmosphere measurements, it is still uncertain as to how much variability exists between humans and test species regarding the actual toxic response to inhaled hydrazine. Therefore, the uncertainty factor of 10 was retained. An uncertainty factor of 3 was applied for intraspecies variability because the port-of-entry effect of the extremely reactive hydrazine is due to direct interaction with biological tissues. This contact irritation is not likely to vary considerably among individuals of the same species. The total uncertainty factor adjustment translated to a 30 (10 x 3) reduction in the exposure concentration from animal data.

The total uncertainty factor of 30 gives values which are reasonable yet protective. The methodology used would give a 2 hour AEGL-3 value of 18 ppm. However, Kulinga (1962) observed altered conditioned reflex in rats and mice exposed to 19 ppm of hydrazine for 2 hours, a reversible effect. Latendrasse et

al. (1995) exposed rats and hamster to 750 ppm of hydrazine for 60 minutes and observed nasal lesions (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, mild apoptosis) 24 hours after exposure. These effects are reversible and the exposure level of 750 ppm is approximately 20-fold more than the one hour AEGL-3 value.

Because the lethal effects of hydrazine appear to be more dependent upon exposure concentration than exposure duration, exponential scaling ($C^n \times t = k$) was used for AEGL derivation. Additionally, 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. To obtain 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.

Hydrazine references:

House, W.B. 1964. Tolerance criteria for continuous exposure inhalation exposure to toxic materials. III. Effects on animals of 90-day exposure to hydrazine, unsymmetrical dimethylhydrazine (UMDH), decaborane, and nitrogen dioxide. ASD-TR-61-519 (iii). Wright-Patterson AFB, Ohio, 84 pp.

HRC (Huntington Research Centre, Ltd.). 1993. Hydrazine 64% aqueous solution: acute inhalation toxicity in rats 1-hour exposure. Huntington Research Centre, Cambridge, England. CMA 8/930523.

Jacobson, K.H., J.H. Clem, H.J. Wheelwright Jr., W.E. Rinehart, and N. Mayes. 1955. The acute toxicity of the vapors of some methylated hydrazine derivatives. A.M.A. Arch. Ind. Health 12: 609-616.

Kulagina, N.K. 1962. The toxicologic characteristic of hydrazine. FTD-HT-66-306. Foreign Technology Division, Wright-Patterson AFB, Ohio. (cited in NRC, 1985)

Latendresse, J.R., G.B. Marit, E.H. Vernot, C.C. Haun, and C.D. Flemming. 1995. Oncogenic potential of hydrazine in the nose of rats and hamsters after 1 or 10 1-hr exposures. Fundam. Appl. Toxicol. 27:33-48.

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Hydrogen chloride

The AEGL values for hydrogen chloride were developed using an intraspecies uncertainty factor of 1 for the AEGL-1 values and 3 for the AEGL-2 and 3 values.

Summary of Proposed AEGL Values For Hydrogen Chloride[ppm (mg/m^3)]						
Classification	**10-min.**	**30-min.**	**1-hr.**	**4-hr.**	**8-hr.**	**Endpoint (Reference)**
AEGL-1 (Non-disabling)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	No-adverse-effect-level 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} (Barrowet 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-Hour rat LC_{50} (Wohlslagel et al., 1976; Vernot et al., 1977)

Hydrogen chloride-rationale for selection of an intraspecies uncertainty factor of 1 for the AEGL-1 tier

Since appropriate human data exist for exposure to hydrogen chloride, they will be utilized to derive values for AEGL-1. Exposure to 1.8 ppm hydrogen chloride for 45 minutes resulted in a no-adverse-effect-level in ten exercising young adult asthmatics (Stevens et al., 1992). **Since the test subjects were exercising asthmatics who are considered to be the sensitive population and the endpoint was essentially a no-effect-level which was below the AEGL-1 threshold, no uncertainty factor has been applied to account for sensitive human subpopulations.** The AEGL-1 value was kept constant across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure time points. Maintaining the concentration at a constant level was considered appropriate since mild irritant effects generally do not vary greatly over time and the endpoint of a no-effect level in a sensitive population is inherently conservative.

Hydrogen chloride-rationale for selection of an intraspecies uncertainty factor of 3 for the AEGL-2 tier

In order to reach a conclusion on the selection of an intraspecies uncertainty factor, the basis for deriving the initial human value derived from the animal data must be considered. In short, the initial species and the interspecies uncertainty factors also represent a part of the “supporting data”. Considering interspecies and intraspecies uncertainty factors independently can lead to an overly conservative AEGL value. When the two uncertainty factors are multiplied together the resultant total uncertainty factor generally represents a worst case times a worst case. Therefore at the total uncertainty factor must be evaluated and the AEGL values compared with all of the supporting data. If the supporting data do not support the AEGL values it may be necessary to decrease one or both of the uncertainty factors using the supporting data

as a rationale.

Although the baboon model is considered more appropriate than rodent models for extrapolation to humans, it is inappropriate to extrapolate from experimental exposure periods of 5 or 15 minutes up to eight hours. However, the baboon data can be used as support for the 10-minute AEGL-2 value. The rat study of Stavert et al. (1991) will be utilized to derive values for AEGL-2 for the 30-minute, 1-, 4-, and 8-hour time points. Of the rodent species, the rat is less sensitive to the effects of hydrogen chloride than are the mouse and guinea pig. Since data suggest that rodents may be more sensitive than primates to the effects of hydrogen chloride, the rat (least sensitive rodent) is the most appropriate rodent species for extrapolation to humans. For example, no deaths were observed in baboons exposed to 11,400 ppm hydrogen chloride for 5 minutes (Kaplan, 1987) or 10,000 ppm for 15 minutes (Kaplan et al., 1988), while the 30 minute LC_{50} for rats was reported as 4,700 ppm (Darmer et al., 1974). Severe nasal effects were observed in nose breathing rats and severe pulmonary effects were observed in mouth breathing rats exposed to 1300 ppm for 30 minutes. To derive the initial human value, an uncertainty factor of 3 was applied to the no effect level for the AEGL-2 tier selected for rats. A modifying factor of 3 also was applied to account for the relatively sparse database describing effects defined by AEGL-2.

An uncertainty factor of 3 was applied to account for susceptible humans. The use of an intraspecies uncertainty factor of 10 would bring the total uncertainty factor and modifying factor to 100 instead of 30. This would generate AEGL-2 values which are not supported by data on exercising asthmatics. No effects were noted in exercising young adult asthmatics exposed to 1.8 ppm HCl for 45 minutes. The AEGL-1 value of 1.8 ppm is unlikely to cause any effects out to 8 hours of exposure because the AEGL-1 endpoint of a no-effect-level in a susceptible population is inherently conservative. Using an intraspecies UF of 10 would yield a 4-hr value of 1.6 ppm (instead of 5.4 ppm) and an 8-hr value of 0.81 ppm (instead of 2.7 ppm). The shorter time points would yield values slightly above 1.8 ppm; however, we have fairly good confidence in the time scaling for this chemical. The value of 'n' was derived from a regression analysis of rat and mouse mortality data ranging from 1 to 100 minutes. In addition, the 30 minute value of 43 ppm derived with an intraspecies UF of 3 is reasonable in light of the fact that baboons exposed to 500 ppm for 15 minutes experienced only a slightly increased respiratory rate. Therefore an intraspecies uncertainty factor of 3 is the most reasonable value.

An additional uncertainty factor of 3 will be applied for interspecies extrapolation. This factor of 3 is considered adequate in light of the fact that values are based on rats and rats appear to be more sensitive than primates. Thus, the total uncertainty factor is 30.

Hydrogen chloride-rationale the selection of an intraspecies uncertainty factor of 3 for the AEGL-3 tier

The 1-hour rat LC_{50} of 3124 ppm (Wohlslagel et al., 1976; Vernot et al., 1977) have been utilized to derive values for AEGL-3 . One-third of the LC_{50} will be utilized as an estimate of a no-effect-level for death. The estimate of one-third the LC_{50} value as a no-effect-level for death is inherently conservative (no deaths were observed in the same study at 1813 ppm). Of the rodent species, the rat is less sensitive to the effects of hydrogen chloride than are the mouse and guinea pig. Since data suggest that rodents may be more sensitive than primates to the effects of hydrogen chloride, the rat (least sensitive rodent) is the most appropriate rodent species for extrapolation to humans. For example, no deaths were observed in baboons exposed to 11,400 ppm hydrogen chloride for 5 minutes (Kaplan, 1987) or 10,000 ppm for 15 minutes (Kaplan et al., 1988), while the 30 minute LC_{50} for rats was reported as 4,700 ppm (Darmer et al., 1974). An uncertainty factor of 3 was be applied for interspecies extrapolation. This factor of 3 is considered adequate in light of the fact that values are based on rats and rodents appear to be more sensitive than primates to the effects of hydrogen chloride.

An uncertainty factor of 3 was applied to account for sensitive humans. A number of factors argue for the use of an intraspecies uncertainty factor of 3 instead of 10: 1) The steep dose-response curve for lethality observed in the Wohlslagel et al. (1976) study in which 1041 ppm (1/3 of the LC_{50} of 3124 ppm) was lower than the non-lethal dose of 1813 ppm. This is a conservative selection of the non-lethal dose and the steep dose-response curve argues for little inter-individual variability; 2) If an intraspecies uncertainty of 10 were used, the total uncertainty factor would be 30. AEGL-3 values generated from a total uncertainty factor of 30 would be close to the derived AEGL-2 values (within a factor of 2), in turn, these values are considered reasonable when compared with data on exercising asthmatics; 3) An interspecies uncertainty factor of 3 has already been applied to data from an animal which is less sensitive than primates, making that uncertainty factor conservative; 4) Sellakumar et al. (1985) exposed rats to 10 ppm of hydrogen chloride for 6 hours a day, 5 days a week for life and only observed increased trachael and laryngeal hyperplasia. The 360 minute AEGL-3 using an intraspecies uncertainty factor of 3 is 17 ppm, close to the level used in the lifetime study in a species less sensitive than primates in which only mild effects were induced; 5) Rats exposed to 50 ppm of hydrogen chloride for 6 hours per day, 5 days a week for 90 days (Toxigenics, 1984) exhibited mild rhinitis. This level is already 3-fold above the AEGL-3 value for death which was derived with an intraspecies uncertainty factor of 3. Although no one factor conclusively supports the use of an intraspecies uncertainty factor of 3, all of the factors considered above provide weight of evidence support to this selection.

The 5-minute rat LC_0 of 30,000 ppm (Higgins et al., 1972) supports the 10-minute AEGL-3 value. Extrapolating this value across time (n = 1) to 10 minutes and

applying an uncertainty factor of 10, yields a value of 1500 ppm, suggesting that the proposed AEGL-3 value is protective. Also, if the 5-minute rat LC_{50} value for HCl vapor of 41,000 ppm (Darmer et al., 1974) is divided by 3 to estimate a no-effect-level for death, extrapolated to 10-minutes, and an uncertainty factor of 10 applied, a supporting value of 683 ppm is obtained.

This summary of the hydrogen chloride data provides a good example of the importance of using all supporting data on a chemical specific basis as the most scientifically credible approach to selecting intraspecies uncertainty factor for irritants or other chemicals.

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Hydrogen fluoride

The AEGL values for hydrogen fluoride were developed using an intrapsecies uncertainty factor of 3 for the AEGL-1,2, and 3 tiers.

Summary Table of AEGL Values [ppm (mg/m^3)]						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1 (Non-disabling)	1.0 (1.2)	1.0 (1.2)	1.0 (1.2)	0.5 (0.6)	0.5 (0.6)	Threshold, pulmonary inflammation - humans (Lund et al., 1997; 1999)
AEGL-2 (Disabling)	95 (78)	34 (28)	24 (20)	12 (9.8)	8.6 (7.0)	NOAEL for lung effects in cannulated rats (Dalbey, 1996; Dalbey et al., 1998);[a] sensory irritation in dogs

						(Rosenholtz et al., 1963)[b]
AEGL-3 (Lethal)	170 (139)	62 (51)	44 (36)	22 (18)	15 (12)	Lethality threshold in cannulated rats (Dalbey, 1996; Dalbey et al., 1998);[c] Lethality threshold in mice (Wohlslagel et al., 1976)[d]

[a] 10-minute AEGL-2 value.
[b] 30-minute and 1-, 4-, and 8-hour AEGL-2 values.
[c] 10-minute AEGL-3 value.
[d] 30-minute and 1-, 4-, and 8-hour AEGL-3 values.

Hydrogen fluoride-rationale for selection of an intraspecies uncertainty factor of 3 for the AEGL-1 tier

Because human data are available, they should be used to derive the AEGL-1. The basis for the AEGL-1 is 3 ppm, the higher exposure concentration in a range of concentrations reported by Lund et al. (1997; 1999). The exposure duration was 1 hour. This exposure can be considered a sub-threshold for lung inflammation as there were no increases in markers of lung inflammation - increases in neutrophils, eosinophils, protein, and methyl histamine. There were no changes in lung function (FVC and FEV_1), and no to minor increased symptoms of irritation at this concentration.

Compared with healthy adults, individuals with asthma may experience bronchial constriction at lower concentrations of HF. **For a number of irritant chemicals, human experimental data assessing irritant responses in normal versus potentially susceptible subjects are available. These studies measure responses that are at or below the AEGL-1 level. Many of the respiratory function changes measured, such as FEV_1 and SRaw, are at a level of statistical but not necessarily biological significance. Some of the more relevant studies were compiled and summarized in order to make general conclusions on the threshold concentrations required to produce an irritant response in normal healthy versus potentially susceptible subgroups. This comparison is useful in determining the appropriate uncertainty factor to use when extrapolating from data in healthy subjects to potentially susceptible subgroups.**

In a number of studies, the normal and potentially susceptible subjects were exposed to the same concentration of irritant gas. This makes assessment of the appropriate UF difficult, since differences in responses at the same

concentration cannot be used to directly estimate different thresholds for a response. In addition, difference in study protocols, including differences in the endpoints measured and the test subjects, make comparisons of effects observed at varying concentrations reported from different studies difficult. A number of studies reported effects in both healthy and potentially susceptible subjects exposed to multiple concentrations of irritant gases. These latter data provide the best information for estimating the appropriate intra-species UF for irritant gases.

The estimated differences in threshold for irritant responses for normal versus potentially susceptible subjects appears varies according to the chemical studies. For some irritant gases (e.g., formaldehyde, hydrogen chloride), no great difference in response is apparent. For other gases (e.g., chlorine, ozone) potentially susceptible subjects such as asthmatics or those with allergic rhinitis respond at a concentration 1 to 3-fold-lower than normal healthy subjects. For a few irritants (sulfur dioxide, sulfuric acid), the threshold concentration to which potentially susceptible subjects respond is somewhat lower, on the order of 3-5 fold. Based on this assessment, an estimate of a 1 to 5-fold difference in the irritant concentrations to which normal subjects and susceptible subjects respond, appears to be a reasonable basis for uncertainty factor selection, in the absence of actual comparative experimental data on the chemical of interest. For hydrogen fluoride the use of an intraspecies uncertainty factor of 3 for the Lund data is reasonable for a number of reasons. There was no evidence of effects on respiratory parameters of healthy adults at concentrations up to 7.8 ppm (Lund et al., 1995) or 8.1 ppm (Largent, 1960; 1961). The AEGL-1 values are lower than these concentrations by a factor of approximately 8 and are considered sufficiently low to protect asthmatic individuals. Because irritant properties would not change greatly between the 10-minute and 1-hour time frames, the 10- and 30-minute values were set equal to the 1-hour value.

The study of Largent et al. (1960; 1961) provides data that supports the safety of the AEGL-1 values. In the Largent study, concentrations of $\frac{\varphi}{\lambda}$ 2 ppm for 6 hours/day were reported as only slightly irritating. This concentration-time relationship for an acute exposure can be considered conservative as this exposure was tolerated repeatedly for up to 50 days without increased irritancy. In addition, industrial exposures of ~4 ppm have been experienced without effects.

Alexeeff et al. (1993) used a "benchmark dose" approach to estimate an exposure level that would protect the public from any irritation during a routine emission of HF. Their approach employed a log-probit extrapolation of concentration-response data to the 95% lower confidence limit on the toxic concentration producing a "benchmark dose" of 1% response called a practical threshold. Species-specific and chemical-specific adjustment factors were applied to develop exposure levels applicable to the general public. The 1-hour value calculated in this manner was 0.7 ppm. This

value is similar to the 1.0 ppm concentration derived for the 1-hour AEGL-1. Alexeeff et al. (1993) also calculated a 1-hour value of 2 ppm which they defined as the concentration that would protect against severe irritation from a once-in-a-lifetime release.

Hydrogen fluoride-rationale for selection of an intraspecies uncertainty factor of 3 for the AEGL-2 tier

Animal data for short-term exposures and human data for long-term exposures were available for consideration in calculating the AEGL-2 values. **Since 10 minute data were available in orally-cannulated rats they are used to derive the 10 minute values. The 30 minute to 8 hours values derived from one hour exposures in dogs.**

Derivation of 10 minute AEGL-2 values:

Because mortality occurred at the 10-minute exposure of cannulated rats to 1764, the next lowest exposure, 950 ppm, was chosen as the threshold for serious effects for the 10-minute AEGL-2. However, no serious effects occurred at this exposure even though hydrogen fluoride was delivered directly to the trachea. **A total uncertainty factor of 10 is reasonable because the endpoint chosen is a mild AEGL-1 type of response which does not approach the definition of an AEGL-2 level effect. In addition, the delivery of hydrogen fluoride in orally-cannulated rats eliminates scrubbing by the nose. The dose to the lungs is greater than in naturally breathing rodents. Therefore, this route of exposure coupled with themild effect is already an inherently conservative exposure from which to derive the 10-minute AEGL-2 value. Figure Hydrogen Fluoride-1 is a plot of all of the data on hydrogen fluoride from 1-60 minutes by category of response. The 10-minute AEGL-2 value is clearly below serious injury categories of data from tests in monkeys, rats, dogs, mice, guinea pigs, and rabbits. Therefore, a total uncertainty factor of 10 applied to the orally-cannulated rat data should be protective.** Using this estimated threshold, a total uncertainty factor of 10 was applied resulting in a proposed 10-minute AEGL-2 value of 95 ppm.

Figure Hydrogen Fluoride-1

Derivation of 30 minute to 8 hour AEGL-2 values:

The 1-hour exposure of dogs to 243 ppm which resulted in signs of irritation and discomfort including blinking, sneezing, and coughing was chosen as the basis for the longer-term AEGL-2 values. These signs/effects appeared to be reversible, but they can be considered the threshold for more serious effects.

A total uncertainty factor of 10 is reasonable and sufficient. If a total uncertainty factor of 30 were used, the predicted 6 hour AEGL-2 level would be 3.3 ppm. However human subjects exposed to 8 ppm for 6 hours over a 25-50 day period (Largent 1960; 1961) experienced only slight irritation. Even a susceptible person should not experience a disabling effect at this concentration. The predicted 360 minute AEGL-2 value using a total uncertainty factor of 10 is

9.9 ppm which is in the range that a healthy person can tolerate with only minor irritation for repeated exposures. A susceptible person should not be incapacitated at this concentration. Figure Hydrogen Fluoride-1 is a plot of all of the data on hydrogen fluoride from 1-60 minutes by category of response. The 30 and 60-minute AEGL-2 values are clearly below serious injury categories of data from tests in monkeys, rats, dogs, mice, guinea pigs, and rabbits.

According to Alarie (1981), 0.1 times the RD_{50} of 151 ppm for the mouse (TNO/RIVM, 1996) can be tolerated for hours by humans with some irritation. A 15 ppm concentration for either the 4- or 8-hour exposure durations would result in higher values than proposed in the table above.

Hydrogen fluoride-rationale for selection of an intraspecies uncertainty factor of 3 for the AEGL-3 tier

Derivation of 10 minute AEGL-3 values:

The concentration causing 1/20 deaths in orally-cannulated rats, 1764 ppm, was chosen as the lethal threshold for the 10-minute AEGL-3. Although 1/20 deaths is higher than the usual threshold for the AEGL-3, 1/100 deaths, the oral cannulation model is conservative compared to normal nose breathing as it bypassed nasal scrubbing and maximized the dose. **A total uncertainty factor of 10 is reasonable because the delivery of hydrogen fluoride in orally-cannulated rats eliminates scrubbing by the nose. The dose to the lungs is greater than in naturally breathing rodents. Therefore, this route of exposure is already an inherently conservative exposure from which to derive the 10-minute AEGL-3 value. Figure Hydrogen Fluoride-1 is a plot of all of the data on hydrogen fluoride from 1-60 minutes by category of response. The 10-minute AEGL-3 value is clearly below levels which cause death in tests in monkeys, rats, dogs, mice, guinea pigs, and rabbits. The use of a total uncertainty factor of 10 would drive the AEGL-3 10 minute value to 58 ppm which is below the AEGL-2 value. Therefore, a total uncertainty factor of 10 applied to the orally-cannulated rat data should be protective.**

Derivation of 30 minute to 8 hour AEGL-3 values:

The AEGL-3 values for disabling, irreversible effects for the longer time periods were derived based on the 60-minute value of 263 ppm which was the highest nonlethal concentration for the mouse reported by Wohlslagel et al. (1976) and application of uncertainty and modifying factors to account for interspecies and intraspecies variability and the steepness of the dose-response curve. Based on LC_{50} data, the mouse was approximately three times more sensitive than the rat to the effects of hydrogen fluoride. Because of the unusual sensitivity of the mouse, an interspecies uncertainty factor of 1 was applied; the intraspecies uncertainty factor of 3 was applied to account for

differences in human sensitivity. In addition, a modifying factor of 2 was applied to account for the steepness of the dose-response curve. The 30-minute and 4- and 8-hour values were calculated based on the $C^2 \times t = k$ relationship as above.

A total uncertainty/modifying factor of 6 is reasonable and sufficient. If a total uncertainty/modifying factor of 20 were used, the predicted 6 hour AEGL-3 level would be 5.4 ppm. However human subjects exposed to 8 ppm for 6 hours over a 25-50 day period (Largent 1960; 1961) experienced only slight irritation. Even a susceptible person should not experience a life threatening effect at this concentration. In addition the use of a total uncertainty/modifying factor of 20 would drive AEGL-3 values below AEGL-2 values. Therefore, a combined uncertainty/modifying factor is reasonable. Figure Hydrogen Fluoride-1 is a plot of all of the data on hydrogen fluoride from 1-60 minutes by category of response. The 30 and 60-minute AEGL-3 values are clearly below the levels which cause death in tests in monkeys, rats, dogs, mice, guinea pigs, and rabbits.

The data base for HF is extensive and many other studies with laboratory animals support the proposed AEGL-3 values. Concentrations resulting in severe effects but no deaths in several animal species were divided by 10 (an interspecies uncertainty factor of 3 to account for the fact that these species may be less sensitive than mice and an intraspecies uncertainty factor of 3 to account for differences in human sensitivity). When scaled across time, the 1-hour values range between 69 and 163 ppm. In addition, the RD_{50} for mice of 151 ppm is above the 30-minute AEGL-3 of 62 ppm. According to Alarie (1981), this concentration could be tolerated for hours by humans but would result in tissue damage.

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