

REVIEW ARTICLE

Evaluation of the experimental basis for assessment factors to protect individuals with asthma from health effects during short-term exposure to airborne chemicals

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ABSTRACT

Background: Asthmatic individuals constitute a large sub-population that is often considered particularly susceptible to the deleterious effects of inhalation of airborne chemicals. However, for most such chemicals information on asthmatics is lacking and inter-individual assessment factors (AFs) of 3–25 have been proposed for use in the derivation of health-based guideline values.

Objective: To evaluate available information in attempt to determine whether a general difference in airway response during short-term exposure between healthy and asthmatic individuals can be identified, and whether current AFs for inter-individual variability provide sufficient protection for asthmatics.

Methods: After performing systematic review of relevant documents and the scientific literature estimated differential response factors (EDRF) were derived as the ratio between the lowest observed adverse effect levels for healthy and asthmatic subjects based on studies in which both groups were tested under the same conditions. Thereafter, the concentration–response relationships for healthy and asthmatic subjects exposed separately to four extensively tested chemicals (nitrogen dioxide, ozone, sulfuric acid, sulfur dioxide) were compared on the basis of combined data. Finally, a Benchmark Concentration (BMC) analysis was performed for sulfur dioxide.

Results: We found evidence of higher sensitivity among asthmatics (EDRF > 1) to 8 of 19 tested chemicals, and to 3 of 11 mixtures. Thereafter, we confirmed the higher sensitivity of asthmatics to sulfuric acid and sulfur dioxide. No difference was observed in the case of ozone and nitrogen dioxide. Finally, our BMC analysis of sulfur dioxide indicated a ninefold higher sensitivity among asthmatics.

Conclusion: Although experimental data are often inconclusive, our analyses suggest that an AF of 10 is adequate to protect asthmatics from the deleterious respiratory effects of airborne chemicals.

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Guideline values, inhalation, nitrogen dioxide, ozone, risk assessment, susceptible populations, sulfuric acid, sulfur dioxide

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Introduction

Health-based guidelines provide important and widely used tools for the management of acute risks related to chemical exposure. These values are intended, among other things, to help protect the general population, as well as occupationally exposed individuals from acute exposure to airborne chemicals. They are used, for example, by governmental agencies, community planners, industrial safety engineers and industrial hygienists.

Examples of guideline values for emergency planning and response include the Acute Exposure Guideline Levels (AEGL) and the Emergency Response Planning Guidelines (ERPG). The AEGL values are developed by the AEGL Program and reviewed and published in Final form by the National Academy of Sciences (NAS) and Environmental Protection Agency (EPA) in the USA. These threshold values cover exposure for five different durations (10 min, 30 min, 1 h, 4 h and 8 h) at three levels (tiers) of severity, namely: AEGL-1: notable discomfort, irritation or certain asymptomatic non-sensory effects. AEGL-2: irreversible and/or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3: life-threatening effects or death. The ERPG values, developed by the American Industrial Hygiene Association (AIHA), cover exposure for 1 h only and three tiers similar to those of the AEGL, below which it is

assumed that nearly all individuals can be exposed without undue effects on health.

Occupational exposure limits (OEL), including short-term and ceiling limits (STEL, CLV), are developed by committees serving under, for example, the American Conference of Governmental Industrial Hygienists (ACGIH) and the European Commissions' Scientific Committee on Occupational Exposure Limit Values (SCOEL). These OELs are utilized to establish safe levels of exposure and for implementation of adequate controls for the protection of workers, in most cases, being intended to safeguard healthy adult workers. Previously, we demonstrated that only occasionally are key findings concerning asthmatics taken into consideration when deciding on OELs (Johansson et al. 2012). It is therefore questionable whether OELs protect subjects with mild asthma, or indeed, other pre-existing, common health problems.

Two important aspects of deciding on guideline values are inter-individual variability in susceptibility and the identification of particularly sensitive sub-populations. Typically, children, the elderly and individuals with pre-existing diseases, such as asthma, are considered to be more sensitive (NRC 2001). Here, we summarize the experimental evidence concerning the sensitivity of asthmatics. Asthma is a common, life-long, chronic inflammatory disease of the airways that afflicts adults and children of all ages. The World Health Organization (WHO) estimates that there are 235 million asthmatics worldwide (WHO 2013). Others estimate that 1–18% of the populations of different countries are currently affected (GINA 2014) and the prevalence has increased in several countries during the last few decades (Eder et al. 2006).

Health-based guidelines are intended to establish a threshold level of exposure below which adverse effects are unlikely. The health risk assessment process consists of four parts: hazard identification, hazard characterization, exposure assessment and risk characterization (IPCS 2004). Assessment factors (AFs; also referred to as safety factors or uncertainty factors) are incorporated in order to account for both biological variability and uncertainty. There is a considerable inter-individual variability in the relationship between exposure dose and target dose (toxicokinetics), as well as that between target dose and adverse effect (toxicodynamics). Extrapolation of experimental data from, for example, laboratory animals and routes of exposure other than inhalation to real-life human situations involves a number of uncertainties (for reviews of AFs, see e.g. ECHA 2010; Falk-Filipsson et al. 2007).

Different expert committees and authorities often arrive at divergent guideline values for one and the same

substance, frequently because of differences in the selection of key studies, consideration of sensitive groups, use of AFs and consideration of adverse health outcomes (Öberg et al. 2010). Earlier, we observed that experimental data or statements concerning asthmatics are lacking in 70% of the AEGL technical support documents, used as basis for short-term guideline values (Johansson et al. 2012), even though most of the 250 chemicals considered by the AEGL committee (in connection with the "Interim" or "Final" stage in 2012) are classified as respiratory irritants and employed in large amounts. Thus, experimental findings on asthmatics were provided for only 15 chemicals. Furthermore, analysis of the support documents for the same 15 chemicals used to develop nine sets of guideline values developed by other committees/authorities revealed that experimental studies on asthmatics, although available at the time of the evaluation, were frequently not included.

When no chemical-specific information is available, risk assessors typically apply a default AF of 10 to account for inter-individual variability (Renwick 1991, 1993, US EPA 1988, 1993). However, for the working and general populations European REACH legislation proposes default AF values of 5 and 10 (ECHA 2010), the Dutch TNO (Netherlands Organization for Applied Scientific Research) 3 and 10 (Hakkert et al. 1996) and the European Centre for Ecotoxicology and Toxicology of Chemicals 3 and 5 (ECETOC 2003). An AF for the general population of 25 was suggested in a report by the German Federal Institute for Occupational Safety and Health and the German Federal Environmental Agency (Kalberlah & Schneider 1998).

To account for variabilities in toxicokinetics and toxicodynamics the inter-individual factor can be subdivided into two equal parts ($10^{0.5} * 10^{0.5}$). This subdivision facilitates later replacement of the default AF with a chemical-specific adjustment factor, as proposed, for example, by IPCS (1994). AFs specific for a mode of action or pathway have also been proposed to allow, e.g. human variability in Phase I metabolism. They constitute an intermediate between the chemical specific and the default AFs (Dorne & Renwick 2005).

Our objective here was to evaluate the experimental basis for AFs intended to take inter-individual variability in susceptibility to irritant chemicals into account. A similar analysis of the variability in response of susceptible groups exposed to a few irritant gases has been investigated by Young et al. (2009). First, we attempted to identify any general differences between healthy and asthmatic individuals with respect to airway

response to short-term exposure and, thereafter, using the information available on four chemicals that have been examined extensively, to determine whether the AFs currently employed for inter-individual variability are adequate for asthmatics.

Methods

Part 1: Estimation of differential response factors on the basis of tests on healthy and asthmatic subjects under the same conditions: strategy for searching the literature

Controlled exposure studies including both healthy and asthmatic subjects exposed under the same conditions to airborne substances via a mouthpiece, head dome, face mask or in chamber with or without nose clip were identified. This literature search was based on the references in the supporting documents for five sets of short-term guideline values for the general population: the AEGL, ERPG, Minimal Risk Levels (US Agency for Toxic Substances and Disease Registry, ATSDR), Reference Exposure Levels (California Office of Environmental Health Hazard Assessment, OEHHA) and French Acute Toxicity Threshold Values (French National Institute for Industrial Environment and Risks, INERIS): and five sets of short-term exposure limits and similar occupational short-term values: the Dutch Expert Committee on Occupational Standards (Health Council of the Netherlands), Maximum Concentration at the Workplace (German Research Foundation, DFG), SCOEL, Swedish Occupational Exposure Limits (Swedish Work Environment Authority, SWEA) and ACGIH Threshold Limit Values (this database is described in detail by Johansson et al. 2012). These references were then supplemented with searches in PubMed and Toxnet databases of the US National Library of Medicine, as well as the Elsevier database EMBASE and Google scholar.

The search profile was "asthma", "human", "exposure", "chamber" and "effect", and this search was expanded by including the following frequently occurring names of authors as search terms: Koenig, Utell, Linn, Gong and Bethel, as well as by searching for specific chemicals thus identified. No temporal or other restrictions were employed. The latest search was performed on 19 February 2015. The approach to the identification of human exposure studies relevant to Part 1 is presented in Figure 1 and characterization of the different parts of the present study and the criteria for quality employed are shown in Tables 1 and 2, respectively.

Statistically significant changes in pulmonary function, levels of inflammatory markers and symptom

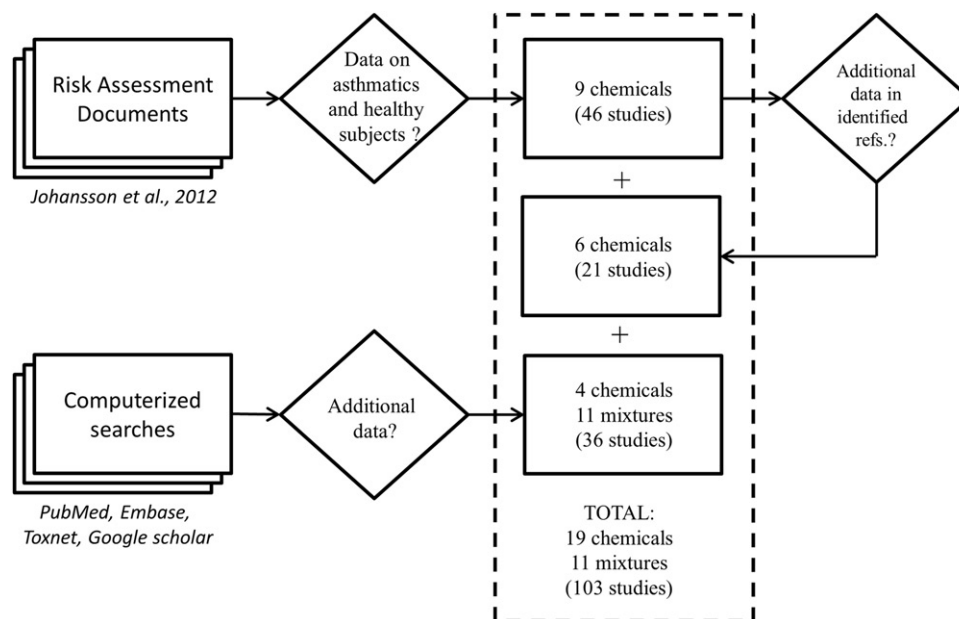


Figure 1. Approach to the identification of studies relevant to Part 1: Estimation of differential response factors on the basis of tests on healthy and asthmatic subjects under the same conditions. Relevant studies were identified from risk assessment documents and a computerized search of the peer-reviewed literature. All studies found were characterized (Table 1) and found to fulfill our criteria for quality (Table 2). Data concerning the total number of chemicals, mixtures and studies were then used as basis to estimate differential response factors.

Table 1. Characterization of the three parts of the present study.

	Part 1 EDRF	Part 2 Concentration–Response	Part 3 Benchmark concentration
Chemicals included	Any	NO ₂ , O ₃ , H ₂ SO ₄ , SO ₂	SO ₂
Form	Individual chemicals or mixtures	Individual chemicals only	Individual chemicals only
Experimental design	Only studies which both asthmatics and healthy subjects were tested under similar conditions	Studies on asthmatic and/or healthy subjects	Studies on asthmatic and/or healthy subjects
Endpoints considered	Lung function parameters, Symptoms, Inflammation markers	SRaw, FEV ₁	SRaw
Nature of data	Group wise	Group wise	Individual
Latest search date	18 February 2015	18 February 2015	18 February 2015
Number of studies	103	144 (healthy), 118 (asthmatics)	2 (healthy), 3 (asthmatics)

Table 2. The criteria for quality applied.

- Published in peer-reviewed journals (most not performed according to GLP).
- The same data published in two separate papers regarded as a single study.
- Methods and data well documented and scientifically sound, e.g. no conference abstracts and short letters
- Studies performed at normal room temperature (18–25 °C) and normal humidity.
- No current smokers included
- No subjects with pre-existing diseases other than asthma (e.g. COPD) included.
- No subjects with occupational or other history of heavy exposure to irritating or sensitizing air pollutants included.
- No subjects diagnosed with severe asthma disease or ongoing allergic symptoms included

scores were used to identify the lowest observed adverse effect levels (LOAEL). For each endpoint and study an estimated differential response factor (EDRF) was calculated as the ratio between the LOAELs for the healthy and the asthmatic subjects. In cases where a

LOAEL could not be identified in healthy subjects the ratio between the no observed adverse effects level (NOAEL) in healthy subjects and the LOAEL in asthmatics were calculated and noted with a greater-than sign.

There is a certain amount of subjectivity involved in combining all studies on a chemical to derive an overall EDRF. We applied a weight of evidence approach, considering factors such as the number of studies, duration of exposure (very short exposures were considered to be inconclusive), type of outcome [forced expiratory volume in one second (FEV₁) and specific airway resistance (SRaw) were considered to be more relevant if the EDRFs from different studies were in disagreement] and the number of subjects (higher weight was given to studies involving more subjects). In addition, the definition of asthma and documentation of asthma therapy was considered. Effects induced by exercise were controlled for by considering the response

of asthmatics to exposure to filtered air exposures. Overall EDRFs were considered to be inconclusive if the study did not meet our criteria or if LOAELs were not determined for either asthmatic or healthy subjects.

It should be noted that the studies retrieved employed endpoints of varying severity, i.e. sensory irritation (e.g. eye, nose or throat irritation and frequency of eye blinking), impairment of pulmonary function (spirometry) or hyperreactivity (bronchial challenge test). Sensory irritation, i.e. unpleasant sensation from the eyes and/or upper airways caused by stimulation of the trigeminal nerve endings by airborne substances (Damgård Nielsen et al. 2007), is often utilized as the critical effect for setting AEGL-1 values. Impairment of pulmonary function is considered more severe and serves as a basis for AEGL-2 values. Here, endpoints related to sensory irritation and impairment of pulmonary function were most important for our determination of overall EDRFs.

Part 2: Comparative analysis of concentration–response relationships

Four chemicals (nitrogen dioxide, ozone, sulfuric acid and sulfur dioxide) were selected for a meta-analysis of concentration–response relationships based on studies in which healthy and asthmatic subjects were tested under either the same conditions or in separate studies. These chemicals were chosen because of the large number of human studies that have been performed with them. In addition to the studies on healthy and asthmatic subjects under the same experimental conditions identified in Part 1, literature searches were designed to find studies involving only healthy or

asthmatic groups. The latest was performed on 19 February 2015 and the approach involved is presented in Figure 2. Again, the characterization and quality criteria are shown in Tables 1 and 2, respectively. In total, 476 separate sets of data on these four chemicals were retrieved and the comparative analysis was based on the data sets that included FEV₁ and/or SRaw ($n=262$).

Group-wise data on FEV₁ and SRaw were extracted from these studies since individual details were usually lacking. The percentage change in FEV₁ and SRaw was determined by deriving the values after-exposure by the baseline values. The responses of subjects to control exposure to filtered air are considered to reflect exposure levels of 0 mg/m³. The US EPA has, based on judgments from medical experts in the Clean Air Scientific Advisory Committee and commenters from the public, used four levels to characterize the severity of the airway responses from short-term exposure to oxides of nitrogen, ozone and sulfur dioxide (US EPA 2007, 2008, 2009): decrements in FEV₁ were rated as “no response” (<3%), “small response” (3–10%), “moderate response” (10–20%) or “large response” (≥20%), while the change in SRaw was graded as “no response” (<20%), “small response” (20–100%), “moderate response” (100–200%) or “large response” (>200%). According to the Global Initiative for Asthma (GINA 2014), the minimal important difference for improvement and worsening in FEV₁ based on asthmatic patient perception of change is about 10%.

Part 3: BMC analysis of sulfur dioxide

Among the 262 studies containing data on FEV₁ and/or SRaw identified in Part 2, we searched in Part 3 for studies

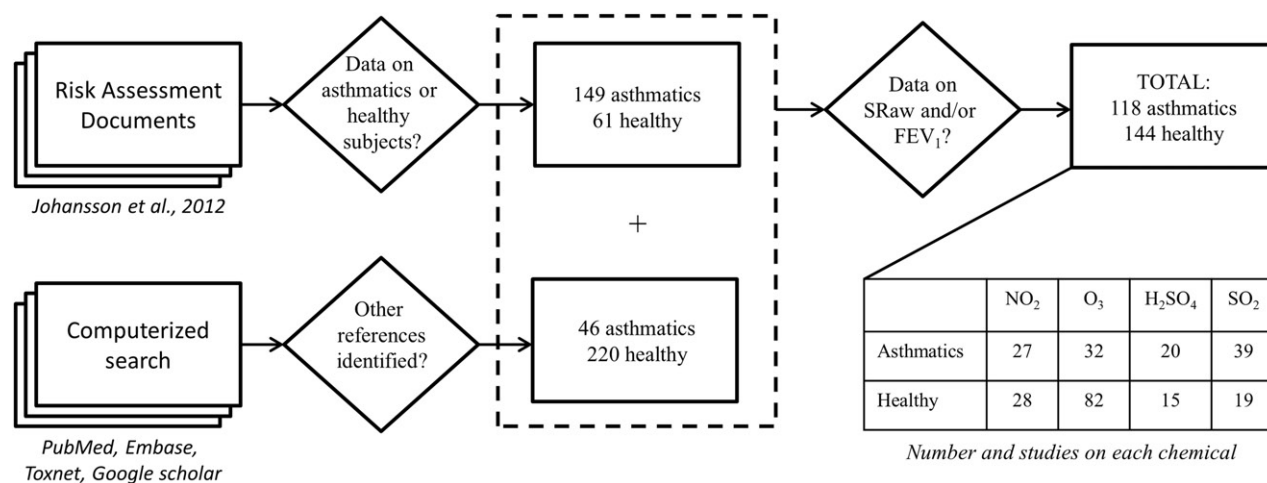


Figure 2. Approach to the identification of studies for Part 2: Comparative analysis of concentration–response relationships. Studies on healthy or asthmatic subjects exposed to nitrogen dioxide, ozone, sulfuric acid or sulfur dioxide were extracted from risk assessment documents and a computerized search of the peer-reviewed literature. All of these studies were characterized (Table 1) and found to fulfill our criteria for quality (Table 2). The studies concerning data on SRaw or FEV₁ were selected for this analysis.

with data on each individual subject. A benchmark concentration (BMC) analysis was performed on SRaw data from five studies involving exposure to sulfur dioxide (breathing at rest from the mouth only). Curve-fitting was carried out with a nested set of exponential and Hill models (Slob 2002) using the R package PROAST version 32.2 (Slob & Cotton 2012) in R version 2.15.2 (R Core Team 2012). The concentration–response curves were fitted to the data employing subject status (asthmatic or healthy) as a covariant. A critical effect size of 20% SRaw was used, according to the definition of a “small”, but clear response above. A more detailed description of this procedure is given in the Supplementary material (Appendix E: “The BMC analysis”).

Criteria for study selection, data extraction and characteristics of the studies included

For all studies identified in Parts 1–3 of the present review, the definition of asthma, experimental design and exercise conditions were recorded, along with the chemical involved, its concentration and duration of exposure. The number of subjects, their age, gender, smoking habits and eventual use of corticosteroids were also noted. In most cases, the asthmatic subjects were diagnosed by a physician, according to the criteria for mild asthma of the American Thoracic Society (American Thoracic Society 1987) and were not allowed to undergo asthma therapy before or during the exposure. Although the severity of asthma and/or diagnostic criteria was not clearly stated in some studies, these subjects were also assumed to have mild asthma.

All experimental data utilized here originated from controlled chamber experiments at rest or during exercise (on a bicycle or treadmill) while breathing oronasally or through the mouth only. The intensity of exercise varied between light, moderate and heavy with a ventilation rate of 20–70 L/min.

Except for five studies involving 135–786 healthy individuals, the number of subjects varied from 4 to 66 including mostly adult men and women between 18 and 54 years of age (although some involved 8–17-year-old children or the elderly aged 60–89). Most of the studies were published between 1982 and 1999, the entire range being 1960–2014 (Seven studies from the 1950s considered in Part 2 did not present data on SRaw or FEV₁). The duration of exposure varied from minutes to almost 8 h. The complete lists of the studies included in the analyses are presented in the Supplementary material (Appendices C and D).

Table 3. Relative response by asthmatic versus healthy subjects to inhalation exposure, expressed as an overall EDRF^a.

Substance	Number of studies	Overall EDRF
Individual chemicals		
Acetaldehyde	3	3
Ammonia	2	Inconclusive
Ammonium bisulfate	4	>1
Ammonium nitrate	1	Inconclusive
Ammonium sulfate	3	Inconclusive
Carbon black/particles	2	Inconclusive
Chlorine	1	2
Ferric sulfate	1	Inconclusive
Formaldehyde	3	1
Nitric oxide	1	Inconclusive
Nitrogen dioxide	14	>1
Ozone	25	>1
Sodium bisulfate	2	Inconclusive
Sodium nitrate	2	Inconclusive
Sulfur dioxide	8	>2
Sulfuric acid	14	>1
Tear gas	1	Inconclusive
2,4-/2,6-Toluenediisocyanate	1	>1
Zinc ammonium sulfate	1	1
Total, 19 chemicals	89	
Mixtures and combined exposures		
Carbon aerosol and sulfuric acid	1	Inconclusive
Diesel particles in ambient air (indoor, Sweden)	1	1
Environmental tobacco smoke	2	>1
Nitrogen dioxide and sulfur dioxide	1	Inconclusive
Ozone in ambient air (Los Angeles)	1	>1
Ozone and limonene	1	Inconclusive
Ozone and nitrogen dioxide	1	Inconclusive
Ozone and sulfur dioxide	1	>1
Ozone, sulfur dioxide and sulfuric acid	1	Inconclusive
Ozone and sulfuric acid	1	1
PM _{2.5} in urban air (Los Angeles)	3	Inconclusive
Total, 11 mixtures	14	

See Appendix A: Table 1 for details.

^aCalculated as the LOAEL in healthy subjects divided by the LOAEL for the same effect in asthmatics. Impaired pulmonary function, increased levels of inflammatory markers in the plasma or bronchoalveolar lavage and respiratory symptoms were the effects considered.

Results

Part 1: Estimation of differential response factors on the basis of tests on healthy and asthmatic subjects under the same conditions

In total, 103 studies involving exposures of healthy and asthmatic subjects under the same conditions, including 19 chemicals and 11 mixtures/combined exposures (Table 3), fulfilled our quality criteria (Table 2), and were used to estimate EDRF values.

Sixteen of the 30 chemicals/mixtures were each investigated in one study only (Table 3). In contrast, nitrogen dioxide, ozone, sulfuric acid and sulfur dioxide were included in 61 of the 103 studies, and these four chemicals were therefore selected for comparative analysis of concentration–response relationships (Part 2).

The overall EDRFs are summarized in Table 3 and a more detailed table with all of the studies, EDRFs and rationales is given in the Supplemental material,

Appendix A. Asthmatics appear to be highly sensitive (respiratory effects and/or symptoms) to acute exposure of acetaldehyde, ammonium bisulfate, chlorine, nitrogen dioxide, ozone, sulfur dioxide, sulfuric acid, toluenediisocyanate, environmental tobacco smoke, ozone in ambient air and combined exposure to ozone and sulfur dioxide. The highest EDRF was derived from an experiment involving exposure to sulfur dioxide, where the concentration at which $SRaw$ was increased significantly was five times lower for asthmatics, than healthy subjects (Sheppard et al. 1980). Based on eight studies, the overall EDRF for sulfur dioxide was estimated to be >2 . EDRF values of 2 and 3 were estimated for chlorine and acetaldehyde, respectively.

The studies with ammonium bisulfate, nitrogen dioxide, ozone, sulfuric acid, toluenediisocyanate, environmental tobacco smoke, ozone in ambient air and combined exposure to ozone and sulfur dioxide resulted in EDRF values >1 . There was no evidence for higher sensitivity among the asthmatics (EDRF = 1) to formaldehyde, zinc ammonium sulfate, diesel particles in ambient air and combined exposure to ozone and sulfuric acid. The remaining 15 chemicals/mixtures did not cause respiratory effects at the concentrations tested, therefore no conclusion regarding the sensitivity of asthmatics could be drawn.

Part 2: Comparative analysis of concentration–response relationships

Experimental studies involving exposure of healthy (220), asthmatic (134) subjects or both (61), to nitrogen dioxide, ozone, sulfuric acid and sulfur dioxide were identified. A complete reference list is available in the Supplementary material (Appendix D). These studies involved both oronasal and mouth-only breathing performed during exercise or at rest. Comparative evaluation of the concentration–response relationships, after exposures compared to baseline values, was based on two commonly employed outcomes, FEV_1 and $SRaw$. Data from experiments involving oronasal breathing (FEV_1 , $SRaw$) or mouth-only breathing (FEV_1) during exercise (FEV_1) were included, but the data from the chamber experiments, with or without noseclip, performed under resting conditions ($SRaw$ or FEV_1) or with a noseclip during exercise ($SRaw$) were too few for analysis.

Part 2: Comparative analysis of concentration–response relationships for nitrogen dioxide

Asthmatics, but not healthy subjects, exhibited a moderate reduction in FEV_1 (–10% to –20%) and

moderate elevation of $SRaw$ (100–200%) in response to oronasal inhalation of nitrogen dioxide at all concentrations while exercising and even after exposure to filtered air (Figure 3). A single incidence of severe reduction in FEV_1 (–34%) after mouth-only inhalation of nitrogen dioxide was seen in one group of asthmatics (Koenig et al. 1988), but not in any other groups of either asthmatics or healthy subjects (Figure 4). No concentration–response relationship was observed in the concentration range explored (0–5.64 mg/m³).

Part 2: Comparative analysis of concentration–response relationships for ozone

Both healthy and asthmatic subjects demonstrated moderate to severe airway responses to oronasal inhalation of ozone at concentrations >0.24 mg/m³ during exercise (Figure 5). Small airway responses were also seen in both groups after exposure to filtered air (0 mg/m³ ozone), probably induced by the exercise. Both healthy and asthmatic subjects also showed moderate responses when exposed to similar concentrations of ozone by mouth-only breathing (Figure 6). The concentration–response relationships for healthy and asthmatic subjects were similar within the concentration range examined (0–1.5 mg/m³).

Part 2: Comparative analysis of concentration–response relationships for sulfuric acid

Asthmatics, but not healthy subjects, exhibited a moderate decrease in FEV_1 and moderate enhancement of $SRaw$ in response to oronasal inhalation of sulfuric acid at all concentrations and to filtered air (0 mg/m³) during exercise (Figure 7). Avol et al. (1988b) observed effects on FEV_1 after exposure to sulfuric acid, but not after filtered air. In this case, the effects of sulfuric acid and filtered air on $SRaw$ were not statistically different, suggesting that they were exercise-induced. Similarly, another study by this same group (Avol et al., 1988a) found that the effects of filtered air and sulfuric acid on FEV_1 and $SRaw$ did not differ significantly. In comparison to both baseline values (before exercise and the exposure) and after exposure to filtered air during exercise, one group of asthmatics did show a statistically significant moderate reduction in FEV_1 following mouth-only inhalation exposure of 0.35 mg/m³ sulfuric acid (Utell et al., 1989) (Figure 8). No concentration–response relationships were detected in the range of concentrations explored (0–2 mg/m³).

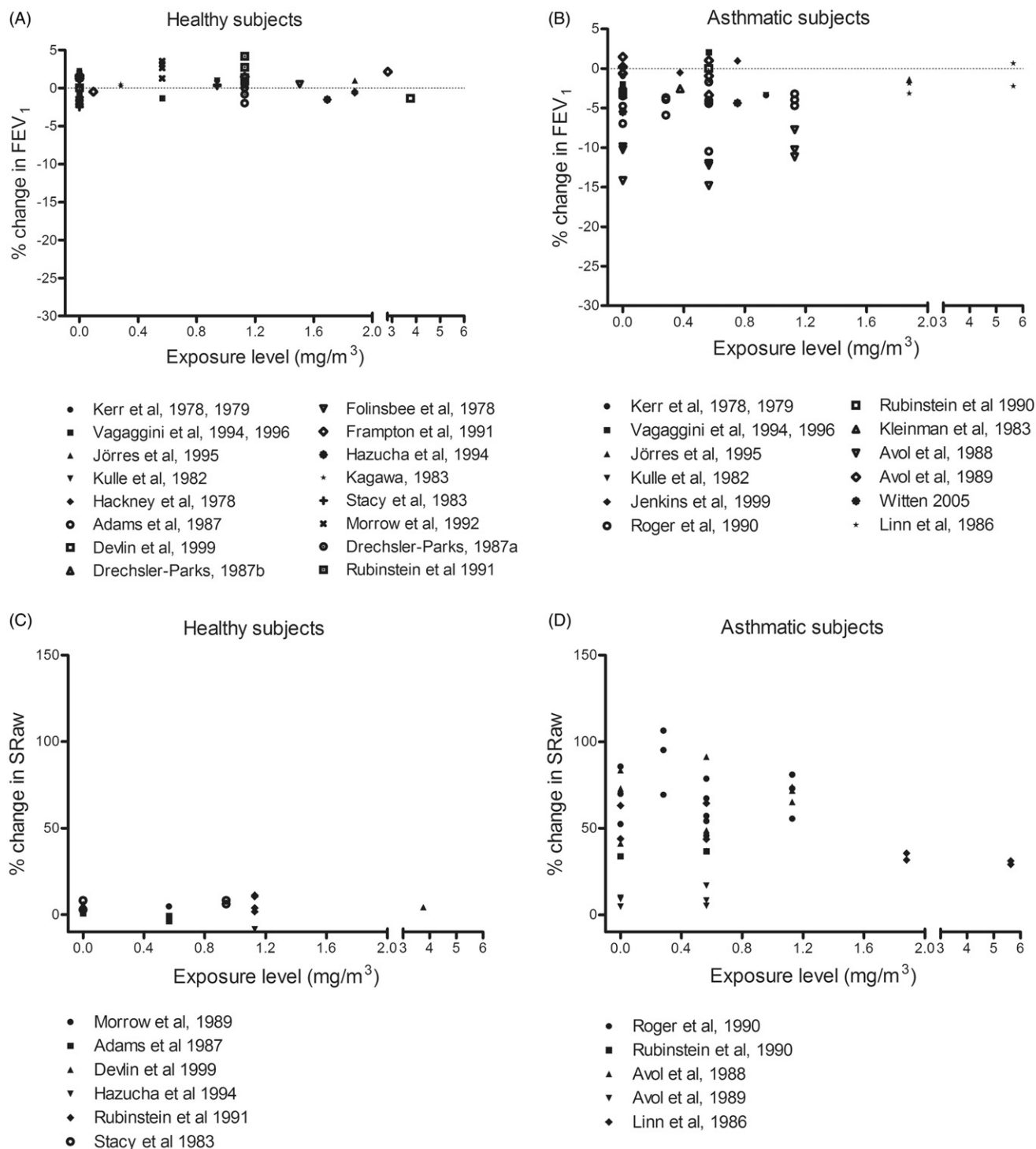


Figure 3. Percentage change (after/before exposure $\times 100$) in FEV_1 and $SRaw$ in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to nitrogen dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

Part 2: Comparative analysis of concentration–response relationships for sulfur dioxide

During exercise with oronasal inhalation of sulfur dioxide, moderate and severe responses occurred in

asthmatics, but not healthy subjects (Figure 9). The effects in asthmatics were observed at concentrations $>1 \text{ mg/m}^3$ (highest concentration tested = 2.88 mg/m^3), whereas healthy individuals showed no response even at 15 mg/m^3 . Small responses in FEV_1 and $SRaw$ were seen

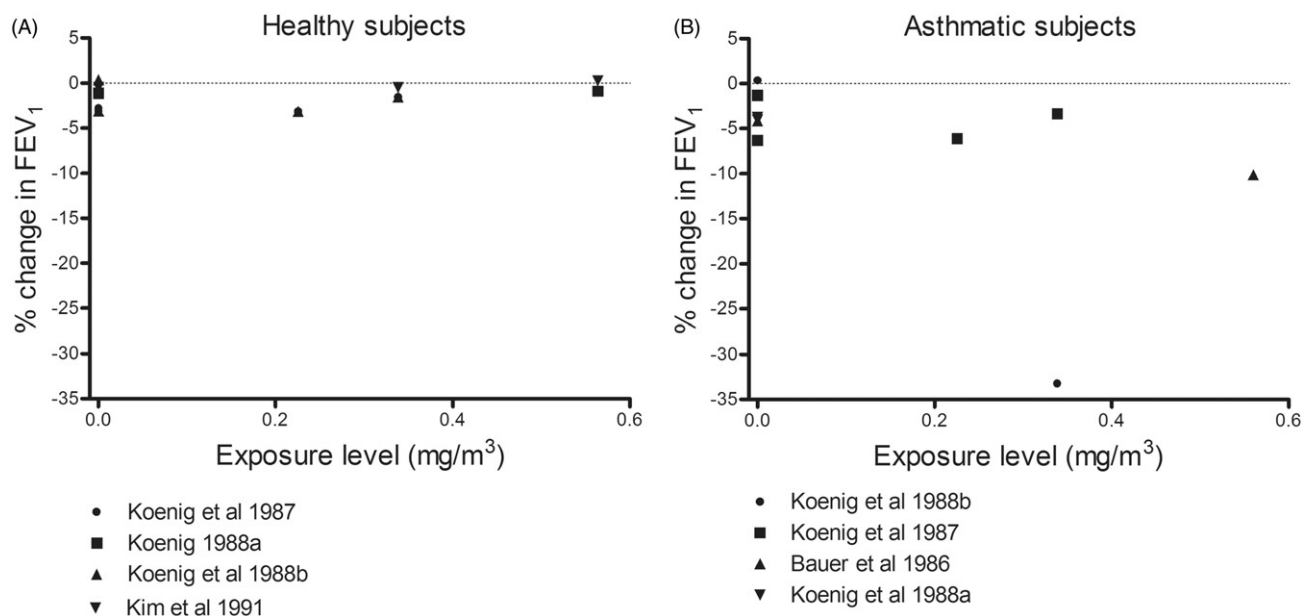


Figure 4. Percentage change (after/before exposure \times 100) in FEV₁ in healthy and asthmatic subjects following inhalation exposure (mouth-only breathing) to nitrogen dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

in asthmatics following control exposure to filtered air, probably induced by exercise (Figure 9b and d). Furthermore, mouth-only inhalation of sulfur dioxide at similar concentrations resulted in a severe reduction of FEV₁ in the asthmatics, but not the healthy subjects. Both groups exhibited small airway responses after control exposure to filtered air (Figure 10).

Part 3: BMC analysis of sulfur dioxide

In addition to analyzing concentration–response relationships at the group level, we retrieved data on individual pulmonary function able for BMC analysis (healthy subjects: Lawther et al. 1975; Sheppard et al. 1980, asthmatics: Bethel et al. 1984; Jörres & Magnussen 1990; Sheppard et al. 1980). These were the only sets of comparable individual data available for all chemicals included in the present study. In total, these studies document SRaw responses following exposure to various levels of sulfur dioxide at rest in 21 healthy and 28 asthmatic subjects (Figure 11). The highest concentrations tested in healthy and asthmatic subjects were 85.8 and 14.3 mg/m³, respectively. At these concentrations, members of both groups experienced severe impairment of lung function (SRaw >200%). Using 20% change in SRaw as the critical effect size, the BMC values were 33.7 and 3.7 mg/m³ in healthy and asthmatic subjects, respectively, resulting in an EDRF value of 9.

Discussion

Selection of the studies for consideration

The incomplete incorporation of experimental data on asthmatics associated with many regulatory programs for acute exposure may lower the trust for and efficiency of actions designed to protect human health (Johansson et al. 2012). Our own experience here shows that the use of technical support documents and the names of specific authors as search terms are good complements to the use of MeSH terms and key words when searching for experimental data on humans. In attempt to identify such studies available, we combined references from technical support documents with references obtained from standard computerized literature databases, an approach with characteristics similar to those of work flow and standard reporting items for systematic reviews (e.g. Moher et al. 2009). Employing a systematic flow, we assessed the data beginning with broad identification, followed by text screening and transparent evaluation of eligibility. This process identified a higher number of studies involving more chemicals than the previous report by Young et al. (2009).

Factors that influence the sensitivity of asthmatics to airborne chemicals

Several factors, including temperature, the severity and phenotype of asthma, other pre-existing diseases, smoking and occupational exposure to chemicals

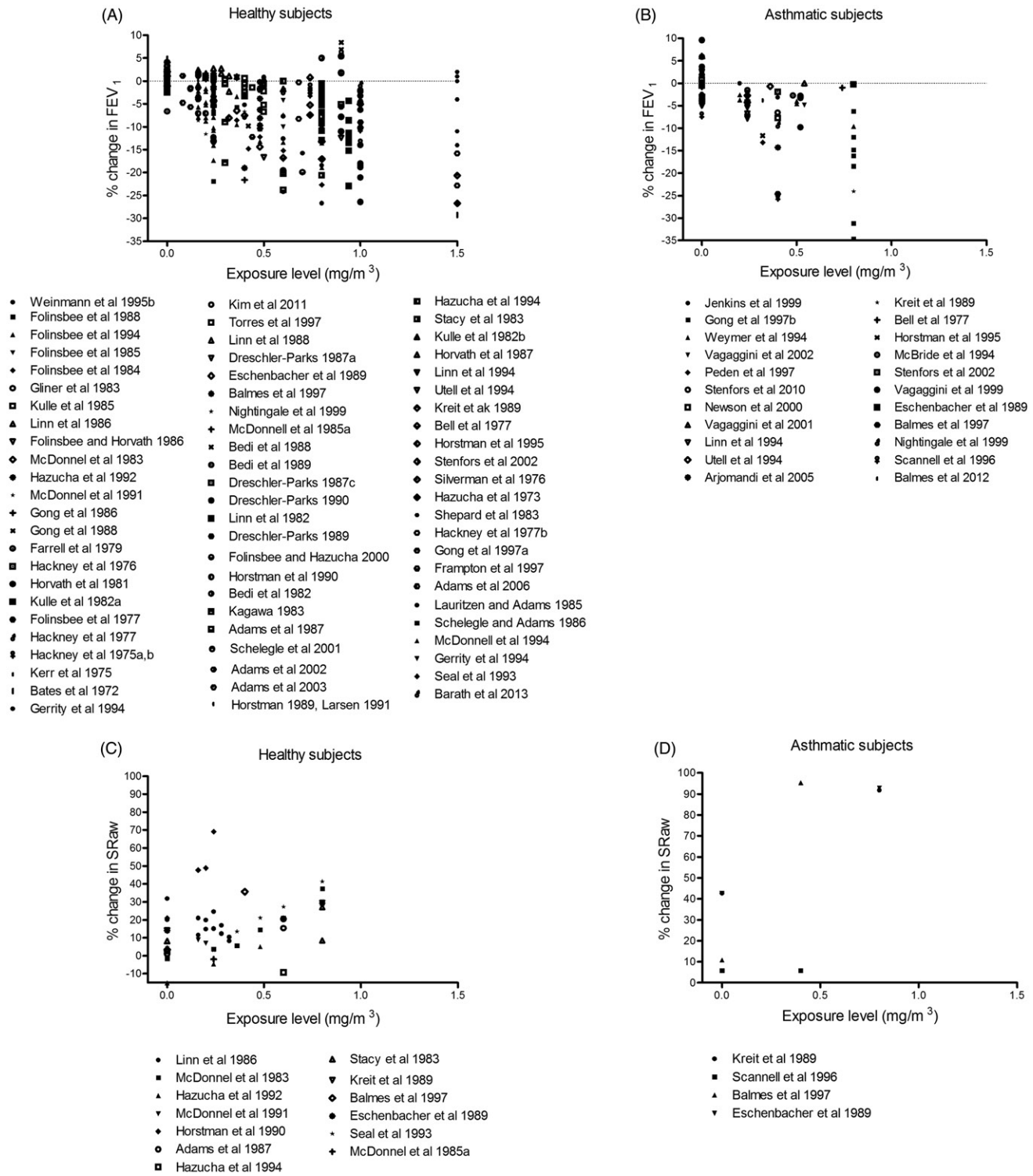


Figure 5. Percentage change (after/before exposure \times 100) in FEV₁ and SRaw in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to ozone during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

might influence the sensitivity of persons with asthma and thereby confound the results of the present study. To reduce the variability between studies, we therefore applied a set of quality criteria (Table 2).

Bethel et al. (1984) compared the airway responses of the same group of asthmatics to 1.43 mg/m³ sulfur dioxide at different temperature and found a severe elevation in SRaw (+222%) at -10.6 °C, but a smaller

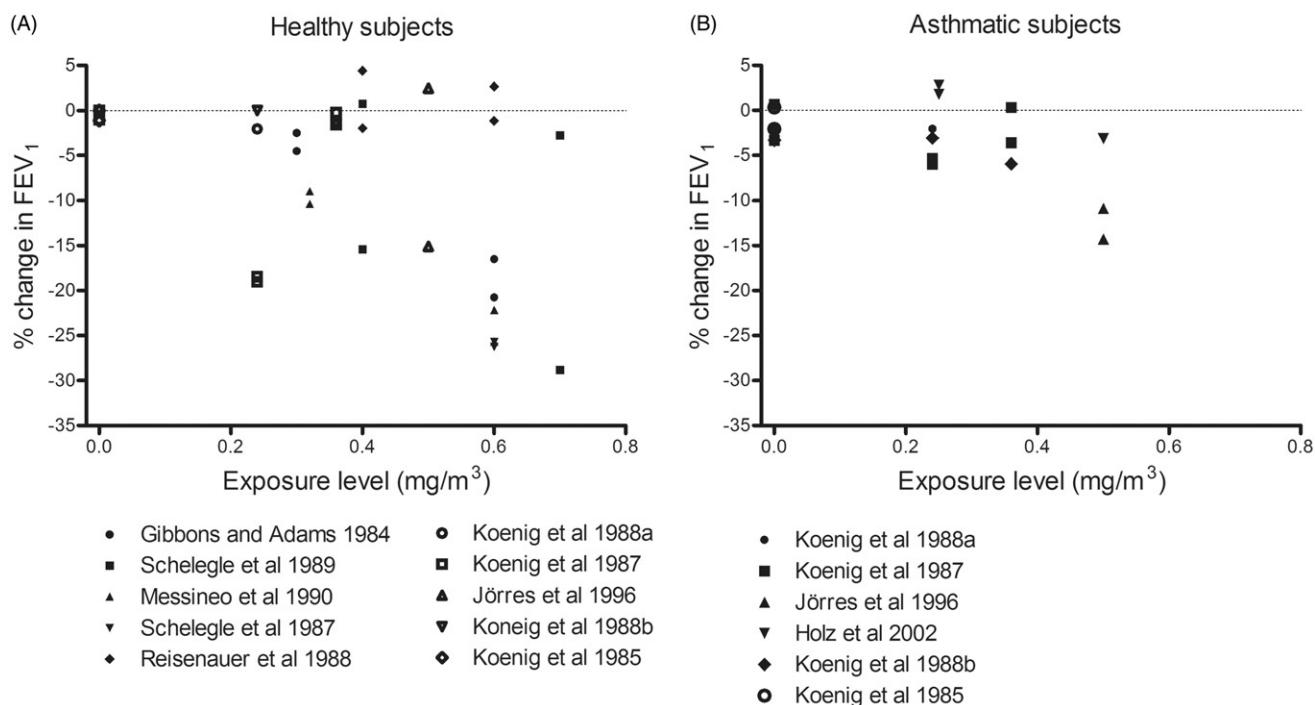


Figure 6. Percentage change (after/before exposure $\times 100$) in FEV₁ in healthy and asthmatic subjects following inhalation exposure (mouth-only breathing) to ozone during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

response (+38%) at 22.8 °C. Since temperature is likely to influence the result, all of the exposure studies included here were performed at temperatures between 18 and 25 °C or, as stated, “within room temperature”.

In one experimental comparison of the airway responses of mild and moderate/severe asthmatics to 0.57–1.7 mg/m³ (0.2–0.6 ppm) sulfur dioxide, those with moderate/severe asthma showed the largest impairments in SRaw and FEV₁, but these differences were not statistically significant (Linn et al. 1987). The AF is not intended to protect hypersensitive sub-populations and studies on individuals with severe asthma were therefore excluded from the present analysis.

The asthma phenotype indicated, diagnosis of the disease and use of therapy varied between the studies and contribute to uncertainty in the EDRF calculations and concentration–response analysis (see Supplementary material, Appendix A for definitions of asthma and medical treatment in the studies considered in Part 1). We reduced the uncertainty related to asthma phenotype by excluding studies involving subjects who were described as having ongoing allergic symptoms. In addition, most of the studies specified that they were performed outside of pollen season and that their asthmatic subjects were not allowed to use inhalators during the period immediately preceding the study. In most studies, but not all, asthmatics were not allowed to use corticosteroid therapy for weeks or months prior to

the experimental exposure. Corticosteroid therapy might underestimate the sensitivity among asthmatics due to its long-term effects.

In attempt to avoid effects on pulmonary function caused by factors other than the chemical/mixture of interest, only studies involving non-smokers and individuals with no previous known occupational or other extensive exposure to irritating or sensitizing air pollutants were included (Table 2). Individuals with other diseases, for example, Chronic Obstructive Pulmonary Disease (COPD), ischemic heart disease or allergy without asthma, were also excluded. In addition, studies on ozone-sensitive, otherwise healthy subjects, and smoke-sensitive atopic asthmatics were excluded.

Work load is an important consideration in the present analysis and studies performed either at rest or while exercising were included in Part 1. We adjusted for exercise-induced effects in the estimation of differential response factors by using exposure to filtered air as a control. Exercise was involved in all exposures in Part 2 (Figures 3–10) and the workload varied between light, moderate and heavy with ventilation rates of 20–70 L/min. The response in subjects after control exposures to filtered air are presented as exposure levels of 0 mg/m³ for each chemical. Exercise can impair pulmonary function in asthmatics. Hazucha et al. (1987) found that such impairment by ozone was more pronounced at higher workloads. The exercise-induced

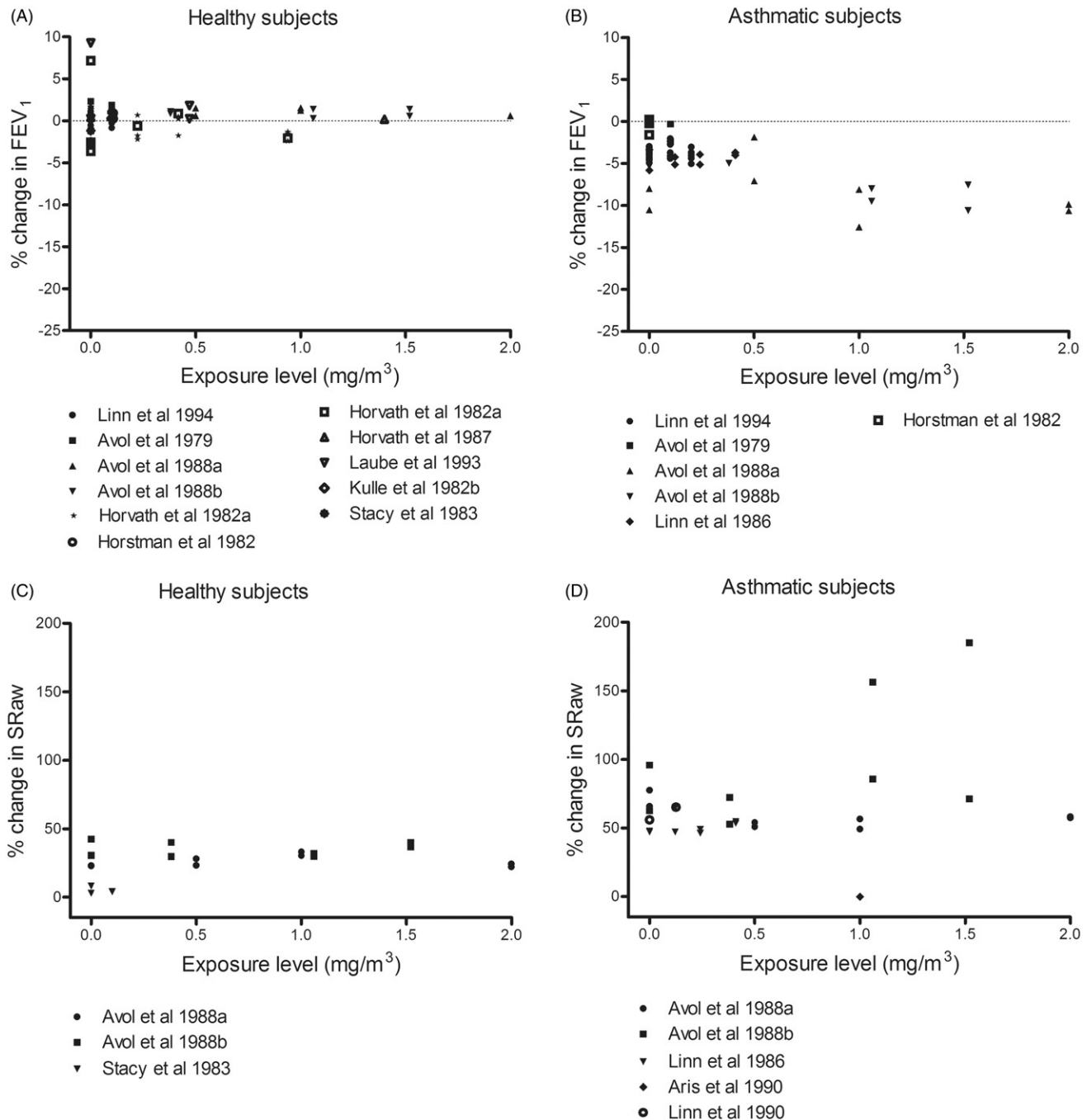


Figure 7. Percentage change (after/before exposure $\times 100$) in FEV_1 and $SRaw$ in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to sulfuric acid during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

effects on $SRaw$ and FEV_1 were adjusted for in a separate analysis presented in the Supplemental material (Appendix F: Figures 1–8).

Most adults (80–90%) utilize nasal breathing at rest, but shift to oronasal breathing during exercise when the minute ventilation rises to between 30 and 40 L/min (Kleinman 1984). Asthmatics are more likely, than healthy subjects, to perform oronasal breathing even at rest (Chadha et al. 1987). Mouth-only inhalation is somewhat artificial, by-passing the natural human

scrubbing system in the nasal airways (Proctor 1981). In the present case, however, the results for exercising subjects breathing freely (oronasal) and through the mouth only did not differ significantly (Figures 3–10).

Age might also influence our interpretations. Children, adolescents and young adults (<18 years of age) appear to demonstrate equivalent spirometric responses to short-term exposure to ozone, but their airway responses are slightly greater and they experience more symptoms than middle-aged and older adults exposed to

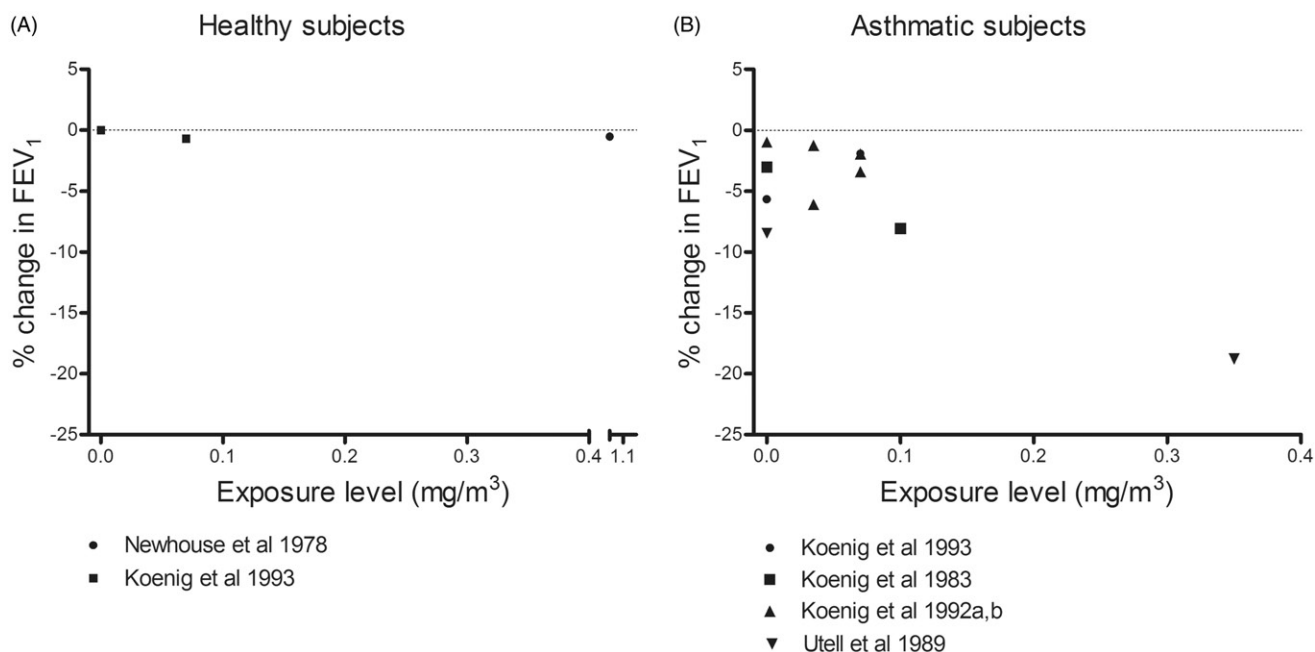


Figure 8. Percentage change (after/before exposure \times 100) in FEV₁ in healthy and asthmatic subjects following inhalation exposure (mouth-only breathing) to sulfuric acid during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

comparable concentrations of ozone (US EPA 2007). A few studies with 8–17- and 60–89-year-olds were included here since their pattern of effects did not differ from available experimental findings on younger and middle-aged adults. Similar responses among all age groups were also supported by de Pee et al. (1991). They observed no difference in the responses of children and adults, healthy or asthmatic, to a methacholine challenge. However, children and infants are two of the sub-populations often considered as more susceptible to the chronic exposure of many air pollutants, including ozone (Kim 2004). Mortimer et al. (2000) examined 846 asthmatic children from urban areas for changes in peak expiratory flow (PEF) related to air pollution. Among all pollutants tested (sulfur dioxide, PM₁₀, ozone and nitrogen dioxide) only ozone was associated with a change in morning PEF (Mortimer et al. 2000). Eighty percent of the alveoli develop postnatally and additional changes occur during adolescence (Dietert et al. 2000). Indeed, the effects from ambient air pollutants are most pronounced during the first year of life (Götschi et al. 2008).

Part 1: Estimation of differential response factors on the basis of tests on healthy and asthmatic subjects under the same conditions

Eleven of the 30 chemicals and mixtures examined produced a more pronounced response in asthmatics than healthy subjects (Table 3). Although it was possible

Table 4. Comparison of our findings to a previous assessment of differences in the responses of asthmatic and healthy subjects to irritant gases.

Chemical	Estimated differential response factor	
	Young et al. (2009)	Present study (2015)
Chlorine	2	2
Formaldehyde	Approx. 1	1
Nitrogen dioxide	3–5	>1
Ozone	2	>1
Sulfur dioxide	3–4	>2
Sulfuric acid	1.3–5	>1

to estimate differential response factors for acetaldehyde (3) and chlorine (2), in certain studies the LOAEL for healthy subjects was not determined for the concentrations selected for exposure resulting in EDRF values of >2 or >1. However, there was no difference in the responses of the groups to four chemicals/mixtures (EDRF = 1), i.e. formaldehyde, zinc ammonium sulfate, diesel particles in ambient air, and ozone and sulfuric acid in combination.

No EDRFs could be estimated for the 15 chemicals and mixtures that evoked no response at any concentration tested. Furthermore, there is substantial uncertainty involved in the estimation of EDRFs on the basis of LOAEL, which are strongly influenced by both the number of subjects and test concentrations. Moreover, the number of available studies varied: for 16 chemicals/mixtures our EDRFs were based on a single study, 11 were based on 2–8 studies and 14–25 studies were

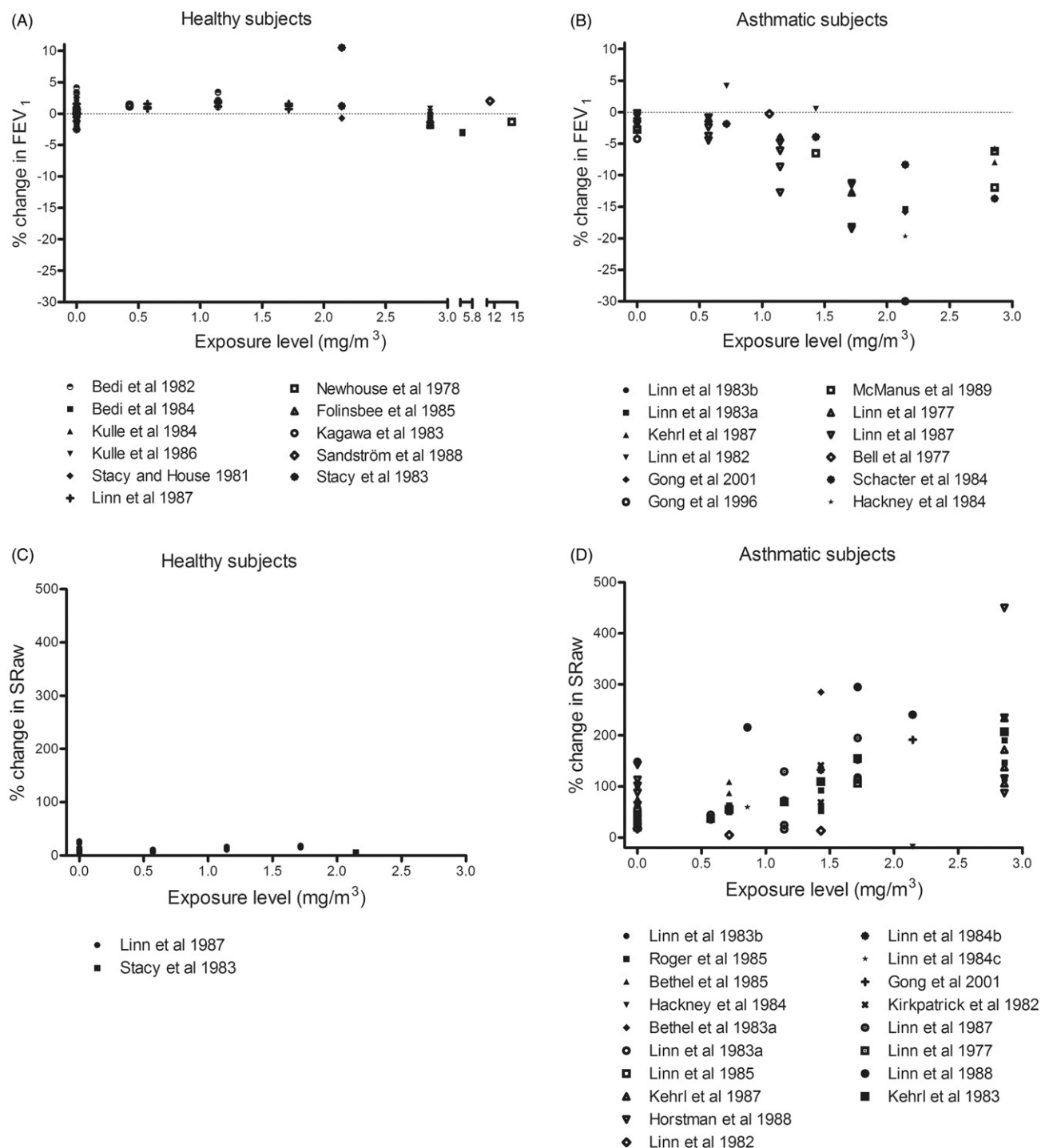


Figure 9. Percentage change (after/before exposure $\times 100$) in FEV_1 and $SRaw$ in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to sulfur dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

available for three of the chemicals. The overall EDRFs that were based on a single study were often estimated to be "inconclusive". However, if judged to be of high quality, a single study on a chemical or mixture could be used as basis for the overall EDRF.

A similar analysis of the EDRFs for six chemicals was carried out by Young et al. (2009) and in general, their estimates of 1–5 are similar to those arrived at here (Table 4). In their comparison of decrements in pulmonary function and symptoms of respiratory distress in healthy subjects and asthmatics, these

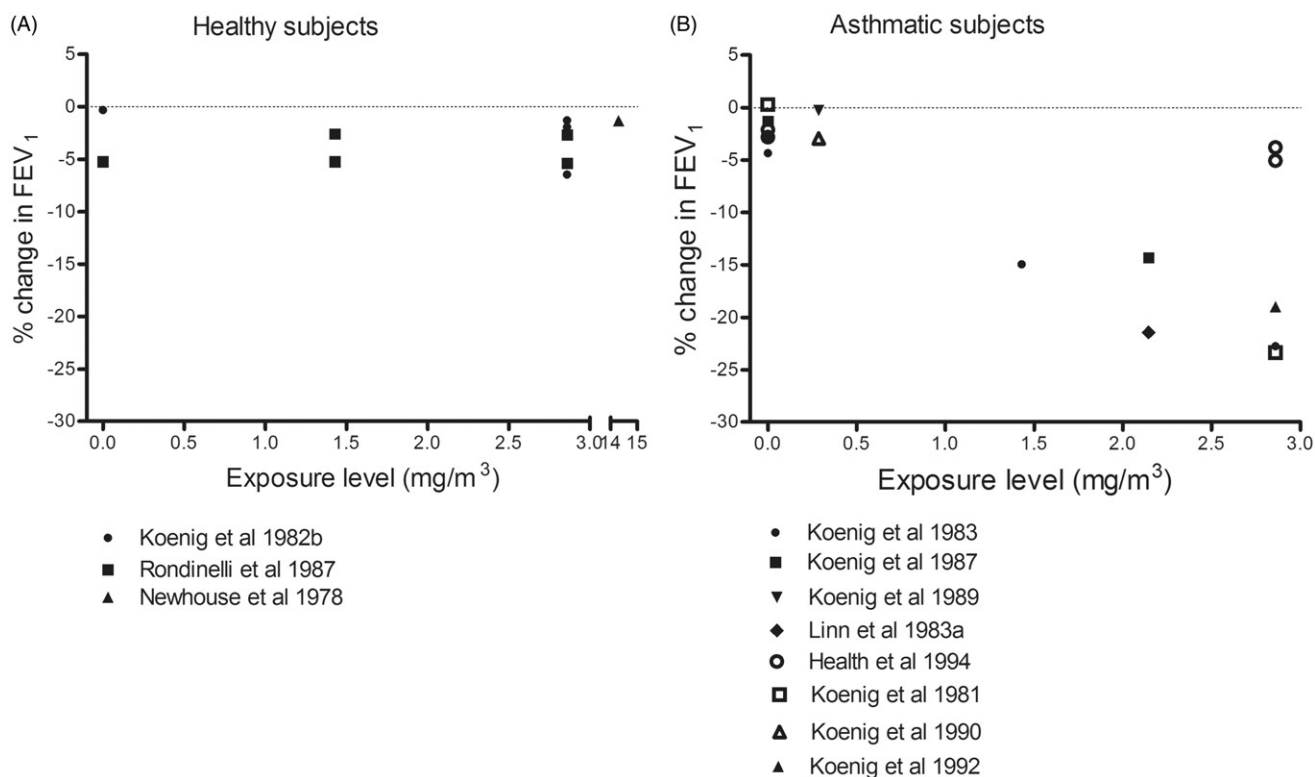


Figure 10. Percentage change (after/before exposure $\times 100$) in FEV₁ in healthy and asthmatic subjects following inhalation exposure (mouth-only breathing) to sulfur dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

investigators selected a single key study (or two) for each chemical, involving healthy and/or asthmatic individuals, as the basis for their calculations.

Part 2: Comparative analysis of concentration–response relationships for nitrogen dioxide

Pulmonary function appears to be more severely impaired in asthmatic than healthy subjects by exposure to nitrogen dioxide (Figures 3 and 4). However, there were no signs of a concentration–response relationship within the range of concentrations tested (up to 6 mg/m³). Furthermore, impairment in FEV₁ and SRaw were even seen when breathing filtered air containing no nitrogen dioxide, suggesting that these effects may be exercise-induced. Here, we were unable to confirm the higher sensitivity of asthmatics observed in Part 1, where healthy and asthmatic subjects were tested under the same experimental conditions (Table 3).

Several thresholds for the respiratory effects of nitrogen dioxide have been proposed. A review of more than 50 articles involving chamber studies conducted by Hesterberg et al. (2009) indicates that a guideline level for nitrogen dioxide in the range of 0.38–1.13 mg/m³ (0.2–0.6 ppm) is adequate to protect the health of both asthmatics and patients with COPD.

Another analysis of 28 studies suggests that concentrations up to 1.13 mg/m³ do not exert a clinically relevant effect on airway hyper-responsiveness in asthmatics (Goodman et al. 2009). At the same time, an analysis of several other studies reveals inflammatory responses at 1.9 mg/m³ (2–3 h) and 0.49 mg/m³ (30 min) in healthy subjects and asthmatics, respectively (US EPA 2008). Moreover, non-specific airway responsiveness was observed at 2.9–3.8 mg/m³ (3 h) in a study involving only healthy subjects and at 0.38–0.56 mg/m³ (30 min) in another study with only asthmatics (US EPA 2008). Overall, the differences between the relevant LOAELs for healthy and asthmatic subjects in these other studies appear to be approximately four- to eightfold. Here, an EDRF > 1 was estimated in Part 1 supported by the studies above. However, we were not able to find a concentration–response relationship for either healthy or asthmatics in Part 2.

Part 2: Comparative analysis of concentration–response relationships for ozone

In contrast to the EDRF > 1 reported previously for ozone in Part 1 (Table 3), we found no difference in the response of asthmatic and healthy subjects to ozone (oronasal inhalation during exercise up to 1.5 mg/m³)

(Figures 5 and 6). Small airway responses were seen in both these groups after breathing filtered air (0 mg/m^3). From our figures the threshold for effects on pulmonary function can be estimated to be 0.24 mg/m^3 for both groups.

In an early review, Folinsbee (1981) concluded that, in general asthmatics are not overly sensitive to ozone, but that certain asthmatic individuals might be. However, only three experimental studies involving low levels of exposure were covered in that review. Five other reviews on healthy subjects exposed to ozone document statistically significant decrements in FEV_1 (Brown et al. 2008; Goodman et al. 2013; Hazucha 1987; Mcdonnell et al. 2012; US EPA 2007). In the review by the US EPA (2007), covering six studies with exposure levels of $0.08\text{--}0.24 \text{ mg/m}^3$ ($0.04\text{--}0.48 \text{ ppm}$), adverse effects on FEV_1 began at 0.12 mg/m^3 and became statistically significant at 0.16 mg/m^3 . No studies involving controlled exposures of asthmatics were included in that report, but it was stated that “new data on airway responsiveness, inflammation, and various molecular markers of inflammation and bronchoconstriction indicate that people with asthma and allergic rhinitis (with or without asthma) comprise susceptible groups for O_3 -induced adverse effects”. In their review, Brown et al. (2008) include a paired comparison of 30 healthy subjects exposed to $0.12\text{--}0.16 \text{ mg/m}^3$ ($0.06\text{--}0.08 \text{ ppm}$) ozone, where the effect levels are without clinical significance (i.e. $<3\%$ decrease). The earliest review by Hazucha (1987) compares data from 24 studies on healthy subjects to ranges of $0.22\text{--}1.54 \text{ mg/m}^3$ ($0.11\text{--}0.77 \text{ ppm}$) during physical exercise at four different levels of intensity (ventilation rates of ≤ 23 , $24\text{--}43$, $43\text{--}63$ and $\geq 64 \text{ L/min}$ during light, moderate, heavy and very heavy exercise, respectively). Regression analysis of the FEV_1 values revealed that statistical significance was reached above 0.4 mg/m^3 during light exercise and above 0.1 mg/m^3 during very heavy exercise. The review by Mcdonnell et al. (2012) fits data from 23 studies into a human exposure-response model. The most recent review by Goodman et al. (2013) evaluates pulmonary function in four controlled chamber studies where healthy subjects were exposed to ozone at levels relevant to the National Ambient Air Quality Standard of 0.15 mg/m^3 (0.075 ppm) and the authors conclude that no adverse effects occur below this level (Goodman et al. 2013). These findings on healthy subjects agree with our observation that no effects were seen here below 0.24 mg/m^3 . Overall, the previous review by Folinsbee (1981) suggests that asthmatics are more sensitive to ozone than healthy subjects. This supports our EDRF of >1 in Part 1 but we were not able to confirm this difference in Part 2.

Part 2: Comparative analysis of concentration–response relationships for sulfuric acid

Similar to what was observed for nitrogen dioxide, upon exposure to sulfuric acid by oronasal (Figure 7) as well as mouth-only breathing (Figure 8), asthmatics, but not healthy subjects, exhibited moderate or severe responses in SRaw and/or FEV_1 . At the same time, small responses were apparent in asthmatics following exposure to filtered air (0 mg/m^3 sulfuric acid), implying the existence of an exercise-induced effect. Overall, the findings with oronasal breathing indicate that pulmonary function is impaired by about 1 mg/m^3 in asthmatics, but remains normal in healthy subjects up to 2 mg/m^3 . Similarly, with mouth-only breathing the FEV_1 was reduced by 0.35 mg/m^3 in asthmatics, but unaffected in healthy subjects at levels as high as 1.1 mg/m^3 . These findings indicate an EDRF above 2 or 3, in support of the $\text{EDRF} > 1$ previously identified in Part 1 (Table 3). No earlier reviews covering experimental data concerning the effects of sulfuric acid on individuals with asthma could be found in the literature.

Part 2: Comparative analysis of concentration–response relationships for sulfur dioxide

Our compilation of studies concerning exposure to sulfur dioxide indicates a reduction in FEV_1 at around 1 mg/m^3 in asthmatics, but no effect in healthy subjects up to 15 mg/m^3 . These results argue for an AF of at least 10. These effects were similar with both oronasal (Figure 9a and b) and mouth-only (Figure 10a and b) inhalation. Regarding SRaw (Figure 9c and d), a concentration–response relationship is apparent for asthmatics, although a small response, probably induced by exercise, seen when asthmatics are exposed to filtered air.

Fifty-five controlled short-term exposure studies of respiratory health-effects in asthmatic subjects are covered in a review that has played an integral role in the integrated assessment of sulfur oxides by the US EPA (Johns & Linn 2011). These same authors analyzed the concentration–response relationships for sulfur dioxide presented in five articles on asthmatic subjects and showed enhanced bronchoconstrictive responsiveness between 0.57 and 2.86 mg/m^3 (0.2 and 1 ppm) (Johns et al. 2010). A report by the US EPA (2009) concluded that “It has been clearly established that subjects with asthma are more sensitive to the respiratory effects of SO_2 exposure than healthy individuals without asthma”.

Ten controlled exposure studies on asthmatics described in that report reveal moderate or greater impairment of pulmonary function ($SRaw \geq 100\%$ and a $\geq 15\%$ reduction in FEV_1) in exercising asthmatics exposed to concentrations as low as $0.57\text{--}0.86\text{ mg/m}^3$ ($0.2\text{--}0.3\text{ ppm}$) for as little as 5–10 min (Bethel et al. 1983; Gong et al. 1995; Linn et al. 1983,1984,1987,1988,1990; Magnussen et al. 1990; Roger et al. 1985; Trenga et al. 1999). In addition, the severity of impairment and proportions of individuals affected rose with increasing concentrations of sulfur dioxide, with severe impairment ($SRaw \geq 200\%$, and/or a $\geq 20\%$ decrease in FEV_1) and respiratory symptoms being observed at levels of $\geq 1.1\text{ mg/m}^3$. Our present compilation confirms these previous findings.

Part 2: Duration of exposures associated with these concentration–response analyses

In general, both the concentration and duration of exposure may influence the risk of deleterious health effects from chemicals. In the present evaluation, the duration of exposure was not taken into consideration neither when estimating the EDRF, nor when analyzing concentration–response relationships. For the experimental studies included in Figures 3–10, this duration varied between 5 min and 8 h. However, replacement of the factor concentration by concentration \times time in the response graphs (Figures 3–10) did not result in any change (see Figures 1–8 in Appendix B). Mild sensory effects are generally not cumulative over a range of exposures of 10 min to 8 h. Individuals may adapt or become inured to sensory irritation developed from exposure to irritant chemicals such that the warning properties are reduced (NRC 2001, p. 108). Consequently the derived AEGL-1 values for nitrogen dioxide, sulfuric acid and sulfur dioxide are identical for all durations up to 8 h, suggesting that the mild effects of which these values are based are not time-dependent. In addition, it is stated that most of bronchoconstriction caused by sulfur dioxide occurs within 10 min and therefore the AEGL-2 values are also held constant across the exposure durations (NRC 2010).

Part 3: BMC analysis of sulfur dioxide

As mentioned earlier, LOAEL-based EDRFs are often uncertain or inconclusive, mainly due to lack of data, the inclusion of few subjects in available studies and extensive inter-individual variability. LOAEL values are highly sensitive to the concentrations tested and, moreover, pronounced inter-individual variability at

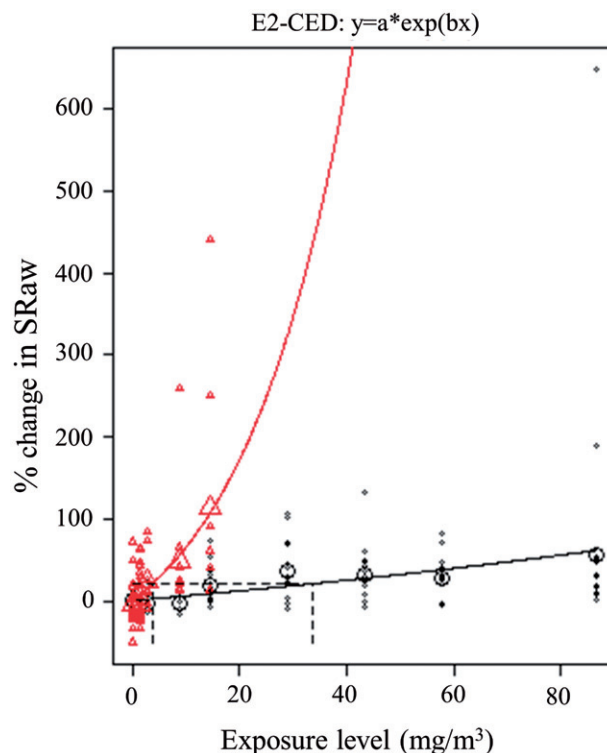


Figure 11. Benchmark concentration analysis of the increase in $SRaw$ following exposure by inhalation to various levels of sulfur dioxide (in a chamber with a noseclip at rest). The upper and lower curves represent the best fits to the experimental data for asthmatics (Δ), and healthy subjects (\circ), respectively. The larger symbols depict mean values.

any concentration will result in higher LOAEL values, since these are based on pairwise comparison with control data. Thus, the BMC approach to comparative analysis of concentration–response relationships is to be preferred. No such analysis of experimental findings on healthy and asthmatic subjects has, to our knowledge, been reported previously. A BMC analysis combines all available data to obtain a mathematical description of the concentration–response relationship for comparison of pre-defined levels of response.

Here, we considered observations on the pulmonary function of each individual subject exposed to sulfur dioxide (at rest while wearing noseclip) rather than group data. The BMC values for a 20% change in $SRaw$ were 33.7 and 3.7 mg/m^3 for healthy and asthmatic subjects, respectively, resulting in an EDRF of 9 (Figure 11), which is higher than the value of 3–4 suggested by Young et al. (2009) (Table 4).

Conclusions

Our current review of 103 studies in Part 1 represents, to our knowledge, the most extensive compilation to date

of experimental studies on asthmatic and healthy subjects exposed under the same conditions. The analyses of comparative-response relationships and estimation of EDRF values indicate that asthmatics are more susceptible to the deleterious effects of inhalation exposure to many irritants than healthy subjects. In the case of several of the irritants we included studies providing sufficient LOAEL data on healthy subjects were lacking, so the overall EDRFs for these chemicals were estimated to >1 or >2 . The findings on almost half of the chemicals and mixtures were inconclusive, due to a lack of significant effects at the concentrations tested.

In addition, we analyzed the concentration-response relationships of four chemicals to characterize differences between asthmatic and healthy individuals. The effects of exposure to nitrogen dioxide on asthmatics are similar to those observed following control exposure to filtered air, indicating that these effects were induced by exercise rather than the chemical. The concentration-response relationships for ozone showed that healthy and asthmatic subjects are equally susceptible to ozone during exercise. Asthmatics appear to be more susceptible to sulfuric acid and sulfur dioxide than healthy subjects.

Our BMC analysis of individual data concerning sulfur dioxide revealed a differential response factor of 9, indicating that for sulfur dioxide, and maybe also other irritants, the default AF lower than 10 may not be adequate for the protection of asthmatics.

Although available data on individual chemicals are often inconclusive, overall, the experimental findings on inter-individual variation provide support for the use of an AF of 10 to estimate the level of exposure below which respiratory symptoms and impairment of pulmonary function are not likely to occur in the general population including asthmatics. However, further studies on healthy and asthmatic subjects employing state-of-the-art quality standards are required to obtain more precise AFs for asthmatics. Such studies should be designed to determine NOAELs and LOAELs for both healthy and asthmatic subjects and preferably be performed at rest in order to avoid exercise-induced effects.

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Declaration of interest

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Supplementary data

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