



How are asthmatics included in the derivation of guideline values for emergency planning and response?

Mia K.V. Johansson ^{*}, Gunnar Johanson, Mattias Öberg

Karolinska Institutet, Institute of Environmental Medicine, Unit of Work Environment Toxicology, Stockholm, Sweden

ARTICLE INFO

Article history:

Received 15 February 2012

Available online 7 June 2012

Keywords:

Acute exposure guideline levels
Asthma
Susceptible groups
Emergency response
Occupational exposure limits
Risk assessment

ABSTRACT

Guideline values for emergency planning and response are aimed to protect the general public, including asthmatics and other susceptible groups, during sudden airborne releases of chemicals. A precondition of asthma may increase the individual susceptibility to acute exposures. This paper studies to what extent experimental data on asthmatics are included in the rationale and derivation of guideline values. An analysis of the Technical Support Documents (TSDs) of the Acute Exposure Guideline Levels (AEGs) shows that only 23 of the 176 TSDs include references to experimental studies on asthmatics, 30 include a statement on asthmatics but no reference to experimental data, and 123 lack any explicit statement on asthmatics. The TSDs were further compared with the support documents of nine other programs for acute or occupational short-term values. All programs were incomplete with respect to experimental data on asthmatics. Omission of asthmatics may interfere with trustful and efficient health protective actions. We suggest that the availability of data on asthmatics should be carefully examined in the development of guideline values, and that the lack of such data should be explicitly noted. In the latter case, available data for other irritants may be used to justify an appropriate assessment factor.

© 2012 Elsevier Inc. All rights reserved.

1. Introduction

Health-based guideline values for short-term exposure are used in planning, preparedness and as decision support during emergency response. There are several programs available, all with the purpose of protecting humans against adverse effects from acute exposure to airborne hazardous chemicals. Examples are given in Table 1. Deviations among emergency short-term values have been shown previously (Öberg et al., 2010). Discrepancies between the available programs for emergency short-term values may hamper an effective risk management and communication during a sudden unintentional or intentional release of chemicals. It is therefore a need for international harmonization. Key factors for broad international acceptance of harmonized values include, e.g. transparency of the decision process and clear definitions on target population. It is therefore important to clarify if and to what extent data on susceptible subpopulations are included in the derivation process.

In general, emergency preparedness related to chemicals aims to protect the entire population, including relatively large but potentially susceptible subpopulations such as children, elderly and asthmatics. However, small groups of hypersensitive individuals, such as severely ill patients, are generally not included. To pro-

tect labor from acute effects related to occupational exposure, work environment authorities define occupational exposure limits for short-term exposure. These values differ from most short-term values for the general population in the definition of target population, i.e. they do not aim to protect sensitive populations that are not likely to be a part of the labor. To study the importance of the definition of target groups, it might therefore be informative to examine how data on asthmatics are included in the support documents for short-term values related to occupational settings as compared to values for the general population.

Among the support documents for the short-term values, the Standing Operating Procedures (SOPs) for the Acute Exposure Guideline Levels (AEGs) program clearly includes asthmatics in their definition of susceptible groups: “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” (NRC, 2001a, p. 3).

Asthmatics constitute a relatively large proportion of the population at all age groups. The World Health Organization (WHO) reports that about 235 million people worldwide suffer from asthma and it is currently one of the most common chronic diseases (WHO, 2011). The prevalence ranges from 1% to 18% in different countries and has increased both among children and adults over the past decades (GINA, 2011; Masoli et al., 2004). Although other preexist-

^{*} Corresponding author. Address: P.O. Box 210, SE-171 77 Stockholm, Sweden. Fax: +46 8 31 41 24.

E-mail address: mia.johansson@ki.se (M.K.V. Johansson).

Table 1
Standard setting programs that include short-term values.

Program	Organization
Short-term values for the general population	
Acute Exposure Guideline Levels (AEGL)	US National Research Council and Environmental Protection Agency (NRC/EPA)
Emergency Response Planning Guidelines (ERPG)	American Industrial Hygiene Association (AIHA)
Minimal Risk Levels (MRL)	US Agency for Toxic Substances and Disease Registry (ATSDR)
Reference Exposure Levels (REL)	California Office of Environmental Health Hazard Assessment (OEHHA)
French Acute Toxicity Threshold Values (VSTAF)	French National Institute for Industrial Environment and Risks (INERIS)
Short-Term Exposure Limits (STEL) and similar occupational short-term values	
Limits recommended by the Dutch Expert Committee on Occupational Standards (DECOS)	Health Council of the Netherlands
Maximum Concentration at the Workplace (MAK)	German Research Foundation (DFG)
Limits recommended by the Scientific Committee on Occupational Exposure Limits (SCOEL)	European Commission
Swedish Occupational Exposure Limits (SE-OEL)	Swedish Work Environment Authority (SWEA)
Threshold Limit Values (TLV)	American Conference of Governmental Industrial Hygienists (ACGIH)

ing diseases (e.g. fatty liver disease) might also be widespread and affected subpopulations regarded as susceptible, there are several reasons to concentrate on asthmatics, as done in the current study. Many airborne hazardous chemicals are clearly irritants to the airways and the acute effects are possible to study in experimental settings using the target population, i.e. persons with mild asthma. In addition, one of the strongest risk factors for developing asthma is inhaled substances and particles that may provoke allergic reactions or irritate the airways (WHO, 2011). A precondition of asthma may therefore increase the individual susceptibility to acute exposure of airborne chemicals, especially chemicals with irritant properties (i.e. the first signs of discomfort due to irritation occur at lower concentrations).

The identification of susceptible populations in AEGL as well as other short-term values is performed on a chemical-by-chemical basis with the aim to use all available data on the chemical in question. If relevant data are missing, an assessment factor (also called uncertainty factor, UF) of 10 is by default used to account for intra-species (interindividual) differences in susceptibility to respiratory irritants (NRC, 2001a). If experimental data from susceptible groups are available there is in most cases no need for this intra-species assessment factors. Experimental data for a large number of chemicals with similar mode of action might also be used as a base for development of chemical specific assessment factors. From a set of 11 studies (6 different chemicals) it has been suggested that the variation between asthmatics and healthy individuals are within a factor of 1–5 (Young et al., 2009). A similar conclusion for chemical irritants was also drafted in 2001 by the National Advisory Committee for the development of AEGL values (NAC/AEGL Committee) as basis for a recommended intraspecies uncertainty factor of 3 (NRC, 2001b).

This paper aims for a systematic overview regarding if and how asthmatics are included in the derivation of short-term values and to what extent experimental data on asthmatics are available and utilized in the derivation of short-term values. Data gaps and inadequacies are also meant to be identified and a database of experimental studies on asthmatics is aimed to be presented as a key to support the selection of interindividual assessment factors for chemicals with irritant properties. This information will be important in the process of harmonizing the procedures for short-term values and to ensure the protection of asthmatics at chemical accidents and other sudden releases of hazardous airborne chemicals.

2. Methods

The principal study design is illustrated in Fig. 1. In the first part of the study, technical support documents (TSDs) from Acute Exposure Guideline Levels (AEGL) are categorized based on information

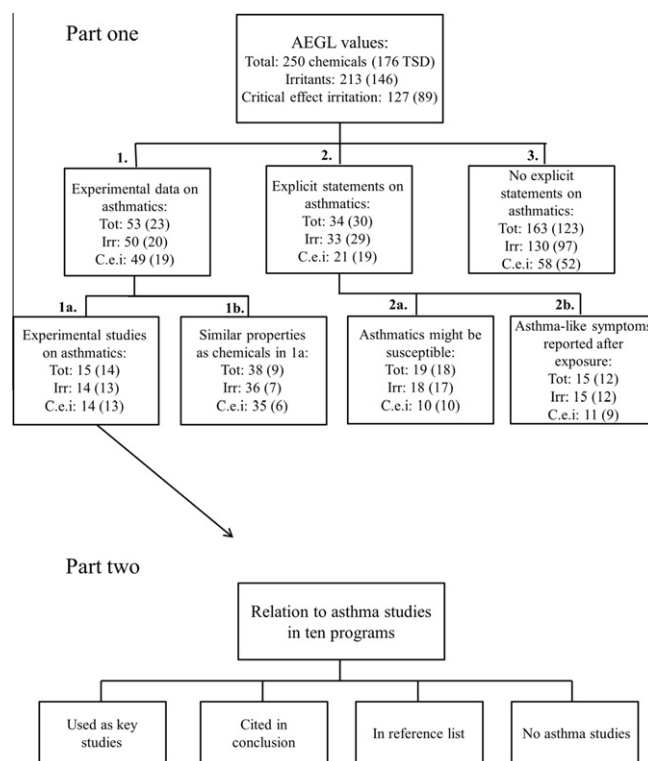


Fig. 1. Chemicals and support documents from 10 programs categorized based on information on asthmatic individuals. Part one of the study was performed on interim and final documents available in the AEGL program. The total number of chemicals in each category is presented. In addition, both the proportion of chemicals with irritating properties and the proportion of chemicals with irritation stated as critical effect at AEGL-1 are presented. Chemicals with other critical effect than irritation (28) or without AEGL-1 value (95) are not presented in the figure. Chemicals without AEGL-1 (whereof 81 in Category 3) did not include statements on critical effect. Four TSDs in Category 2a did not include explicit statements on asthmatics. However, individuals with compromised lung function or pulmonary conditions were stated as a possible susceptible population. In Part two, the consideration of asthmatics was studied in all 10 programs by comparing the 15 AEGL chemicals with data from experimental studies, Category 1a.

about asthmatic individuals to obtain an overview on the consideration of this subpopulation. The reasoning for choosing AEGL as the prime source relates to the fact that the AEGL documents as well as the process for their derivation are well defined and transparent. In addition, all documents have open access and have undergone both peer and public review. The AEGL values are also widely used in an international context.

A database with information about AEGL values for short-term exposure to hazardous airborne chemicals was made by collecting all final and interim TSDs from the AEGL webpage (US EPA, 2010a). The documents were searched for words related to asthma (search terms: asthma, asthmatic, asthmatics, susceptible, susceptibility, pulmonary, respiratory and lung function) and categorized as Category 1, Experimental data on asthmatics, Category 2, Explicit statements on asthmatics, or Category 3, No explicit statements on asthmatics. The TSD for hydrogen selenide was not available at the AEGL website and it was therefore not included in this study. Chemicals with original data from experimental studies on asthmatics were further categorized as Category 1a, whereas chemicals with similar structure or that easily oxidize or hydrolyze into one of the studied chemicals were included in Category 1b. Out of the chemicals in Category 1a, three (nitric acid, nitrogen dioxide and sulfur dioxide) also included references to epidemiological studies relating air pollution to increased incidence of asthma. Seven additional chemicals (chlorine, fluorine, formaldehyde, hydrogen chloride, methyl methacrylate and 2,4- and 2,6-TDI) in Category 1 had information on occupational exposure and asthma. In this study epidemiological and occupational case studies are excluded because such studies are often based on long-term exposure scenarios, lack controlled exposure concentrations or focus on development of asthma rather than sensitivity of persons with preexisting asthma. Solely controlled experimental studies on asthmatics were included.

TSDs with some statement, although without supporting data, regarding the susceptibility of individuals with asthma, compromised lung function or pulmonary conditions were put in Category 2a, whereas chemicals without any explicit statement on susceptibility, but with reported data showing asthma-like symptoms in otherwise healthy individuals after occupational exposure, were categorized as Category 2b.

The consideration of asthmatics was further analyzed in the 23 TSDs (53 chemicals) with experimental data on asthmatics, i.e. Category 1. The final conclusions stated in the AEGL documents regarding susceptibility of asthmatics at AEGL-1 were listed along with the use of assessment factors, i.e. intraspecies uncertainty factor (UF), modifying factor (MF) and molar adjustment factor (MAF).

In the second part, a comparison was made between 10 programs (including AEGL) for short-term values addressing the level of documentation on asthmatics (Fig. 1). All experimental studies with asthmatic subjects in the support documents for the 15 chemicals in Category 1a were identified for each program. The level of documentation on persons with asthma in the support documents and the use of experimental studies during derivation of the final short-term values were analyzed.

The present study includes five programs related to short-term values for the general population and five programs related to occupational short-term values, mostly Short-Term Exposure Limits (STEL). All programs are briefly described below and summarized in Table 1.

The United States' National Research Council (NRC) and Environmental Protection Agency (EPA) have developed AEGLs for selected airborne chemicals (US EPA, 2010b). The work procedures and derivation process are defined in the Standing Operating Procedures (SOP) (NRC, 2001a). The values are derived at three tiers, corresponding to increased levels of severity (tiers 1, 2 and 3). Effects at concentrations above AEGL-1 are assumed to be reversible and include e.g. mild respiratory effects or nuisance and experimental data on asthmatics are typically relevant for defining point of departure at this tier (US EPA, 2010c). In this study, information related to AEGL-1 from interim and final AEGL-documents (available in PDF-format) were included (US EPA, 2010d). In some cases several individual chemicals were

included in the same TSDs. Therefore the number of documents differs from the number of chemicals in the analyses.

The American Industrial Hygiene Association (AIHA) is responsible for the Emergency Response Planning Guidelines (ERPG) program. As in the AEGL program, the ERPG values are developed for three tiers. The underlying definitions and procedures are described in a handbook (AIHA, 2008) as well as in a separate article (Cavender et al., 2008). The ERPG documents are available as loose-leaf documents. In this study the full version from 2008 with update sets until 2010 was included (AIHA, 2010).

The US Agency for Toxic Substances and Disease Registry (ATSDR) has developed Minimal Risk Levels (MRL). Only the MRL values for acute exposure via inhalation (1–14 days) were included in the present study (Pohl and Abadin, 1995). The toxicology profiles for MRLs were available via internet (PDF-format) together with information on the derivation procedure (ATSDR, 2011).

The California Office of Environmental Health Hazard Assessment (OEHHA) has developed threshold values called Reference Exposure Levels (REL). The present study focuses on parts of the documents that are related to mild adverse effects with exposure averaging 1 h duration. The derivation procedure (Denton and Hickox, 1999) as well as the toxicity summaries for each substance were available via internet (PDF-format) (OEHHA, 2011).

The French Acute Toxicity Threshold Values (VSTAF) are developed by the French Ministry of Environment, the National Institute for Industrial Environment and Risks (INERIS), the National Research and Safety Institute for Occupational Risk Prevention (INRS) and the Institute for Nuclear Safety and Protection (IPSN). In this study we include data from the Reversible Effects Threshold (SER) which is similar to the lowest tier previously described for other short-term values. The methodology for developing SER values were presented in a report written partly in English (INERIS, 2009). Finalized documents from the VSTAF program were available via internet in French (PDF-format) (INERIS, 2011).

Several countries have expert committees that scientifically evaluate the toxicity data of substances to inform the setting of indicative or binding occupational short-term values. The documents related to five of these programs were included in the present study to investigate if the occupational setting influence the use of data related to persons with asthma.

The Dutch Expert Committee on Occupational Standards (DECOS) have a defined methodology for the development of short-term values (DECOS, 2003) and the support document of each evaluated substance were available from internet (PDF-format) (DECOS, 2011).

The German Research Foundation (DFG) has developed the Maximum Concentration at the workplace (MAK) values for short-term exposure. The derivation procedure was available from internet (DFG, 2011). In this study, six from the MAK program were written in German (DFG, 1970–1988) and five were available from the English translated MAK-collection (Greim, 1991–2005).

The Swedish Work Environment Authority (SWEA) produces a scientific basis for the Swedish Occupational Exposure Limits (SE-OEL) (Montelius, 2006). Further information on the procedure for developing values is available from a report written in Swedish (AFS, 2005). The documents related to individual chemicals used in this study were all available in English (Montelius et al., 1981–2011).

The American Conference of Governmental Industrial Hygienists (ACGIH) have for many decades been publishing a documentation list of Threshold Limit Values (TLV) (ACGIH, 2011a). The operation manual has been published on internet (ACGIH, 2011b). In this study, the full version of loose-leaf documents from 2001 with update sets until 2005 was used (ACGIH, 2001).

In addition to national expert committees, the European Commission has appointed the Scientific Committee on Occupational

Exposure Limits (SCOEL) to develop short-term exposure limits for Europe. The methodology for the development of values (SCOEL, 2009) and the series of key documents were available from internet (PDF-format) (SCOEL, 2011).

3. Results

In October 2010, the AEGL values (final and interim) consisted of 250 chemicals (corresponding to 176 TSDs). For 213 of the chemicals (146 TSDs) it was stated that it may cause respiratory or eye irritation (Fig. 1) and 127 chemicals (89 TSDs) of them had identified irritation as the critical effect in the AEGL-1 derivation. Other critical effect such as headache, dizziness or systemic toxicity were given for 28 chemicals (22 TSDs). The remaining 95 chemicals (65 TSDs) had no identified critical effect and no recommendation for AEGL-1. In the categorization of chemicals and TSDs, it was found that documents with experimental data, i.e. Category 1, constituted about 21% of the chemicals (corresponding to 13% of all the 176 TSDs), documents with explicit statements on asthmatics, i.e. Category 2, composed about 14% of the chemicals (17% of the TSDs), leaving 65% of the chemicals (70% of the TSDs) in Category 3 where no explicit statements on asthmatics were present.

Of the 53 chemicals in Category 1, 15 were identified with data from experimental studies on asthmatics, defined as Category 1a (Fig. 1). These data were also used in the derivation of AEGL values for 38 additional chemicals, defined as Category 1b. In Category 1, 50 of the 53 chemicals were classified as chemical irritants and for 49 of them irritation was stated as critical effect for AEGL-1. Two chemicals included other critical effects and there was no recommended AEGL-1 value for two chemicals.

Of the 34 chemicals identified in Category 2, twelve had explicit statements that the asthmatic population “*might be more susceptible than healthy individuals*”. For seven chemicals, we assumed that asthmatic individuals were included in general statements of susceptible populations regarding persons with “*compromised lung function*” or “*pulmonary conditions*”. These 12 + 7 chemicals were therefore classified as Category 2a (Fig. 1). The remaining 15 chemicals, in Category 2b, had no data on individuals with preexisting asthma and no explicit statement related to susceptibility of the asthmatic population. However, the documents included case reports of otherwise healthy workers without preexisting asthma that reacts with asthma-like symptoms after occupational exposure. In the present study we assumed that these reports implicitly suggest that people with preexisting asthma may react to exposure at similar or lower dose levels as these workers. Thirty-three out of 34 chemicals in Category 2 described respiratory or eye irritants and 10 of them included irritation as critical effect for AEGL-1. For 12 chemicals there were no recommended AEGL-1 value.

About two thirds of the analyzed chemicals fall in Category 3, with no explicit statements on asthmatics (Fig. 1). For six chemicals this lack of data was noted “No information on asthmatics” but for the remaining 157 no explicit statement was available about whether the asthmatic population had been considered or not during the AEGL derivation. In this third category, the number of chemical irritants was 130 and 58 chemicals included irritation as critical effect for AEGL-1 derivation. As asthmatics were not explicitly mentioned in the documents, it is unclear if the authors had considered their potential susceptibility. For 24 chemicals there were other critical effects than irritation and 81 chemicals had no AEGL-1 value.

Conclusions and statements in the AEGL documents related to susceptibility of asthmatics for chemicals in Category 1 are presented in Table 2, together with information about the use of assessment factors (intraspecies UF, MF or MAF). In short, for eleven chemicals in Category 1a human experimental studies were

used as point-of-departure in the AEGL-1 derivation. In such cases the intraspecies UF was set to 1. For the remaining four chemicals (acetaldehyde, methyl methacrylate, nitric acid and tear gas) data on asthmatics were not used as a point-of-departure. In these cases, an UF of 3 was used to account for variability among individuals, although for a slightly differing reasons. In the case of acetaldehyde, the available experimental studies on asthmatics only included short exposure durations of 2–4 min. The TSD for methyl methacrylate cited an abstract (Andrews et al., 1979) where no significant effects were seen in asthmatics. This abstract was, however, neither used as a key study, nor as a basis for statements regarding susceptible populations. Instead, an UF 3 was applied to data from healthy workers. The effects on asthmatic persons exposed to nitric acid in a chamber were not significantly different as compared with healthy subjects (Koenig et al., 1989). However, epidemiological data cited in the TSD indicate a slightly higher susceptibility among asthmatics. An UF of 3 was used because the mechanism of action of a direct acting irritant is not expected to differ greatly among individuals. For tear gas, the UF of 3 was supported by a statement that the portal-of-entry effect will not vary among people. Data from experimental studies on asthmatics were also used as a basis for deriving AEGL for the 38 chemicals within Category 1b. An intraspecies factor of 1 was applied to all these chemicals except bromine, fluorine, hydrogen bromide and hydrogen iodide, for which the information from chlorine or hydrogen chloride was used to support an UF of 3 to account for asthmatics. For fluorine, an additional MF of 2 was used to compensate for limited data on occupational asthma.

Asthmatics were concluded to be a susceptible population for eight chemicals in Category 1a: chlorine, hydrogen chloride, hydrogen sulfide, nitrogen dioxide, sulfur dioxide, sulfuric acid and 2,4-/2,6-TDI (Table 2). As mentioned above, the data for three compounds were considered to be inadequate (acetaldehyde), conflicting (nitric acid) or just not commented in the TSD (methyl methacrylate). Remaining chemicals (ammonia, formaldehyde, tear gas and HFC-134a) were stated to show adverse effects at similar levels of exposure among asthmatics as compared with healthy subjects.

The number of available documents and the number of experimental studies on asthma, focusing on the 14 TSDs (15 chemicals) identified in the AEGL program are shown for each program in Table 3. In total, there were 107 support documents available for the 10 programs. Most programs had documents related to at least 10 chemicals, except the MRL and DECOS programs that only covered five and six chemicals, respectively. The total number of experimental studies identified was 170 (Table 4). Of these 108 were found in the AEGL document, whereas 62 were identified from the other programs. All programs (except VSTAF and TLV) had some unique references in relation to experimental studies and asthma. Fifty-seven studies were only available in documents for one single program (Table 3).

The number of studies varied greatly among the tested chemicals, ranging from 1 study (chlorine, hydrogen sulfide, methyl methacrylate and tear gas) to 48 studies (sulfur dioxide) (Table 4). Sulfur dioxide (48), nitrogen dioxide (43), and sulfuric acid (38) together constituted 76% of the identified asthma studies.

In the second part of the study, the level of documentation on asthmatics was analyzed for all programs and for all chemicals with available experimental data (Fig. 1, Table 4). In some cases (chlorine, hydrogen chloride, hydrogen sulfide and 2,4-/2,6-TDI), the same study on asthmatics were used as key study by several programs. In other cases, the selection of key study was different. As mentioned above, the majority of studies related to nitrogen dioxide, sulfur dioxide and sulfuric acid. Not surprisingly, the selected key study varied among programs for these chemicals. Several programs included studies of asthmatics in their conclusions

Table 2

Conclusions on susceptibility of asthmatics at the AEGL-1 tier for chemicals with experimental or read-across data on asthmatics (Categories 1a and 1b in Fig. 1). The uses of intraspecies Uncertainty Factors (UF), Modifying Factors (MF) and Molar Adjustment Factors (MAF) during value derivation are presented.

Chemical	CAS	Conclusion
Acetaldehyde	75-07-0	An UF 3 was applied to account for variability among individuals but asthmatics were not mentioned. There were several chamber studies in the document describing the susceptibility of asthmatics but they were not suitable for AEGL-1 derivation because of short exposure duration (2–4 min)
Ammonia	7664-41-7	No susceptible population was identified and UF 1 was applied. The odor threshold is lower than the threshold for irritation. It is therefore unlikely that concentration detected by odor would reach the tracheobronchial and pulmonary regions of the respiratory tract and cause adverse effects in asthmatics. Asthmatics and healthy subjects experienced similar effects in an exposure study (McLean et al., 1979)
Chlorine	7782-50-5	Susceptible. UF 1 because AEGL-1 values were based on an asthma study (D'Alessandro et al., 1996)
–Bromine	7726-95-6	May be susceptible due to structural similarity to chlorine and UF 3 was applied
–Fluorine	7782-41-4	May be susceptible due to structural similarity to chlorine and UF 3 was applied. In addition, MF 2 was applied based on a limited database including cases of occupational asthma
Formaldehyde	50-00-0	Not susceptible and UF 1 was used. When tested on asthmatic individuals (several studies), subjects found to be as sensitive as the healthy subjects were to the irritant effects of exposure below 3 ppm
Hydrogen chloride	7647-01-0	Susceptible. UF 1 because AEGL-1 values were based on an asthma study (Stevens et al., 1992)
–Hydrogen bromide	10035-10-6	May be susceptible. Data from asthmatics exposed to HCl supported the use of UF3 (Stevens et al., 1992)
–Hydrogen iodide	10034-85-2	May be susceptible. Data from asthmatics exposed to HCl supported the use of UF3 (Stevens et al., 1992)
–Monochlorosilanes (4 chemicals)		Susceptible. MAF 1 because HCl is a hydrolysis product. (Same TSD as the other chlorosilanes)
–Dichlorosilanes (6 chemicals)		Susceptible. MAF 2, see above
–Trichlorosilanes (15 chemicals)		Susceptible. MAF 3, see above
–Silicon tetrachloride	10026-04-7	Susceptible. MAF 4, see above
Hydrogen sulfide	7783-06-4	Susceptible. AEGL-1 values were based on an asthma study. UF 1 and MF 3 were applied because the asthmatics complained about headache (Jappinen et al., 1990)
Methyl methacrylate	80-62-6	UF 3 for susceptible populations but asthmatics was not mentioned. However, a study in the document described that asthmatics responded to exposure by various respiratory symptoms (Andrews et al., 1979)
Nitric acid	7697-37-2	Asthmatics might be susceptible based on epidemiological data. UF 3 for susceptible populations. No effects were seen in an exposure study that was described in the document (Koenig et al., 1989).
Nitrogen dioxide	10102-44-0	Susceptible. UF 1 because AEGL-1 values were based on several asthma studies
–Nitrogen tetroxide	10544-72-6	Susceptible. Vaporizes and dissociates to NO ₂ (same TSD as NO ₂)
–Nitric oxide	10102-43-9	Not mentioned as a susceptible population but NO is easily oxidized to NO ₂ . One study on asthmatics but all AEGL values were adopted from NO ₂
Sulfur dioxide	7446-09-5	Susceptible. UF 1 because AEGL-1 values were based on several asthma studies
–Thionyl chloride	7719-09-7	Not mentioned as a susceptible population but AEGL values were adopted from sulfur dioxide
Sulfuric acid	7664-93-9	Susceptible. UF 1 because AEGL-1 values were based on several asthma studies
–Sulfur trioxide	7446-11-9	Susceptible. Reacts with water (air, respiratory tract, skin) and produces H ₂ SO ₄ (Same TSD as H ₂ SO ₄)
–Oleum	8014-95-7	Susceptible. Reacts with water (air, respiratory tract, skin) and produces H ₂ SO ₄ (Same TSD as H ₂ SO ₄)
–Chlorosulfonic acid	7790-94-5	Not mentioned as susceptible but AEGL values from the hydrolysis product H ₂ SO ₄ were adopted
Tear Gas (O-Chlorobenzylidenemalonitrile)	2698-41-1	Not susceptible. UF 3 was applied because the portal-of-entry effect probably won't vary among people. MF 10 was applied to reduce a LOAEL to a NOAEL. Asthmatic and healthy subjects had similar response to exposure, but a higher percentage of asthmatics had more severe chest symptoms. However, no wheezing or rhonchi were heard, and recovery was as rapid as that seen in other exposure groups
1,1,1,2-tetrafluoroethane (HFC-134a)	811-97-2	Not susceptible, and UF 1 was used, because exposure studies were performed for the use as propellant in metered-dose inhalers in asthma treatment
–Methyl-nonafluorobutyl (HFE-7100) (40%)	163702-07-6, 163702-08-7	Not susceptible, because of structural similarity to HFC-134a
–1,1-dichloro-1-fluoroethane (HCFC-141b)	717-00-6	Not susceptible, because of structural similarity to HFC-134a
2,4-toluenediisocyanate	584-84-9	Susceptible. UF 1 because AEGL-1 values were based on an asthma study (Baur, 1985)
2,6-toluenediisocyanate	91-08-7	

Data collected from AEGL, 2010. Acute Exposure Guideline Levels (AEGLs) Program. (<http://www.epa.gov/oppt/aegl/pubs/final.htm> and <http://www.epa.gov/oppt/aegl/pubs/interim.htm> [assessed 1 October 2011]).

Table 3

Support documents and number of cited experimental studies involving asthmatics for 10 programs for short-term values.^a

Program	Number of support documents (max 14)	Number of cited chamber studies involving asthmatics	
		In total	Unique to the program
<i>Short-term values for the general population</i>			
AEGL	14	108	21
ERPG	12	39	6
MRL	5	52	9
REL	11	49	3
VSTAF	10	13	0
<i>Short-Term Exposure Limits (STEL) and similar occupational short-term values</i>			
DECOS	6	32	1
MAK	12	55	11
SCOEL	10	37	3
SE-OEL	14	34	3
TLV	13	17	0
Total	107	436	57

^a Only support documents from Category 1a were used (Fig. 1 and Table 2).

without using the data as point-of-departure. For example, in seven cases the SE-OEL documents referred to studies on asthmatics in their final conclusion. Other programs included the studies on asthmatics in their main text or only in the list of references, showing that they are aware of the data but do not use it as key information. Finally, there were several programs that did not include any information on asthmatics at all in their documents. The German MAK documents had all their documents in the latter two levels of documentation, i.e. omitted all asthma-data or only included data on asthmatics in their reference list.

The number of support documents in relation to the level of documentation and use of experimental data from asthmatics for all programs are presented in Fig. 2. The major part (74%) of the support document for the programs related to short-term exposure to the general population (VSTAF excluded due to exclusion of asthmatics in their target population) included asthma studies as key studies or as studies cited in the conclusion. A small part (13%) of the support documents (VSTAF included) lacked data on asthmatics. The level of documentation and use of experimental data was significantly lower among the programs related to occupational short-term values (11%). Here, the majority of documents (49%) lacked references on asthmatics.

4. Discussion

According to the SOP for AEGL, the program should include “susceptible subpopulations, such as... persons with asthma” (NRC, 2001a). In the present study we show that the vast majority (70%) of TSDs are lacking explicit comments or statements related to asthmatics (Fig. 1). The proportion of asthmatics in most Western societies is substantial and growing. Reports on the prevalence of asthma show a range of 1–18% (Masoli et al., 2004). One of the strongest risk factors for developing asthma is inhaled substances and particles that may provoke allergic reactions or irritate the airways (WHO, 2011) and this group have the right to protection during sudden release of chemicals. The reason for not mentioning asthmatic individuals in TSDs is not obvious. Most likely, either no information was found on experimental studies involving this subpopulation or asthmatics are not expected to be more susceptible due to e.g. non-irritating chemicals. However, some kind of statement would make the implicit conclusion more transparent to the reader. Chemical irritants constituted 85% out of all chemicals in AEGL and asthmatics might therefore be considered as a susceptible subpopulation and an intraspecies UF 3 utilized in

the derivation according to the white paper on asthma (NRC, 2001b). The remaining 15% were non-irritating chemicals and the majority of these (33 out of 37) did not include statements on asthmatics (Category 3). There were 130 chemical irritants (out of 163) in Category 3 (58 included irritation as critical effect) but lack of data on asthmatics was only noted in six of them. Out of the 95 chemicals without recommended AEGL-1 values (no critical effect mentioned), 81 belonged to Category 3. A majority of these chemicals were irritants which asthmatics might be susceptible to. Fifty-three chemicals included references to experimental data on asthmatics, Category 1, and only 15 different chemicals were identified with experimental studies. In addition, 34 compounds had some clear or implicit statement related to the susceptibility of asthmatics, Category 2. We suggest that lack of data (including lack of data from structurally similar compounds) should always be noted in order to justify the selection of uncertainty factors and to ensure that the short-term values are protective for asthmatics.

In Category 1, articles with asthmatics exposed to chemicals in controlled conditions via chamber, mouthpiece, head-dome or face-mask were included. A study with exposure to Tear gas in a wind tunnel was also included. The conclusions related to susceptibility of asthmatics for tested chemicals were investigated together with the use of assessment factors (Table 2). Several consistent studies on asthmatics are available to support the use of an intraspecies UF 1 for nitrogen dioxide, sulfur dioxide and sulfuric acid and supported by a multitude of experimental studies on asthmatics. However, the number of experimental studies was limited to one or two for chlorine, hydrogen chloride, hydrogen sulfide and 2,4-/2,6-TDI. Even though the number of studies was limited, an intraspecies UF 1 was used for all of these chemicals. In such cases, supporting data or statements about the quality of the critical study would have increased the credibility and transparency. This lack of transparency is also evident for hydrogen sulfide. The intraspecies UF 1 used in the derivation of AEGL for hydrogen sulfide are supported by one study on asthmatics (Jappinen et al., 1990). This key study concludes that 2 ppm of hydrogen sulfide “do not cause noticeable effects on respiratory function”. However, AEGL introduces an additional MF 3 to compensate for variations among asthmatics at the tested concentration. These effects include headache (3/10) and increased airway resistance (8/10). None of these changes were statistically significant from control. It seems like the AEGL committees either interpret the data as a LOAEL (in opposite to the authors) and therefore use MF 3 or that they consider the limited amount of data (only 10 subjects) and therefore introduce MF 3. Whatever, it is a potential for improvements of transparency within the TSD. In conclusion, the use of experimental data related to the assumed most sensitive subpopulation result in an uncertainty factor of one, which is well in accordance with the SOP.

Methyl methacrylate had only one study on asthmatics (an abstract without stated concentration) (Andrews et al., 1979) and no comments were made in relation to susceptible populations. However, an intraspecies UF 3 was introduced to extrapolate from working population to sensitive subpopulations. This seems to be justified and in accordance with the SOP due to the lack of data.

Also nitric acid had only one chamber study available that showed no specific effects in asthmatics (Koenig et al., 1989). However, the use of UF 3 was supported by epidemiological data and could therefore be justified and in accordance with the SOP.

Based on data from experimental studies, asthmatics were not considered a susceptible population in the assessment of six chemicals (ammonia, formaldehyde, HFC-134a, HFE-7100, HCFC-141b and Tear gas). Nevertheless, experimental data on asthmatics were used as point-of-departure and combined with an intraspecies UF 1. Ammonia had only one experimental study on asthmatics cited in the TSD, which was used to support the decision to use intraspe-

Table 4
Use of experimental on asthmatics in 10 programs for short-term values.^a

Chemical	Asthma studies used in the derivation of values or stated as key studies	Key studies	Asthma studies cited and mentioned in conclusion	Asthma studies cited in text or only presented in list of references	No asthma studies	Number of articles for each chemical
Acetaldehyde	REL	Prieto et al. (2000)		AEGL, ERPG	MAK, SE-OEL, TLV	9
Ammonia	AEGL	McLean et al. (1979)	REL, SE-OEL		ERPG, MRL, VSTAF, MAK, TLV SCOEL, VSTAF, MAK, SE-OEL, TLV	3
Chlorine	AEGL, ERPG, MRL, REL SCOEL	D'Alessandro et al. (1996)			SCOEL	1
Formaldehyde	AEGL	Kulle et al. (1986), Green et al. (1987), Sauder et al. (1987) and Sheppard et al. (1984)	REL	ERPG, MRL, VSTAF, MAK, DECOS, SE-OEL, TLV		11
Hydrogen chloride	AEGL, ERPG, REL, TLV	Stevens et al. (1992)	SE-OEL	VSTAF	MAK, SCOEL	2
Hydrogen sulfide	AEGL, MRL	Jappinen et al. (1990)	DECOS	REL, VSTAF, SCOEL	ERPG, SE-OEL, TLV	1
Methyl methacrylate	–		SCOEL, TLV	AEGL, DECOS	MAK, SE-OEL	1
Nitric acid	ERPG	Linn et al. (1985) (NO ₂)	SE-OEL	AEGL, VSTAF	MAK, SCOEL, TLV	5
	REL	Koenig et al. (1989)				
Nitrogen dioxide	AEGL	Kerr et al. (1979), Kerr et al. (1978), Bauer et al. (1985), Jorres et al. (1995)	DECOS, SE-OEL	VSTAF, MAK	TLV	43
	AEGL, SCOEL	Bauer et al. (1986), Roger et al. (1990), Koenig et al. (1988), Avol et al. (1989)				
	SCOEL	Linn et al. (1985)				
Sulfur dioxide	ERPG, REL	Linn et al. (1983b), Bethel et al. (1985), Jorres and Magnussen (1990)	SE-OEL	VSTAF	MAK, TLV	48
	AEGL	Schachter et al. (1984)				
	AEGL, DECOS	Roger et al. (1985)				
	AEGL, REL	Linn et al. (1983a, 1987)				
	REL	“Several studies”				
	ERPG	Sheppard et al. (1981)				
	MRL	Tunnicliffe et al. (2003), Devalia et al. (1994)				
Sulfuric acid	SCOEL	Avol et al. (1979)	SE-OEL	VSTAF, MAK, SCOEL		38
	AEGL, ERPG	Horvath et al. (1982)				
	AEGL	Utell et al. (1982, 1983)				
	ERPG	Utell et al. (1984)				
	REL	Koenig et al. (1985), Utell et al. (1989)				
	TLV					
Tear Gas (O-Chlorobenzylidenemalonitrile)	–		AEGL, ERPG	TLV	DECOS, SE-OEL	1
1,1,1,2-tetrafluoroethane (HFC-134a)	AEGL	Smith et al. (1994), Taggart et al. (1994), Woodcock (1995)			MAK, SE-OEL	5
2,4-toluenediisocyanate	AEGL, ERPG	Baur (1985)	SE-OEL	MAK	REL, VSTAF, TLV	2
2,6-toluenediisocyanate						
						Total: 170

^a Only support documents from Category 1a were used (Fig. 1, Table 2).

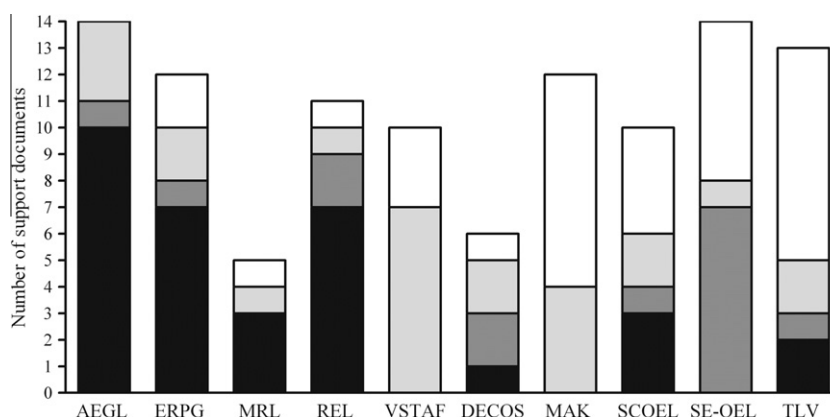


Fig. 2. Use of experimental data on asthmatics in support documents from the 10 programs for short-term values. No asthma studies cited (white); Asthma studies presented in text or only in list of references (light gray); Asthma studies cited and mentioned in conclusion (dark gray); Asthma studies used in the derivation of values or stated as key studies (black).

cies UF 1. Ten chamber studies on asthmatics were included in the TSD for formaldehyde and data showed that asthmatics are not more susceptible compared to healthy subjects at low exposure (up to 3 ppm) and an intraspecies UF 1 was therefore applied. In the case of HFC-134a (and the structurally related HFE-7100 and HCFC-141b) the UF 1 was also supported by the fact that HFC-134a had been used for asthma inhalation therapy. Finally, an intraspecies UF 3 was applied for Tear gas. The TSD states that the portal-of-entry effect is not expected to vary greatly between individuals. In the section for susceptible populations, a study is included that shows more severe chest symptoms among subjects with a history of allergic disease and asthma, “many of them laying prostrate on the ground for several minutes. However, no wheezing or rhonchi were heard, and recovery was as rapid as that seen in other exposure groups”. A statement on the interpretation of this study, in regard to asthmatics, would certainly increase transparency of the AEGL derivation. As in all cases where data is limited, supporting data or statements about the quality of the critical study would have increased the credibility and transparency.

In the second part of the present study, all supporting documents from AEGL and nine additional programs were compared (Table 3). About 2/3 of the asthma studies were identified in the AEGL documents, whereas 1/3 of the studies were only identified in other programs. We therefore conclude that literature searches in any of the programs are generally incomplete in relation to experimental data on asthmatics.

Support documents were categorized by the use of asthmatics in the conclusions and/or during the derivation of short-term values (Table 4, Fig. 2). Ten out of 14 support documents from AEGL had key studies with asthmatics. In the remaining four documents the asthma studies were not used in the derivation either due to the fact that asthmatics in the experimental studies were not concluded to be more susceptible (nitric acid, tear gas), that the quality of data was not considered as sufficient (acetaldehyde, methyl methacrylate). According to the ERPG program guideline values are applicable to the general population including, as stated in the definition, “nearly all individuals”, persons with asthma were not mentioned per se (Cavender et al., 2008). From the analysis we can however conclude that persons with asthma seem to be included in the target group, since 7 out of 12 support documents included asthmatic studies in the section for value derivation. In the definition of MRL people with “preexisting diseases” is a susceptible population (Pohl and Abadin, 1995). Asthma is not mentioned specifically, but might well be included, supported by the fact that three out of five support documents contained key studies with asthmatics in the derivation of values. In the methodology for the REL program it is stated that “asthmatics are frequently identi-

fied as a sensitive group” (Denton and Hickox, 1999). Eight out of 11 support documents also used studies on asthmatics as key studies. The only program for short-term values for the general population that clearly does not include asthmatics in their target group is the French VSTAF. No key studies on asthmatics were present in support documents, which coincides with the statement in the methodology that hypersensitive populations such as asthmatics are not included (INERIS, 2007).

The occupational short-term values are developed for the healthy working population. No information about asthmatics was therefore included in any of the stated methodologies for derivation of these values. Despite of the lack of information on asthmatics, the SCOEL-, TLV-, and DECOS-programs used studies on asthmatics as key studies in some of their support documents (Table 4). It is stated in the SCOEL methodology that information on groups of people of special risk should be included but not used in the derivation of OELs and asthmatics are stated a risk group in several of the support documents. Nevertheless, studies on asthmatics were included as key studies in the derivation of values for three out of 10 support documents (Fig. 2). Also, one out of six support documents in the DECOS program and two out of 13 in the TLV program included key studies on asthmatics in the derivation of values. The MAK- and the SE-OEL programs had no key studies with data from asthmatics. Although persons with asthma seem to be included in some cases most occupational short-term values exclude this group of people. We therefore conclude that occupational short-term values are not suited for protection of the entire population. It could however be questioned why persons with asthma are not included, given the high prevalence of asthma in the general population. It seems though, that persons with asthma might be included to some extent despite of the statements in the methodology documents. It has to be noted, that SE-OEL documents only provide scientific basis for setting OELs, but does not derive the actual values.

We observe that references and the use of these references in the derivation process vary in relation to the overarching purpose of the short-term values, i.e. general population vs. occupational settings (Fig. 2). As an alternative hypothesis, we analyzed if part of this might be related to the geographical bias, but found no tendency that American risk assessors exclude European studies and vice versa (data not shown).

A major area of uncertainty is that of intraspecies (interindividual) variability due to preexisting conditions such as disease (e.g. asthma) or deficient detoxication capacity. It has to be clearly stated that the guideline values discussed in this study are not intended to protect hypersensitive groups. In this context, hypersensitive responders are characterized as those individuals

exhibiting very rare and therefore unpredictable effects that are generally discontinuous with the known range of expected responses. The AEGL SOP suggests that an UF of 10 should be used as default to compensate for intraspecies variability in susceptibility within the general population. An intraspecies UF of less than the default value may be applied if data for sensitive individuals are available, or if the mechanism of toxicity (e.g. airway irritation) is not expected to differ greatly among individuals. Our analyses show that the AEGL documents in the case of irritants generally use a factor of 3 to account for asthmatics and a factor of 1 if the key study includes asthmatics. This practice is in accordance with that suggested in the “white paper” drafted in 2001 (NRC, 2001b).

In a previous study, the difference in sensitivity between asthmatics and healthy individuals was analyzed in a set of 11 studies covering 6 chemicals. Based on this limited database it was suggested that the variation between asthmatics and healthy individuals are within a factor of 1–5 (Young et al., 2009). If the use of an assessment factor of 1–5 is inadequate or inappropriate remains to be evaluated and the database of experimental studies needs to be enlarged.

As a basis for the present study we created a database with experimental studies on asthma. In all, 15 compounds were identified from the AEGL support documents. By combining the AEGL TSDs with the support documents from the other nine programs 170 experimental studies were identified. Hopefully, this database will be useful to strengthen the basis for a default UF for asthmatics. The issue is of importance as a default UF is needed e.g. for the 58 chemicals evaluated by the AEGL committee that had irritation as the critical effect, but no data on asthmatics (Fig. 1).

The focus in this study has been persons with asthma since this is conceivably the most important and most common subpopulation that is expected to be more sensitive to chemical irritants, compared to healthy individuals. An aspect not considered is that children with asthma may be more sensitive than adult asthmatics. One circumstance that would support such an assumption is that children have smaller airways and may thus react more severely to irritant-induced bronchoconstriction (NRC, 2001b). For obvious ethical reasons, the issue of child specific sensitivity is difficult to study experimentally. In addition, when asthmatic and nonasthmatic children and adults were challenged with methacholine no difference in response was found (de Pee et al., 1991). It was concluded from another experiment that severity of the disease, rather than age, had an effect on metacholine response in asthmatic children aged 1–17 (Avital et al., 1991). In a third chamber study, groups of asthmatic, allergic and nonasthmatic children (age 9–12) were exposed to a mixture of ozone, sulfur dioxide and sulfuric acid. None of the statistical analyses showed significant effects in lung function or symptoms (Linn et al., 1997). Overall, it seems that children and adult asthmatics are equally sensitive, so that no extra UF for children with asthma is needed. This conclusion is in accordance with that of the AEGL-committee (NRC, 2001b).

In our analysis of different standard setting programs we included several that develop occupational short-term values. These programs did not include asthmatics in their target population and the risk assessors often disregarded experimental data from asthmatics. Occupational short-term values might therefore not be protective for asthmatics and should be avoided as decision support during emergency planning, preparedness and response.

In summary, the present study presents the first overview of how persons with asthma are considered in the development of AEGL values. It shows that over two thirds of the TSDs lack data or even comments about asthmatics and that experimental data from asthmatics are referred to for 15 chemicals only. A comparison of the support documents for these 15 chemicals from 10 different programs for setting of short-term values reveals that the literature searches are generally incomplete. The exclusion of asth-

matics and/or exclusion of data on asthmatics in the development of guideline values for the general population may interfere with trustful and efficient risk and crisis management. Lack of data for asthmatics should be explicitly stated in the documentation. The available data on asthmatics experimentally exposed to irritant chemicals should be analyzed in depth, as they may strengthen the choice of a default UF for intraspecies variability in sensitivity to irritants.

Conflict of interest statement

The authors acknowledge that Dr. Mattias Öberg is a member of the AEGL Advisory Committee. Professor Gunnar Johanson is a member of the SCOEL and the NAS Subcommittee on AEGL. He is also vice chair of the Criteria Group of SWEA.

Acknowledgments

This project was performed within the National Centre for Disaster Toxicology (KcC). Financial support was received from the Swedish National Board of Health and Welfare [15523/2011] and the Swedish Civil Contingencies Agency [2685/2011].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.yrtph.2012.05.010>.

References

- Agency for Toxic Substances and Disease Registry (ATSDR). Minimal risk levels (MRL). Available at: <<http://www.atsdr.cdc.gov/mrls/index.asp>> (accessed 20.07.11).
- American Conference of Governmental Industrial Hygienists (ACGIH), 2001. Documentation of Threshold Limit Values and Biological Exposure Indices, seventh ed., Cincinnati.
- American Conference of Governmental Industrial Hygienists (ACGIH). Threshold Limit Values, History. Available at: <<http://www.acgih.org/about/history.htm>> (accessed 15.06.11).
- American Conference of Governmental Industrial Hygienists (ACGIH), 2011. Operations manual: threshold limit values for chemical substances committee. Available at: <http://www.acgih.org/TLV/Approved_Revised_TLV-CS_Comm_Ops_Manual-final.pdf> (accessed 15.06.11).
- American Industrial Hygiene Association (AIHA), 2008. The AIHA 2008 Emergency Response Planning Guidelines (ERPG) and Workplace Environmental Exposure Level (WEEL) Handbook Fairfax. AIHA press, Virginia.
- American Industrial Hygiene Association (AIHA), 2010. Emergency Response Planning Guidelines (ERPG), 2007 ERPG Complete list #AEAR 07–545, AIHA, 2008 ERPG update set 08–561, AIHA, 2009 ERPG update set 09–561 and AIHA, 2010 ERPG update set 10–561. AIHA press, Virginia.
- Andrews, C.P., Smith, J.D., Johanson, W.G., 1979. Pulmonary effects of methylmethacrylate vapor exposure in dental students. Clin. Res. 27 (5), A759 (Abstract).
- Arbetsmiljöverkets författningssamling (AFS), 2005. Hygieniska gränsvärden och åtgärder mot luftföroreningar. Arbetsmiljöverket, Stockholm.
- Avital, A., Noviski, N., Bar-Yishay, E., Springer, C., Levy, M., Gidfrey, S., 1991. Nonspecific bronchial reactivity in asthmatic children depends on severity but not on age. Am. Rev. Respir. Dis. 144, 36–38.
- Cavender, F., Phillips, S., Holland, M., 2008. Development of emergency response planning guidelines (ERPGs). J. Med. Toxicol. 4 (2), 127–131.
- Denton, J.E., Hickox, W.H., 1999. Air Toxics Hot Spots Program Risk Assessment Guidelines Part I The Determination of Acute Reference Exposure Levels for Airborne Toxicants, California Environmental Protection Agency (Cal EPA) and Office of Environmental Health Hazard Assessment (OEHA).
- de Pee, S., Timmers, M.C., Hermans, J., Duiverman, E.J., Sterk, P.J., 1991. Comparison of maximal airway narrowing to metacholine between children and adults. Eur. Respir. J. 26 (4), 421–428.
- Deutsche Forschungsgemeinschaft (DFG), 1970–1988b. Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-werten. Loseblattsammlung. Weinheim Verlag Chemie.
- Deutsche Forschungsgemeinschaft (DFG), 2011. Maximale Arbeitsplatzkonzentrationen (MAK), Derivation of MAK-values. Available at: <http://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/structure/working_groups/derivation_mak/index.html> (accessed 13.07.11).

- Dutch Expert Committee on Occupational Standards (DECOS), 2003. Formaldehyde. Health-based recommended occupational exposure limit. Health Council of the Netherlands, The Hague.
- Dutch Expert Committee on Occupational Standards (DECOS). Health-based recommended occupational exposure limits. Available at: <http://www.gezondheidsraad.nl/nl/adviezen/gezonde-arbeidsomstandigheden/results> (accessed 05.04.11).
- Global Initiative for Asthma (GINA), 2011. The Global Strategy for Asthma Management and Prevention. Available at: <http://www.ginasthma.org/> (accessed 20.06.11).
- Greim, H. (Ed.), 1991–2005. Deutsche Forschungsgemeinschaft (DFG). Occupational Toxicants: Critical Data Evaluation for MAK Values and Classification of Carcinogens. Wiley-VCH, Weinheim.
- Institut National de l'Environnement industriel et des risques (INERIS), 2009. Rapport d'étude: Guide pratique de choix des valeurs seuils de toxicité aiguë en cas d'absence de valeurs françaises.
- Institut National de l'Environnement industriel et des risques (INERIS), 2011. Valeurs seuils de toxicité aiguë françaises (VSTAF), Available at: <http://www.ineris.fr/fr/rapports-de-seuils-de-toxicite-aigue/rapports-de-seuils-de-toxicite-aigue/503> (accessed 11.03.11).
- Institut National de l'Environnement industriel et des risques (INERIS), 2007. Rapport d'étude: Méthodologie de détermination des valeurs seuils de toxicité aiguë françaises en cas d'émission accidentelle de substances chimiques dans l'atmosphère, 28.
- Jappinen, P. et al., 1990. Exposure to hydrogen sulphide and respiratory function. *Br. J. Ind. Med.* 47 (12), 824–828.
- Koenig, J.Q., Covert, D.S., Pierson, W.E., 1989. Effects of inhalation of acidic compounds on pulmonary function in allergic adolescent subjects. *Environ. Health Perspect.* 79, 173–178.
- Linn, W.S., Gong Jr., H., Shamoo, D.A., Anderson, K.R., Avol, E.L., 1997. Chamber exposures of children to mixed ozone, sulfur dioxide, and sulfuric acid. *Arch. Environ. Health* 52 (3), 179–187.
- Masoli, M., Fabian, D., Holt, S., Beasley, R., 2004. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 59 (5), 469–478.
- Montelius, J. (Ed.), 2006. Swedish Criteria Group for Occupational Standards. Scientific Basis for Swedish Occupational Standards XXVII. (Translator; z Frances Van Sant). Arbete och hälsa. National Institute for Working Life, Stockholm.
- Montelius, J., Lundberg, P., et al., 1981–2011. Swedish Criteria Group for Occupational Standards. Scientific Basis for Swedish Occupational Standards, vol. 31. Arbete och hälsa, Stockholm.
- National Research Council (NRC), 2001a. Standing Operating Procedures for Developing Acute Guidance Levels for Hazardous Chemicals. National Academic Press, Washington, DC.
- National Research Council (NRC), 2001b. The relative susceptibility of childhood asthmatics and adult asthmatics to acute exposures of irritant chemicals (unpublished draft). Available at: http://www.tceq.state.tx.us/assets/public/implementation/tox/dsd/comments/public_comments_and_tceq_responses_xylene.pdf (Appendix 3) (accessed 25.03.12).
- Öberg, M., Palmén, N., Johanson, G., 2010. Discrepancy among acute guideline levels for emergency response. *J. Hazard. Mater.* 184, 439–447.
- Office of Environmental Health Hazard Assessment (OEHA), 2011. Acute Reference Exposure Levels (RELs). Available at: <http://oehha.ca.gov/air/allrels.html> (accessed 22.03.11).
- Pohl, H.R., Abadin, H.G., 1995. Utilizing uncertainty factors in minimal risk levels derivation. *Regul. Toxicol. Pharmacol.* 22 (2), 180–188.
- Scientific Committee on Occupational Exposure Limits (SCOEL). Recommendations of the scientific committee for occupational exposure limits. Available at: <http://ec.europa.eu/social/keyDocuments.jsp?type=0&policyArea=0&subCategory=0&country=0&year=0&advSearchKey=scoel+&mode=advancedSubmit&langId=en> (accessed 24.03.11).
- Scientific Committee on Occupational Exposure Limits (SCOEL), 2009. Methodology for the Derivation of Occupational Exposure Limits: Key Documentation (version 6). European Commission.
- US Environmental Protection Agency (US EPA), 2010. Acute Exposure Guideline Levels (AEGs), Final and Interim Technical Support Documents. Available at: <http://www.epa.gov/oppt/aegl/pubs/humanhealth.htm> (accessed 01.10.10).
- US Environmental Protection Agency (US EPA), 2010. Acute Exposure Guideline Levels (AEGs) Program, History of AEGs. Available at: <http://www.epa.gov/oppt/aegl/pubs/history.htm> (accessed 01.10.10).
- US Environmental Protection Agency (US EPA), 2010. Acute Exposure Guideline Levels (AEGs) Program, Definition of values. Available at: <http://www.epa.gov/oppt/aegl/pubs/define.htm> (accessed 01.10.10).
- US Environmental Protection Agency (US EPA), 2010. Acute Exposure Guideline Levels (AEGs) Program, Process. Available at: <http://www.epa.gov/oppt/aegl/pubs/process.htm> (accessed 01.10.10).
- World Health Organization (WHO), 2011. Asthma, Available at: <http://www.who.int/mediacentre/factsheets/fs307/en/index.html>. (accessed 20.07.11).
- Young, R.A., Bast, C.B., Wood, C.S., Adeshina, F., 2009. Overview of the Standing Operating Procedure (SOP) for the development of Provisional Advisory Levels (PALs). *Inhal. Toxicol.* 21 (S3), 1–11.

References (Table 2 and 4)

- Andrews, C. P., J. D. Smith, and W. G. Johanson 1979, Pulmonary Effects of Methylmethacrylate Vapor Exposure in Dental Students, *Clin Res*, 27(5), A759-A759.
- Avol, E. L., M. P. Jones, R. M. Bailey, N. M. Chang, M. T. Kleinman, W. S. Linn, K. A. Bell, and J. D. Hackney 1979, Controlled exposures of human volunteers to sulfate aerosols. Health effects and aerosol characterization, *Am Rev Respir Dis*, 120(2), 319-327.
- Avol, E. L., W. S. Linn, R. C. Peng, J. D. Whynot, D. A. Shamoo, D. E. Little, M. N. Smith, and J. D. Hackney. 1989. Experimental exposures of young asthmatic volunteers to 0.3 ppm nitrogen dioxide and to ambient air pollution, *Toxicol Ind Health*, 5(6), 1025-1034.
- Bauer, M. A., M. J. Utell, P. E. Morrow, D. M. Speers, and F. R. Gibb 1986, Inhalation of 0.30 ppm nitrogen dioxide potentiates exercise-induced bronchospasm in asthmatics, *Am Rev Respir Dis*, 134(6), 1203-1208.
- Bauer, M. A., Utell, M.J., Morrow, P.E., Speers, D.M., and Gibb, F.R. 1985. Route of inhalation influences airway responses to 0.30 ppm nitrogen dioxide in asthmatic subjects., *Am. Rev. Respir. Dis.*, 131, A171.
- Baur, X. 1985, Isocyanate hypersensitivity. Final report to the International Isocyanate Institute III File No. 10349; III Project E-AB-19, Munich, Germany.
- Bethel, R. A., D. Sheppard, B. Geffroy, E. Tam, J. A. Nadel, and H. A. Boushey 1985, Effect of 0.25 ppm sulfur dioxide on airway resistance in freely breathing, heavily exercising, asthmatic subjects, *Am Rev Respir Dis*, 131(4), 659-661.
- 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(2), 331-337.
- Devalia, J. L., C. Rusznak, M. J. Herdman, C. J. Trigg, H. Tarraf, and R. J. Davies 1994, Effect of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation, *Lancet*, 344(8938), 1668-1671.
- Green, D. J., L. R. Sauder, T. J. Kulle, and R. Bascom 1987, Acute response to 3.0 ppm formaldehyde in exercising healthy nonsmokers and asthmatics, *Am Rev Respir Dis*, 135(6), 1261-1266.
- Horvath, S. M., L. J. Folinsbee, and J. F. Bedi 1982, Effects of large (0.9 micrometers) sulfuric acid aerosols on human pulmonary function, *Environ Res*, 28(1), 123-130.
- Jappinen, P., V. Vilkkä, O. Marttila, and T. Haahtela 1990, Exposure to hydrogen sulphide and respiratory function, *Br J Ind Med*, 47(12), 824-828.
- Jorres, R., and H. Magnussen 1990, Airways response of asthmatics after a 30 min exposure, at resting ventilation, to 0.25 ppm NO₂ or 0.5 ppm SO₂, *Eur Respir J*, 3(2), 132-137.

Jorres, R., D. Nowak, F. Grimminger, W. Seeger, M. Oldigs, and H. Magnussen 1995, The effect of 1 ppm nitrogen dioxide on bronchoalveolar lavage cells and inflammatory mediators in normal and asthmatic subjects, *Eur Respir J*, 8(3), 416-424.

Kerr, H. D., T. J. Kulle, M. L. McIlhany, and P. Swidersky 1979, Effects of nitrogen dioxide on pulmonary function in human subjects: an environmental chamber study, *Environ Res*, 19(2), 392-404.

Kerr, H. D., Kulle, T.J., McIlhany, M.L., and Swidersky, P. 1978, Effects of nitrogen dioxide on pulmonary function in human subjects. An environmental chamber study Rep., 20 pp.

Koenig, J. Q., D. S. Covert, and W. E. Pierson 1989, Effects of inhalation of acidic compounds on pulmonary function in allergic adolescent subjects, *Environ Health Perspect*, 79, 173-178.

Koenig, J. Q., M. S. Morgan, M. Horike, and W. E. Pierson 1985, The effects of sulfur oxides on nasal and lung function in adolescents with extrinsic asthma, *J Allergy Clin Immunol*, 76(6), 813-818.

Koenig, J. Q., D. S. Covert, M. S. Smith, G. van Belle, and W. E. Pierson 1988, The pulmonary effects of ozone and nitrogen dioxide alone and combined in healthy and asthmatic adolescent subjects, *Toxicol Ind Health*, 4(4), 521-532.

Kulle, T. J., D. J. Green, and L. R. Sauder 1986, Acute pulmonary effects of 3.0 ppm formaldehyde in exercising healthy nonsmokers and asthmatics, *American Review Respiratory Disease*, 133, A355.

Linn, W. S., E. L. Avol, R. C. Peng, D. A. Shamoo, and J. D. Hackney 1987, Replicated dose-response study of sulfur dioxide effects in normal, atopic, and asthmatic volunteers, *Am Rev Respir Dis*, 136(5), 1127-1134.

Linn, W. S., D. A. Shamoo, C. E. Spier, L. M. Valencia, U. T. Anzar, T. G. Venet, and J. D. Hackney 1983a, Respiratory effects of 0.75 ppm sulfur dioxide in exercising asthmatics: influence of upper-respiratory defenses, *Environ Res*, 30(2), 340-348.

Linn, W. S., T. G. Venet, D. A. Shamoo, L. M. Valencia, U. T. Anzar, C. E. Spier, and J. D. Hackney 1983b, Respiratory effects of sulfur dioxide in heavily exercising asthmatics. A dose-response study, *Am Rev Respir Dis*, 127(3), 278-283.

Linn, W. S., J. C. Solomon, S. C. Trim, C. E. Spier, D. A. Shamoo, T. G. Venet, E. L. Avol, and J. D. Hackney 1985, Effects of exposure to 4 ppm nitrogen dioxide in healthy and asthmatic volunteers, *Arch Environ Health*, 40(4), 234-239.

McLean, J. A., K. P. Mathews, W. R. Solomon, P. R. Brayton, and N. K. Bayne 1979, Effect of ammonia on nasal resistance in atopic and nonatopic subjects, *Ann Otol Rhinol Laryngol*, 88(2 Pt 1), 228-234.

Prieto, L., F. Sanchez-Toril, B. Brotons, S. Soriano, R. Casan, and J. L. Belenguer 2000, Airway responsiveness to acetaldehyde in patients with asthma: relationship to methacholine responsiveness and peak expiratory flow variation, *Clin Exp Allergy*, 30(1), 71-78.

Roger, L. J., H. R. Kehrl, M. Hazucha, and D. H. Horstman 1985, Bronchoconstriction in asthmatics exposed to sulfur dioxide during repeated exercise, *J Appl Physiol*, 59(3), 784-791.

Roger, L. J., D. H. Horstman, W. McDonnell, H. Kehrl, P. J. Ives, E. Seal, R. Chapman, and E. Massaro 1990, Pulmonary function, airway responsiveness, and respiratory symptoms in asthmatics following exercise in NO₂, *Toxicol Ind Health*, 6(1), 155-171.

Sauder, L. R., D. J. Green, M. D. Chatham, and T. J. Kulle 1987, Acute pulmonary response of asthmatics to 3.0 ppm formaldehyde, *Toxicol Ind Health*, 3(4), 569-578.

Schachter, E. N., T. J. Witek, Jr., G. J. Beck, H. B. Hosein, G. Colice, B. P. Leaderer, and W. Cain 1984, Airway effects of low concentrations of sulfur dioxide: dose-response characteristics, *Arch Environ Health*, 39(1), 34-42.

Sheppard, D., W. L. Eschenbacher, and J. Epstein 1984, Lack of bronchomotor response to up to 3 ppm formaldehyde in subjects with asthma, *Environ Res*, 35(1), 133-139.

Sheppard, D., A. Saisho, J. A. Nadel, and H. A. Boushey 1981, Exercise increases sulfur dioxide-induced bronchoconstriction in asthmatic subjects, *Am Rev Respir Dis*, 123(5), 486-491.

Smith, D. L., Aikman, S.L. Coulby, L.J. Sutcliffe, J. and O'Conner. B.J. 1994, The attenuation of methacholine-induced bronchoconstriction by salmeterol; comparison between an alternative metered dose inhaler propellant GR106642X and chlorofluorocarbons 11 and 12. , *Eur. Resp. J.*, 7(Suppl. 18), 318s.

Stevens, B., J. Q. Koenig, V. Rebolledo, Q. S. Hanley, and D. S. Covert 1992, Respiratory effects from the inhalation of hydrogen chloride in young adult asthmatics, *J Occup Med*, 34(9), 923-929.

Taggart, S. C. O., Custovic, A. Richards, D.H. and Woodcock. A. 1994, An alternative metered dose inhaler propellant GR106642X: comparison to chlorofluorocarbon 11 and 12 in the attenuation of histamine-induced bronchoconstriction by salbutamol. , *Eur. Resp. J.*(Suppl. 18), 400s.

Tunnicliffe, W. S., R. M. Harrison, F. J. Kelly, C. Dunster, and J. G. Ayres. 2003, The effect of sulphurous air pollutant exposures on symptoms, lung function, exhaled nitric oxide, and nasal epithelial lining fluid antioxidant concentrations in normal and asthmatic adults, *Occup Environ Med*, 60(11), e15.

Utell, M., Mariglio, J.A., Morrow, P.E., Gibb, F.R. and Speers. D.M. 1989, Effects of inhaled acid aerosols on respiratory function: the role of endogenous ammonia. , *J. Aerosol Med.* , 2((2)), 141-147.

Utell, M. J., P. E. Morrow, and R. W. Hyde. 1982, Comparison of normal and asthmatic subjects' responses to sulphate pollutant aerosols, *Ann Occup Hyg*, 26(1-4), 691-697.

Utell, M. J., P. E. Morrow, and R. W. Hyde. 1984, Airway reactivity to sulfate and sulfuric acid aerosols in normal and asthmatic subjects, *J Air Pollut Control Assoc*, 34(9), 931-935.

Utell, M. J., P. E. Morrow, D. M. Speers, J. Darling, and R. W. Hyde. 1983, Airway responses to sulfate and sulfuric acid aerosols in asthmatics. An exposure-response relationship, *Am Rev Respir Dis*, 128(3), 444-450.

Woodcock, A. 1995, Continuing patient care with metered-dose inhalers, *J Aerosol Med*, 8 Suppl 2, S5-10.

