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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 ($10^{0.5} \times 10^{0.5}$). 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

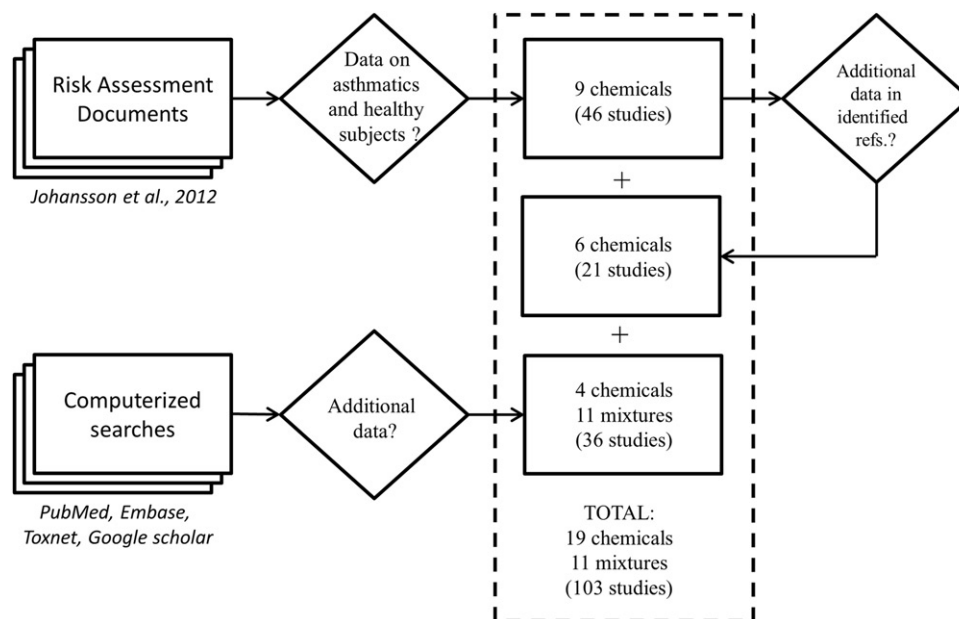


Figure 1. Approach to the identification of studies relevant to Part 1: Estimation of differential response factors on the basis of tests on healthy and asthmatic subjects under the same conditions. Relevant studies were identified from risk assessment documents and a computerized search of the peer-reviewed 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

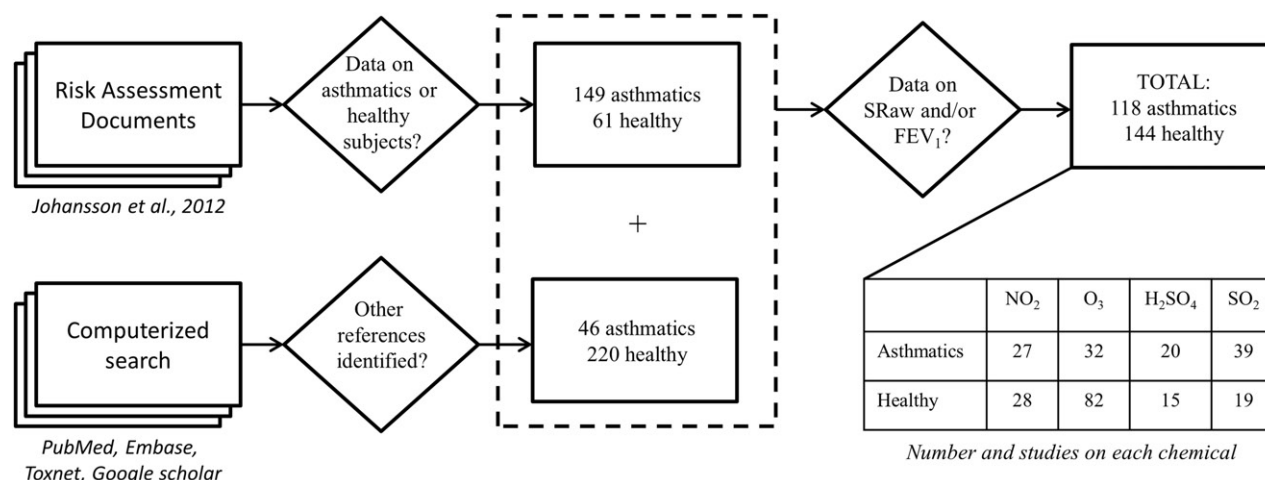


Figure 2. Approach to the identification of studies for Part 2: Comparative analysis of concentration–response relationships. Studies on healthy or asthmatic subjects exposed to nitrogen dioxide, ozone, sulfuric acid or sulfur dioxide were extracted from risk assessment documents and a computerized search 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, FEV₁ and SRaw. Data from experiments involving oronasal breathing (FEV₁, SRaw) or mouth-only breathing (FEV₁) during exercise (FEV₁) were included, but the data from the chamber experiments, with or without noseclip, performed under resting conditions (SRaw or FEV₁) 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 FEV₁ (–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 FEV₁ (–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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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).

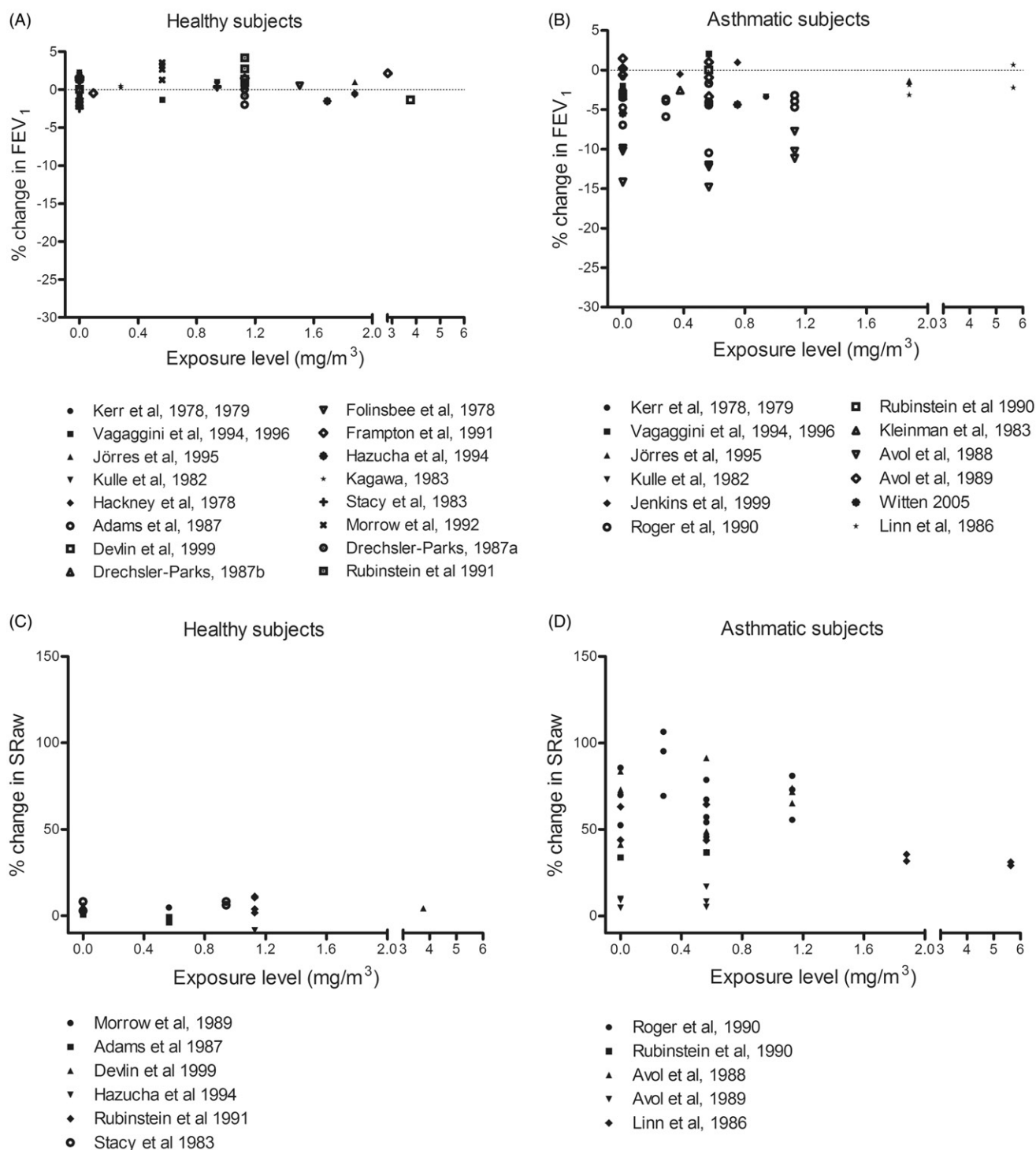


Figure 3. Percentage change (after/before exposure $\times 100$) in FEV_1 and S_{Raw} in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to nitrogen dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level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

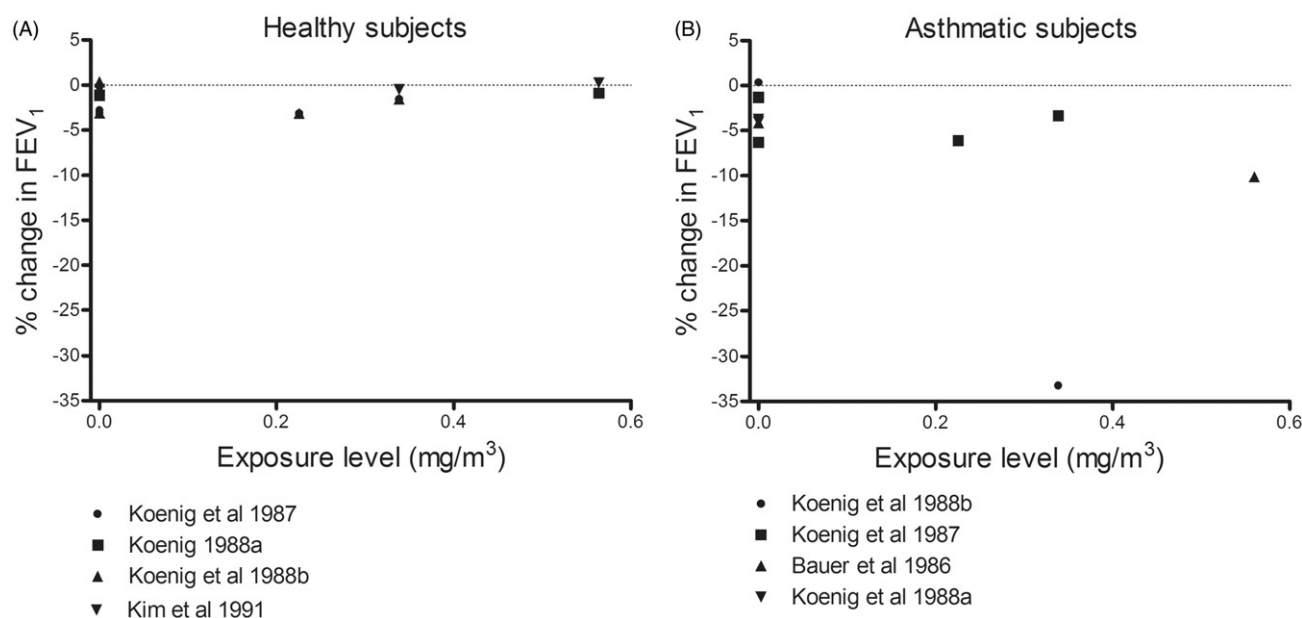


Figure 4. Percentage change (after/before exposure $\times 100$) in FEV₁ in healthy and asthmatic subjects following inhalation exposure (mouth-only breathing) to nitrogen dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

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

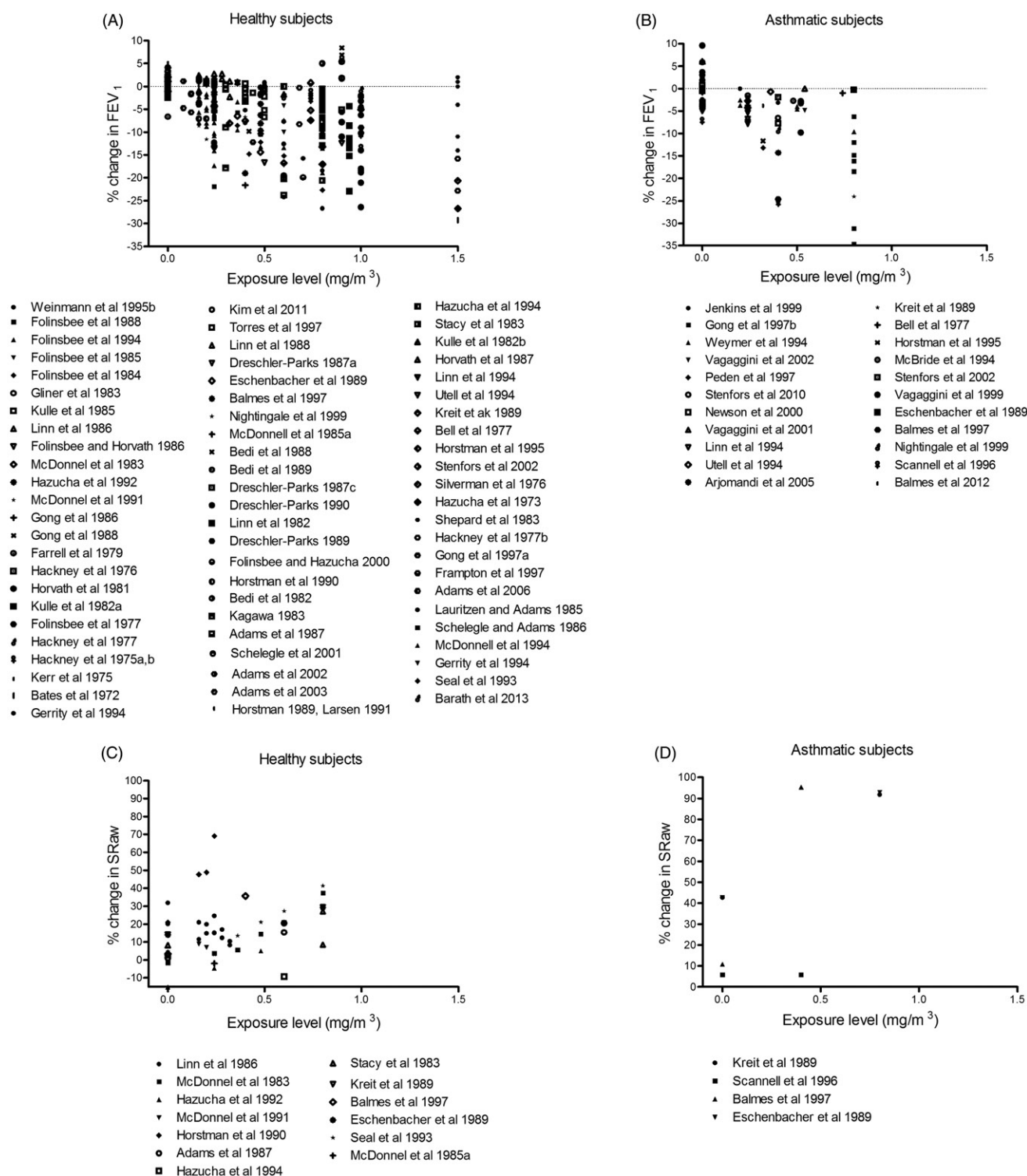


Figure 5. Percentage change (after/before exposure $\times 100$) in FEV₁ and SRaw in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to ozone during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

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

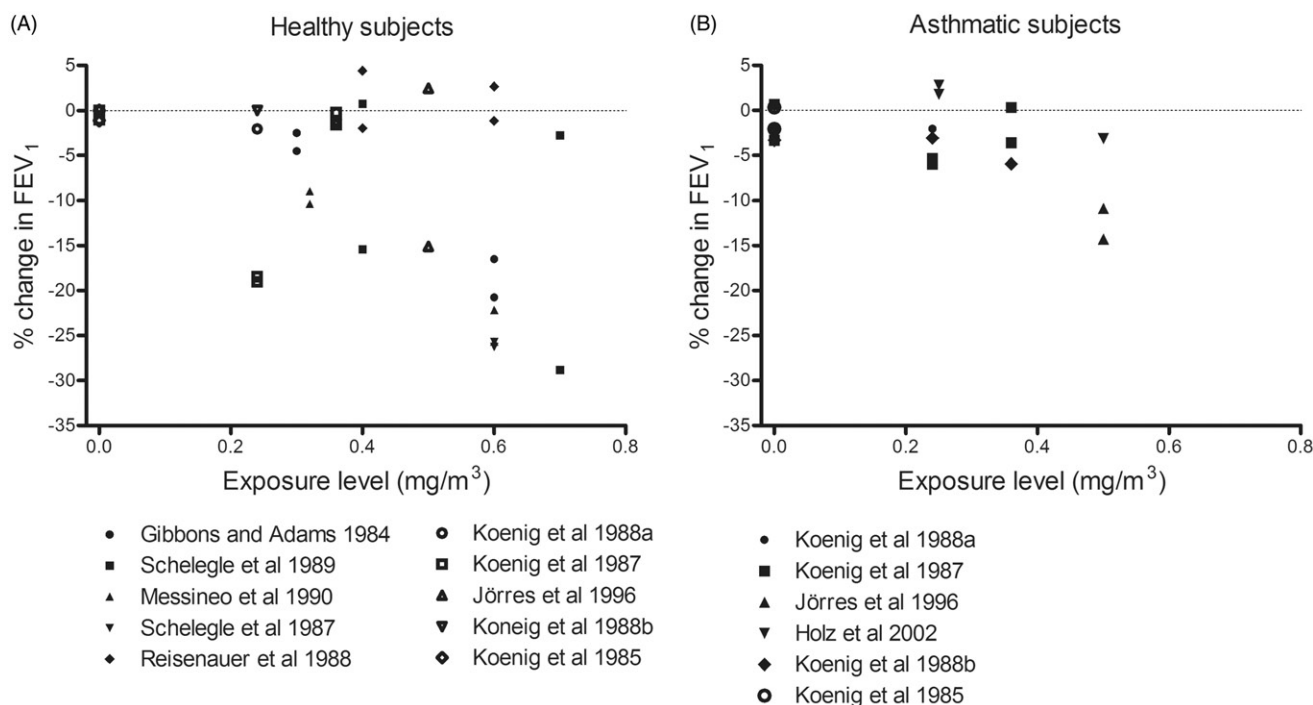


Figure 6. Percentage change (after/before exposure $\times 100$) in FEV₁ in healthy and asthmatic subjects following inhalation exposure (mouth-only breathing) to ozone during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

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

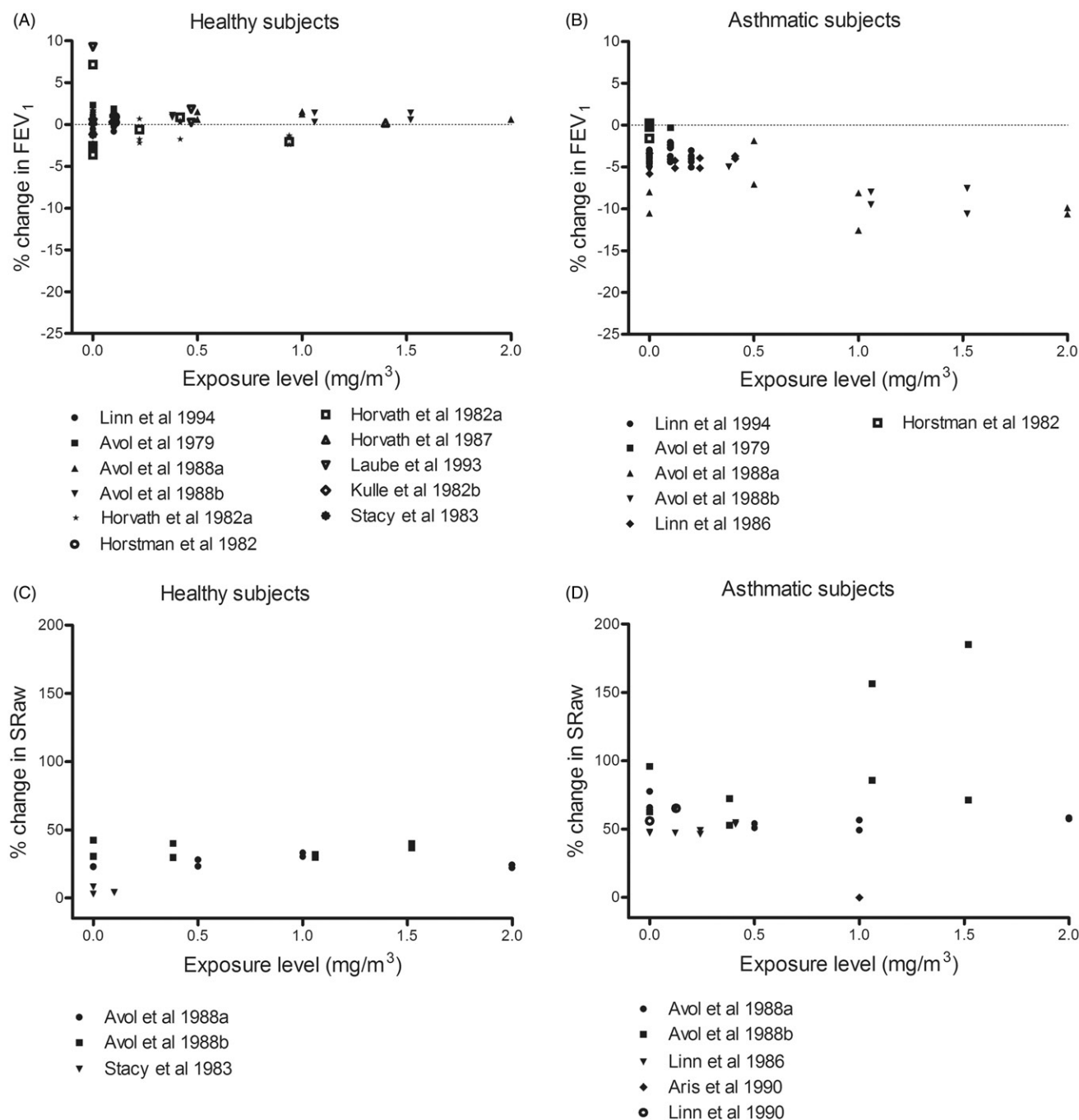


Figure 7. Percentage change (after/before exposure $\times 100$) in FEV₁ and SRaw in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to sulfuric acid during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

effects on SRaw and FEV₁ 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

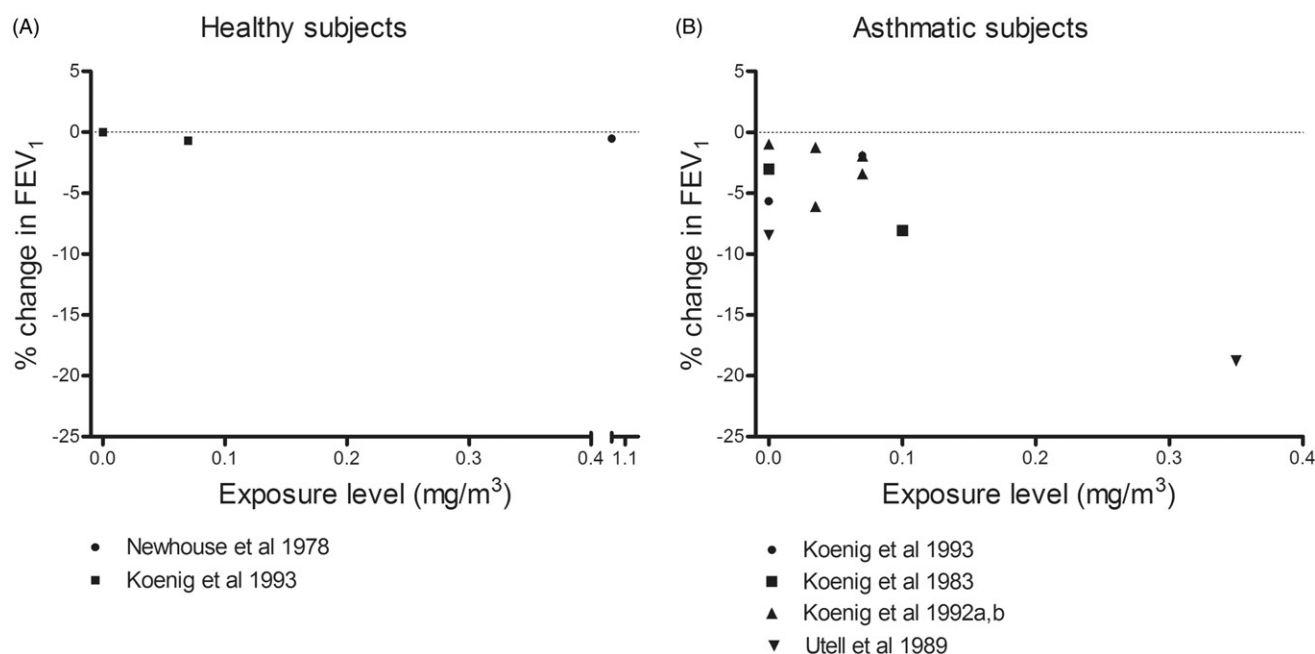


Figure 8. Percentage change (after/before exposure $\times 100$) in FEV₁ in healthy and asthmatic subjects following inhalation exposure (mouth-only breathing) to sulfuric acid during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

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

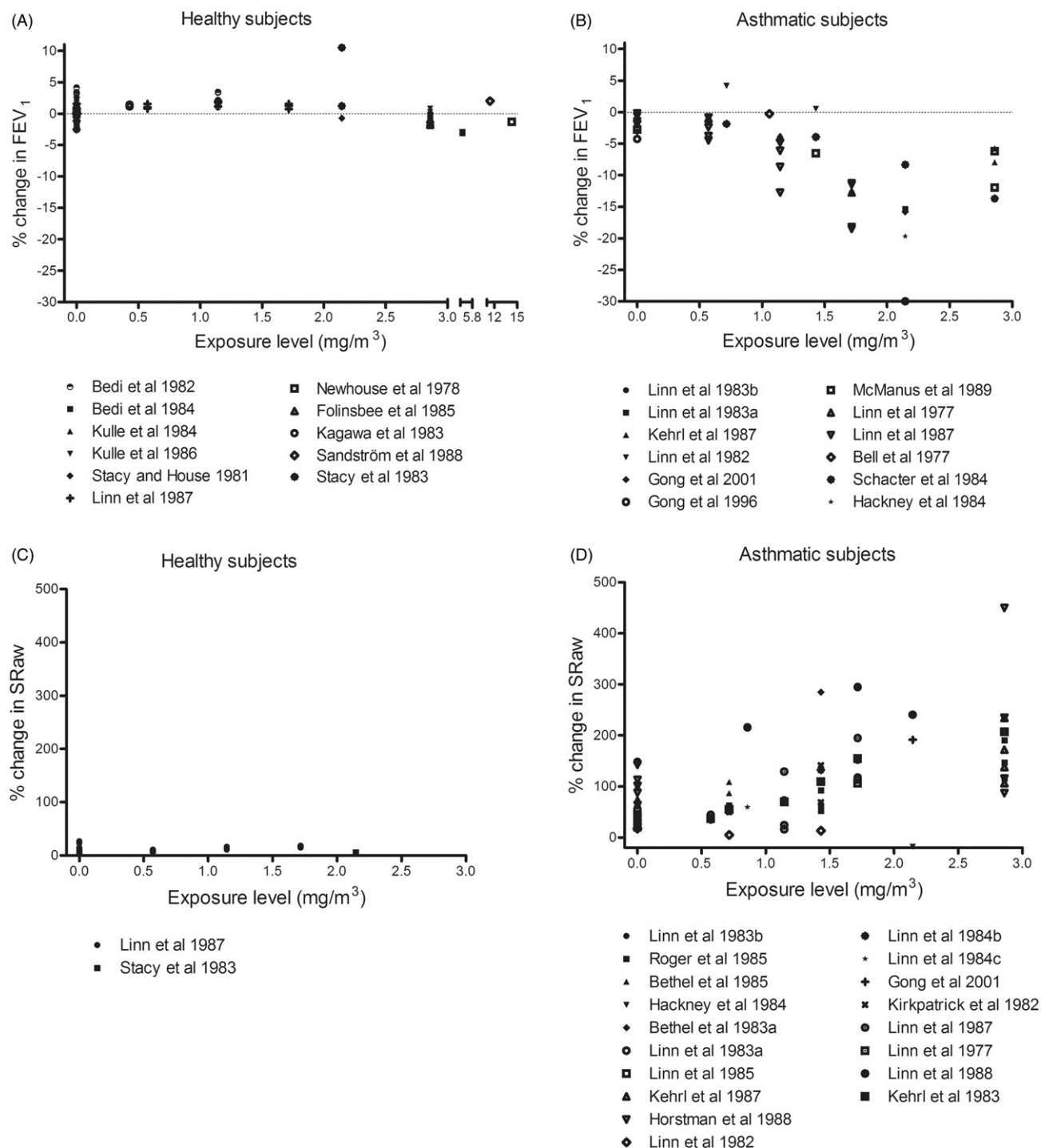


Figure 9. Percentage change (after/before exposure $\times 100$) in FEV₁ and SRaw in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to sulfur dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

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

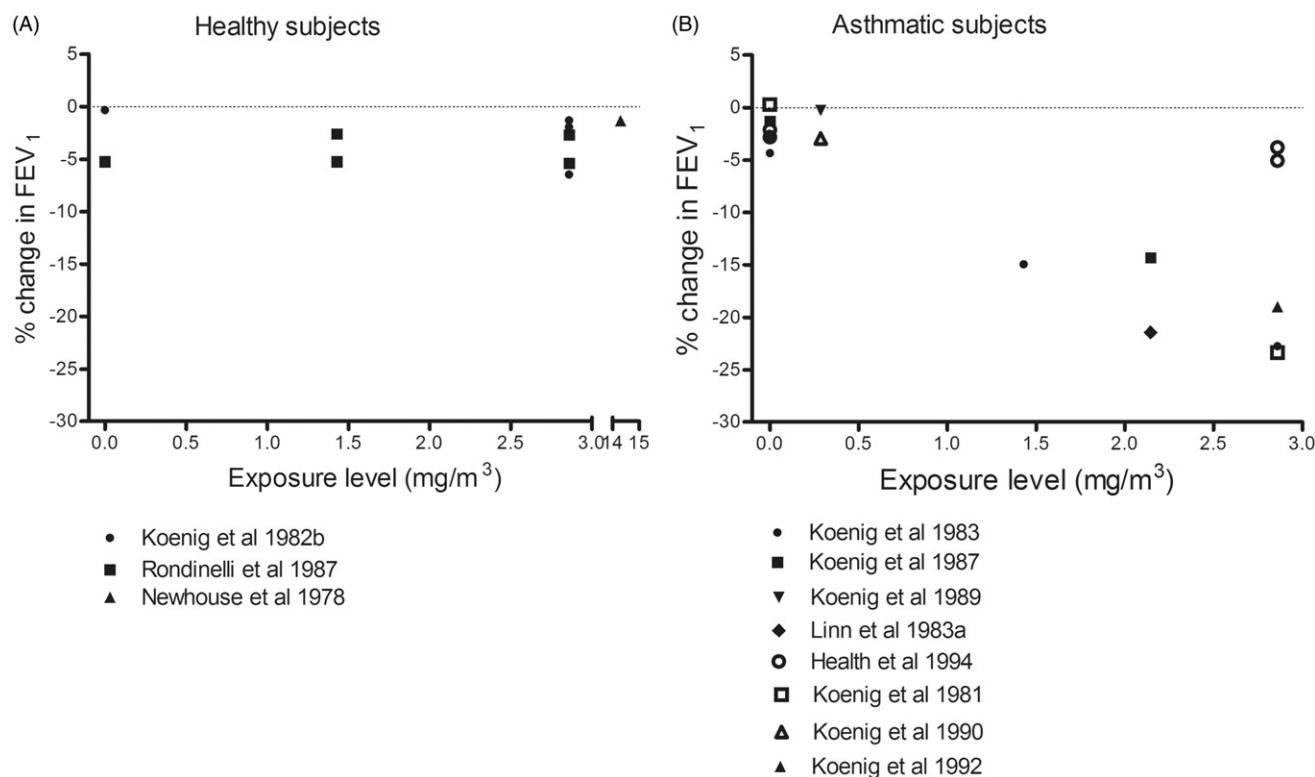


Figure 10. Percentage change (after/before exposure $\times 100$) in FEV₁ in healthy and asthmatic subjects following inhalation exposure (mouth-only breathing) to sulfur dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

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 – 0.24 mg/m^3 (0.04 – 0.48 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 – 0.16 mg/m^3 (0.06 – 0.08 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 – 1.54 mg/m^3 (0.11 – 0.77 ppm) during physical exercise at four different levels of intensity (ventilation rates of ≤ 23 , 24 – 43 , 43 – 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

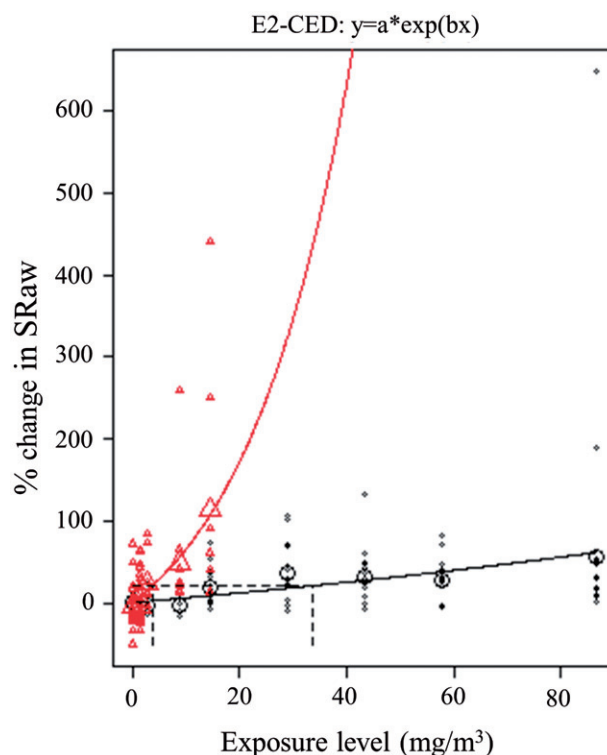


Figure 11. Benchmark concentration analysis of the increase in $SRaw$ following exposure by inhalation to various levels of sulfur dioxide (in a chamber with a noseclip at rest). The upper and lower curves represent the best fits to the experimental data for asthmatics (Δ), and healthy subjects ($\circ$),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

The authors acknowledge that Professor Gunnar Johanson is a member of the SCOEL and has been a member of the NAS Subcommittee on AEGL. Dr Mattias Öberg has been a member of the AEGL Advisory Committee. The authors' affiliations are as shown on the cover page. We take sole responsibility for the writing and content of this paper. The project was performed at the National Center for Disaster Toxicology with financial support from the Swedish National Board of Health and Welfare and the Swedish Civil Contingencies Agency [44668/2012 and 15523/2011].

References

- American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225–243.
- Avol EL, Linn WS, Whiteman JD, Whynot JD, Anderson KR, Hackney JD. Short-term respiratory effects of sulfuric acid in fog: a laboratory study of healthy and asthmatic volunteers. *JAPCA* 1988a;38:258–263.
- Avol EL, Linn WS, Whynot JD, Anderson KR, Shamoo DA, Valencia LM, Little DE, Hackney JD. Respiratory dose-response study of normal and asthmatic volunteers exposed to sulfuric acid aerosol in the sub-micrometer size range. *Toxicol Ind Health* 1988b;4:173–184.
- Bethel RA, Epstein J, Sheppard D, Nadel JA, Boushey HA. Sulfur dioxide-induced bronchoconstriction in freely breathing, exercising, asthmatic subjects. *Am Rev Respir Dis* 1983;128:987–990.
- Bethel RA, Sheppard D, Epstein J, Tam E, Nadel JA, Boushey HA. Interaction of sulfur dioxide and dry cold air in causing bronchoconstriction in asthmatic subjects. *J Appl Physiol Respir Environ Exerc Physiol* 1984;57:419–423.
- Brown JS, Bateson TF, McDonnell WF. Effects of exposure to 0.06 ppm ozone on FEV1 in humans: a secondary analysis of existing data. *Environ Health Perspect* 2008;116:1023–1026.
- Chadha TS, Birch S, Sackner MA. Oronasal distribution of ventilation during exercise in normal subjects and patients with asthma and rhinitis. *Chest* 1987;92:1037–1041.
- Damgård Nielsen G, Wolkoff P, Alarie Y. Sensory irritation: risk assessment approaches. *Regul Toxicol Pharmacol* 2007;48:6–18.
- de Pee S, Timmers MC, Hermans J, Duiverman EJ, Sterk PJ. Comparison of maximal airway narrowing to methacholine between children and adults. *Eur Respir J* 1991;4:421–428.
- Dietert RR, Etzel RA, Chen D, Halonen M, Holladay SD, Jarabek AM, Landreth K, et al. Workshop to identify critical windows of exposure for children's health: immune and respiratory systems work group summary. *Environ Health Perspect* 2000;108:483–490.
- Dorne JLCM, Renwick AG. The refinement of uncertainty/safety factors in risk assessment by the incorporation of data on toxicokinetic variability in humans. *Toxicol Sci* 2005;86:20–26.
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). Derivation of assessment factors for human health risk assessment. Technical Report No. 86. Brussels: European Centre for Ecotoxicology and Toxicology of Chemicals; 2003.

- ECHA (European Chemicals Agency). (2010). Chapter R.8: characterisation of dose [concentration]–response for human health. Available from: http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf [last accessed 1 Nov 2012].
- Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355:2226–2235.
- Falk-Filipsson A, Hanberg A, Victorin K, Warholm M, Wallen M. Assessment factors – applications in health risk assessment of chemicals. *Environ Res* 2007;104:108–127.
- Folinsbee LJ. Effects of ozone exposure on lung function in man: a review. *Rev Environ Health* 1981;3:211–240.
- GINA GIFA. (2014). The global strategy for asthma management and prevention. Available from: <http://www.ginasthma.org/> [last accessed 28 Jan 2015].
- Gong H, Jr, Lachenbruch PA, Harber P, Linn WS. Comparative short-term health responses to sulfur dioxide exposure and other common stresses in a panel of asthmatics. *Toxicol Ind Health* 1995;11:467–487.
- Goodman JE, Chandalia JK, Thakali S, Seeley M. Meta-analysis of nitrogen dioxide exposure and airway hyper-responsiveness in asthmatics. *Crit Rev Toxicol* 2009;39:719–742.
- Goodman JE, Prueitt RL, Chandalia J, Sax SN. Evaluation of adverse human lung function effects in controlled ozone exposure studies. *J Appl Toxicol* 2013;34:516–524.
- Götschi T, Heinrich J, Sunyer J, Künzli N. Long-term effects of ambient air pollution on lung function: a review. *Epidemiology* 2008;19:690–701.
- Hakkert BC, Stevenson H, Bos PM, van Hemmen JJ. Methods for establishment of health based recommended occupational limits for existing substances. TNO Report 1996:V96.463. Zeist: TNO, Nutrition and Food Research; 1996.
- Hazucha MJ. Relationship between ozone exposure and pulmonary function changes. *J Appl Physiol* 1987;62:1671–1680.
- Hesterberg TW, Bunn WB, McClellan RO, Hamade AK, Long CM, Valberg PA. Critical review of the human data on short-term nitrogen dioxide (NO₂) exposures: evidence for NO₂ no-effect levels. *Crit Rev Toxicol* 2009;39:743–781.
- IPCS (International Panel on Chemical Safety). Environmental Health Criteria No. 170: assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits. Geneva: World Health Organization; 1994.
- IPCS (International Panel on Chemical Safety). PCS risk assessment terminology. Part 1: IPCS/OECD key generic terms used in chemical hazard/risk assessment. Part 2: IPCS glossary of key exposure assessment terminology. Geneva: World Health Organization, International Programme of Chemical Safety; 2004.
- IPCS (International Panel on Chemical Safety). Chemical-specific adjustment factors (CSAFs) for interspecies differences and human variability: guidance document for the use of data in dose/concentration–response assessment. WHO/IPCS/01.4. Geneva: International Panel on Chemical Safety, World Health Organization; 2005. pp 1–96.
- Johansson MK, Johanson G, Öberg M. How are asthmatics included in the derivation of guideline values for emergency planning and response? *Regul Toxicol Pharmacol* 2012;63:461–470.
- Johns DO, Linn WS. A review of controlled human SO₂ exposure studies contributing to the US EPA integrated science assessment for sulfur oxides. *Inhal Toxicol* 2011;23:33–43.
- Johns DO, Svendsgaard D, Linn WS. Analysis of the concentration–respiratory response among asthmatics following controlled short-term exposures to sulfur dioxide. *Inhal Toxicol* 2010;22:1184–1193.
- Jörres R, Magnussen H. 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* 1990;3:132–137.
- Kalberlah F, Schneider K. Quantification of extrapolation factors. Final Report of the Research Project No. 116 06 113 of the Federal Environmental Agency. Wirtschaftsverl, NW: Verlag für Neue Wiss; 1998.
- Kim JJ. Ambient air pollution: health hazards to children. *Pediatrics* 2004;114:1699–1707.
- Kleinman MT. Sulfur dioxide and exercise: relationships between response and absorption in upper airways. *J Air Pollut Control Assoc* 1984;34:32–37.
- Koenig JQ, Pierson WE, Covert DS, Marshall SG, Morgan MS, van Belle G. The effects of ozone and nitrogen dioxide on lung function in healthy and asthmatic adolescents. *Res Rep Health Eff Inst* 1988;5–24.
- Lawther PJ, Macfarlane AJ, Waller RE, Brooks AG. Pulmonary function and sulphur dioxide, some preliminary findings. *Environ Res* 1975;10:355–367.
- Linn WS, Avol EL, Peng R, Shamoo DA, Hackney JD. Replicated dose–response study of sulfur dioxide effects in normal, atopic, and asthmatic volunteers. *Am Rev Respir Dis* 1987;136:1127–1134.
- Linn WS, Avol EL, Shamoo DA, Peng RC, Spier CE, Smith MN, Hackney JD. Effect of metaproterenol sulfate on mild asthmatics' response to sulfur dioxide exposure and exercise. *Arch Environ Health* 1988;43:399–406.
- Linn WS, Avol EL, Shamoo DA, Venet TG, Anderson KR, Whynot JD, Hackney JD. Asthmatics' responses to 6-hr sulfur dioxide exposures on two successive days. *Arch Environ Health* 1984;39:313–319.
- Linn WS, Shamoo DA, Peng RC, Clark KW, Avol EL, Hackney JD. Responses to sulfur dioxide and exercise by medication-dependent asthmatics: effect of varying medication levels. *Arch Environ Health* 1990;45:24–30.
- Linn WS, Venet TG, Shamoo DA, Valencia LM, Anzar UT, Spier CE, Hackney JD. Respiratory effects of sulfur dioxide in heavily exercising asthmatics. A dose–response study. *Am Rev Respir Dis* 1983;127:278–283.
- Magnussen H, Jorres R, Wagner HM, von Niding G. Relationship between the airway response to inhaled sulfur dioxide, isocapnic hyperventilation, and histamine in asthmatic subjects. *Int Arch Occup Environ Health* 1990;62:485–491.
- Mcdonnell WF, Stewart PW, Smith MV, Kim CS, Schelegle ES. Prediction of lung function response for populations exposed to a wide range of ozone conditions. *Inhal Toxicol* 2012;24:619–633.
- Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- Mortimer KM, Tager IB, Dockery DW, Neas LM, Redline S. The effect of ozone on inner-city children with asthma: identification of susceptible subgroups. *Am J Respir Crit Care Med* 2000;162:1838–1845.

- NRC (US National Research Council). Standing operating procedures for developing acute guideline levels for hazardous chemicals. Washington (DC): NRC; 2001.
- NRC (US National Research Council). Acute exposure guideline levels for selected airborne chemicals. Vol. 8: Committee on acute exposure guideline level; Committee on Toxicology; National Research Council; 2010. p. 464. ISBN: 0-309-14516-3. Available from: http://www.epa.gov/oppt/aegl/pubs/sulfur-dioxide_final_volume8_2010.pdf [last accessed 11 Mar 2015].
- Öberg M, Palmén N, Johanson G. Discrepancy among acute guideline levels for emergency response. *J Hazard Mater* 2010;184:439–447.
- Proctor DF. Oronasal breathing and studies of effects of air pollutants on the lungs. *Am Rev Respir Dis* 1981;123:242–243.
- R Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2012. Available from: <http://www.R-project.org/> [last accessed 28 Jan 2015].
- Renwick AG. Safety factors and establishment of acceptable daily intakes. *Food Addit Contam* 1991;8:135–149.
- Renwick AG. Data-derived safety factors for the evaluation of food additives and environmental contaminants. *Food Addit Contam* 1993;10:275–305.
- Roger LJ, Kehrl HR, Hazucha M, Horstman DH. Bronchoconstriction in asthmatics exposed to sulfur dioxide during repeated exercise. *J Appl Physiol* 1985;59:784–791.
- Sheppard D, Wong WS, Uehara CF, Nadel JA, Boushey HA. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Respir Dis* 1980;122:873–878.
- Slob W. Dose–response modeling of continuous endpoints. *Toxicol Sci* 2002;66:298–312.
- Slob W, Cotton R. Proast: benchmark dose modelling. R package, version 32.2. National Institute for Public Health and the Environment (RIVM); 2012. Available from: http://www.rivm.nl/en/Documents_and_publications/Scientific/Models/PROAST [last accessed 10 Oct 2012].
- Trenga CA, Koenig JQ, Williams PV. Sulphur dioxide sensitivity and plasma antioxidants in adult subjects with asthma. *Occup Environ Med* 1999;56:544–547.
- US EPA (U.S. Environmental Protection Agency). Recommendations for and documentation of biological values for use in risk assessment. Washington, DC: U.S. Environmental Protection Agency; PB-179874: EPA 600/6-87/008. 1988. p 395. Available from: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855#Download> [last assessed 1 Nov 2013].
- US EPA (U.S. Environmental Protection Agency). IRIS reference dose (RfD): description and use in health risk assessments. 1993. p 19. Available from: <http://www.epa.gov/iris/rfd.htm> [last accessed 1 Nov 2013].
- US EPA (U.S. Environmental Protection Agency). Review of the national ambient air quality standards for ozone: policy assessment of scientific and technical information (QAQPS Staff Paper). Research Triangle Park (NC): Office of Air Quality Planning and Standards; 2007.
- US EPA (U.S. Environmental Protection Agency). Final Report: Integrated science assessment for oxides of nitrogen health criteria. Washington, DC: U.S. Environmental Protection Agency. EPA/600/R-08/071; 2008. 260 pp. Available from: <http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=194645> [last assessed 1 Nov 2013].
- US EPA (U.S. Environmental Protection Agency). Risk and exposure assessment to support the review of the SO₂ primary national ambient air quality standard: final report. Research Triangle Park (NC): Office of Air Quality Planning and Standards; 2009.
- Uttell M, Mariglio JA, Morrow PE, Gibb FR, Speers DM. Effects of inhaled acid aerosols on respiratory function: the role of endogenous ammonia. *J. Aerosol Med* 1989;2:141–147.
- WHO (World Health Organization). Asthma. 2013. Available from: <http://www.who.int/mediacentre/factsheets/fs307/en/index.html>. [last accessed 31 Oct 2013].
- Young RA, Bast CB, Wood CS, Adeshina F. Overview of the standing operating procedure (SOP) for the development of Provisional Advisory Levels (PALs). *Inhal Toxicol* 2009;21:1–11.

Supplementary data

Supplementary material available online at <http://dx.doi.org/10.3109/10408444.2015.1092498>

Appendix A: Table 1. Experimental data and the rationale for our estimation of EDRF values on the basis of tests on healthy and asthmatic subjects under the same conditions. EDRFs were calculated as the ratio between the Lowest Observed Adverse Effect Levels (LOAEL) for statistically significant effects on pulmonary function, inflammatory markers or severity of symptoms in healthy and asthmatic subjects.

Chemical	Level of exposure (mg/m ³)	Duration of exposure (min)	Exposure condition	No of healthy/asthmatic subjects	Significant outcome	LOAEL (mg/m ³)		EDRF	Comments	Definition of asthma	Use of corticosteroids	Reference
						Healthy	Asthmatic					
Acetaldehyde	2.5-80 mg/ml aerosol	2 (tidal breathing)	Rest	19/16	PC ₂₀ FEV ₁	80.0	35.5	2.25	Overall EDRF estimated to be 3	American Thoracic Society*	No	(Prieto et al. 2002a)
	5-40 mg/ml aerosol	2 (tidal breathing)	Rest	20/61	PC ₂₀ FEV ₁	>40	17.55	>2.78		American Thoracic Society*	No (2 months without)	(Prieto et al. 2000)
	5, 10, 20, 40 mg/ml aerosol	2 (tidal breathing)	Rest	9/9	PC ₂₀ FEV ₁	>40	20	>2		American Thoracic Society*	No (8 weeks without)	(Myou et al. 1993)
Ammonia	71	5-20 sec	Rest	-	NAR	71	71	1	Overall EDRF: inconclusive	History†, allergy‡	Not stated	(McLean et al. 1979)
	11.3-14.2	30	Rest	6/8	-	>14.2	>14.2	-		Physician¶, methacholine challenge	Not stated (only bronchodilators on occasion)	(Sigurdarson et al 2004)
Ammonium bisulfate	0.1, 0.450, 1	16	Rest	14/17	FEV ₁ , SGaw	>1.0	1.0	>1	FEV ₁ judged to be the most relevant effect. Overall EDRF estimated to be >1.	Carbachol challenge	No	(Utell et al 1984)
					FEF _{40-60%}	1.0	>1.0	<1				
	0.2, 2	60	Rest	12/12	-	>2	>2	-		History†, physician	Yes, some of them	(Tunnicliffe et al 2003)

	0.1, 1	16	Rest	16/17	FEV ₁ , SGaw	>1	1	>1		Carbachol challenge	No	(Utell et al 1982)
					60% TLC on MEFV, 40-60% TLC on PEFV	1	1	1				
	0.1	120	Intermittent exercise for 15 min every 30 min on bicycle. Workloads of 150-300 kg m/min. Doubled minute volume of ventilation	5/6	-	>0.1	>0.1	-		History†, physician¶, mild to more severe asthma	Yes (oral if needed)	(Avol et al. 1979)
Ammonium nitrate	1, 2, 3	10	Rest	5/5	-	>3	>3	-	Overall EDRF: inconclusive.	Not stated	Not stated	(Sackner et al 1981)
	3	10	Rest		-	>3	>3	-				
Ammonium sulfate	0.1, 1	16	Rest	16/17	Flow at 40% and 60% of TLC on MEFV and PEFV curves	1	1	1		Carbachol challenge	No	(Utell et al 1982)
	0.1	120	Intermittent exercise for 15 min every 30 min on bicycle. Workloads of 150-300 kg m/min. Doubled minute volume of ventilation	7/6	-	>0.1	>0.1	-	Only Utell et al. 1982 demonstrated effects but for uncommon parameters. No effects on, e.g., FEV ₁ and SGaw. Overall EDRF: inconclusive.	History†, physician¶, mild to more severe asthma	Yes (oral if needed)	(Avol et al. 1979)

ventilation												
	0.07	40	Light exercise on a treadmill for the last 10 min of exposure.	8/9	-	>0.07	>0.07	-				
Carbon black, 0.5 µm diam.	0.25	60	Intervals of 10 min heavy exercise on bicycle ergometers. Mean ventilation 50 L/min.	15/15	-	>0.25	>0.25	-	Highest dose (0.05) not tested in asthmatics.	History†, physician‡, methacholine challenge or bronchodilator	Not stated	(Koenig et al. 1993)
Carbon particles, 0.1 µm diam.	0.01, 0.025, 0.05	120	Bicycle ergometer for 15 min in each half hour. Approx. 20 L/min/m2.	40/16	-	0.05	>0.025	-	Overall EDRF: inconclusive	American Thoracic Society *, National Institutes of Health	No (1 month without oral, 12h without inhaled)	(Frampton et al 2004) (Pietropaoli et al 2004)
Chlorine	1.16, 2.9	60	Rest	5/5	FEV ₁ , SRaw, FEF _{25-75%}	2.9	2.9	1	More pronounced impairment of lung function in asthmatics, although same LOAEL in both groups. Overall EDRF estimated to be 2.	History†, methacholine challenge	Yes 1 out of 5 subjects.	(D'Allesandro et al. 1996)
Ferric sulfate	0.075	120	Bicycle ergometer	20/18	-	>0.075	>0.075	-	Overall EDRF: inconclusive	History†, physician‡, allergy‡	Not stated.	(Kleinman et al 1981)
Formaldehyde, overall assessment									Marginal impairment of lung function at 3.75 in healthy			

									subjects (Green et al.) and asthmatics (Kulle et al.). Overall EDRF estimated to be 1.			
Formaldehyde	3.75	60	15 min on a bicycle ergometer two times. 37 L/min.	22/16	FEV ₁ , FVC, FEV ₃	3.75	>3.75	<1		American Thoracic Society- *, methacholine challenge, allergy‡	No	(Green et al. 1987)
					Odor, nose/throat and eye irritation.	3.75	3.75	1				
	2.5	30	Moderate exercise for 10 min. (450 kp m/min on a cycle ergometer.)	15/15	-	>2.5	>2.5	-		American Thoracic Society*	Not stated	(Witek et al. 1986)
	3.75	60	15 min exercise. Healthy: heavy (60-70 L/min) asthmatics: moderate (30- 40L/min).	22/16	FVC	>3.75	3.75	>1	Small significant effect in FVC and two asthmatics showed >10% decrease in FEV ₁ . Data after filtered air exposures not presented.	Not stated	Not stated	(Kulle et. al 1986)
Nitric oxide	98.4	10	Rest	6/13	-	>98.4	>98.4	-	Overall EDRF: inconclusive	Physician¶	Yes	(Högman et al. 1993)

Nitrogen dioxide, overall assessment									Most studies inconclusive as no effects were seen in either group. EDRF >1 in the two studies where effects were seen. Overall EDRF estimated to be >1			
Nitrogen dioxide	1.88	180	Intermittent moderate exercise, 10 min six times on a bicycle ergometer.	8/12	-	>1.88	>1.88	-		National Institutes of Health, methacholine, atopic‡	No (3 months without)	(Jörres et al. 1995)
	0.23	60	Rest	10/10	-	>0.23	>0.23	-		History†, exercise induced bronchospas m, atopic‡	No	(Koenig et al. 1985)
	0.94	120	Bicycle ergometer at 60 rpm for 15 min during the first hour of each exposure.	10/13	-	>0.94	>0.94	-	More symptoms among asthmatics (7/13 vs 0/10). No effect on lung function. EDRF estimated to be >1.	History†	Not stated	(Kerr et al. 1978, 1979) (Kulle et al. 1982)
	0.56	60	Intermittent exercise for 10 min every 15 min. 25 l/min	7/8	-	>0.56	>0.56	-		American Thoracic Society*	Yes 4/8 subjects	(Vaggaggini et al. 1994, 1996)
	0.23, 0.34	40	Treadmill for 10 min at the end of	10/10	-	>0.34	>0.34	-		History†, exercise- induced	No	(Koenig et al. 1987)

			exposure. 32.5 L/min.							bronchospas m, atopic‡		
0.56	240		Exercise (no details presented)	20/20	-	>0.56	>0.56	-		Carbachol challenge, bronchodilato r	Not stated	(Morrow et al. 1989)
0.19	60		Rest	24/22	-	>0.19	>0.19	-		History†, physician¶, methacholine challenge	No	(Hazucha et al. 1983)
0.19	60		Rest	20/20	-	>0.19	>0.19	-		Not stated	Not stated	(Ahmed et al 1983)
0.23, 0.46, 0.91	20		Rest	8/8	Bronchial reactivity, TGV	>0.91	0.91	>1	No effect on lung function except SRaw, where healthy subjects showed significant increase after 20 min at 0.46, but not at 0.91 mg/m ³ , i.e. no concentration -response relationship. EDRF estimated to be >1.	History†, Histamine challenge, 4/8 had allergic asthma‡	Not stated (only bronchodil ators on occasion)	(Bylin et al 1985)
					SRaw	0.46	>0.91	-				
0.56	60		Moderate exercise 32.8 ±6 L/min	12/12	-	>0.56	>0.56	-		Physician¶, methacholine challenge, exercise challenge	No (only bronchodil ators regularly)	(Koenig et al 1988a)
0.19	60		Rest	15/15	-	>0.19	>0.19	-		History†, methacholine challenge, some allergic‡	Not stated	(Hazucha et al 1982)

	1.88	180	Bicycle every 30 min.	8/12	-	>1.88	>1.88	-		Physician¶, asymptomatic asthma†	Not stated	(Magnussen et al 1994)
	7.52	75	Bicycle, 15 min light exercise for 15 min at 25 L/min and then heavy exercise after 55 min at 50L/min.	25/23	SRaw	>7.52	7.52	-	Effects caused by exercise rather than nitrogen dioxide. Effects in SRaw from filtered air exposure were significant in both groups compared to baseline.	History†, physician¶, SO ₂ challenge	Not stated	(Linn et al. 1983, 1984, 1985a)
	0.23	60, 40, 30	Rest	10/10	-	>0.34	>0.34	-		Physician¶, methacholine challenge, exercise challenge, allergy‡	No (only bronchodilators regularly)	(Koenig et al. 1988b)
	0.23, 0.34	60, 40, 30	moderate exercise for the last 10 min	10/10	-	>0.34	>0.34	-				
Ozone, overall assessment									Thirteen studies received an EDRF value of >1, eight a value of 1 and four were inconclusive. Half of the EDRF>1 assignments were primarily based on increases in levels of			

									inflammatory markers. Overall EDRF is estimated to be >1.			
Ozone	0.24	390	Six 50-min exercise periods per exposure day. Mean ventilation volume of 29 L/min	15/30	FEV ₁ , SRaw	0.24	0.24	1	EDRF estimated to be 1.	History†, physician¶, methacholine challenge	Yes (some used inhaled, none oral)	(Linn et al. 1994)
	0.4	240	25 l/min/m ² body surface area. 30 min of each hour.	15/14	FEV ₁ , FVC	0.4	0.4	1	Significantly increased lower respiratory symptom score in asthmatics. EDRF estimated to be >1.	Physician¶, methacholine challenge, atopy‡	Off oral: 3 months, Off inhaled: 2 weeks	(Arjomandi et al 2005) (Christian et al 1998)
	0.8	120	15 min intervals rest and exercise. Cycle ergometer.48-70 l/min. Intermittent, moderate exercise.	9/9	FEV ₁ , FVC, IC(s), FEF _{25-75%}	0.8	0.8	1	Significantly impaired lung function in asthmatics compared to healthy (FEV ₁ , IC(s), FEF _{25-75%}). Study EDRF estimated to be >1.	History†, physician¶, methacholine challenge	Yes, 1 subject	(Kreit et al 1989)
					SRaw	>0.8	0.8	>1				
					Symptoms	0.8	0.8	1				
	0.4	240	50 min exercise and 10 min rest for 4 h. Cycle ergometer /jogging for 25 l/min/m ²	23/18	FEV ₁ , FVC, SRaw	0.4	0.4	1	Levels of inflammatory markers in bronchoalveolar lavage higher in asthmatics	History†, physician¶	Yes, 4/18 subjects	(Scannell et al 1996)

		body surface area.			Inflammatory markers	>0.4	0.4	>1	than healthy subjects. EDRF estimated to be >1.			
					Symptoms	0.4	0.4	1				
0.5	180	Intermittent exercise adjusted for each individual. About 30 L/min. Six cycles of rest and exercise.	10/24	FEV ₁ , VC	0.5	0.5	1	EDRF estimated to be 1.	National Institutes of Health, methacholine challenge, atopic‡	No (3 months without)	(Jörres et al 1996)	
				Symptoms	0.5	0.5	1					
0.8	120	Cycle ergometer, 30 l/min/m ² of body surface area.	9/9	FEV ₁ , FEF ₂₅₋₇₅ , TLC, SRaw, R _V , IC	0.8	0.8	1	Significantly decreased FEV ₁ and FEF ₂₅₋₇₅ % in asthmatics compared to healthy individuals. EDRF estimated to be >1.	History†, physician¶, methacholine challenge	Not stated	(Eschenbacher et al 1989)	
0.4	120	bicycle ergometer 20 l/min/m ² for 15-min periods.	15/15	FVC	0.4	0.4	1	Decrease in FEV ₁ not significantly different between groups, although NOAELs were different. Significant increase in mast cell and lymphocyte counts in asthmatics	Methacholine challenge, allergy‡	No (only bronchodilator on occasion)	(Stenfors et al 2002)	
				FEV ₁	0.4	>0.4	<1					
				Inflammatory markers	0.4	0.4	1					

									compared to healthy subjects. Neutrophil counts increased in both groups. EDRF estimated to be >1.			
0.4	240	Moderate exercise 32.8 ±6 L/min	23/18	FEV ₁ , FVC, SRaw	0.4	0.4	1	Levels of inflammatory markers in bronchoalveolar lavage (neutrophils, total protein, IL-8, GM-CSF, MPO, TGF-β2 and fibronectin.) increased in asthmatics compared to healthy subjects. EDRF estimated to be >1.	History†, methacholine challenge, allergy (20/66) ‡	No	(Balmes et al 1997)	
				Inflammatory markers	>0.4	0.4	>1					
				Symptoms	0.4	0.4	1					
0.8	240	15 min intervals of moderate exercise	13/10	FEV ₁	0.8	0.8	1	EDRF estimated to be 1.	Physician¶, methacholine challenge, allergy‡	No	(Esther et al 2011)	
0.24	60	Moderate exercise 32.8 ±6 L/min	12/12	Raw	>0.24	0.24	>1	No effects on lung function parameters other than Raw and symptoms. No effects from filtered air exposure. EDRF estimated to be >1.	Physician¶, methacholine, exercise challenge	No (only bronchodilators regularly)	(Koenig et al 1988a)	

0.24	60	Rest	10/10	FRC	>0.24	0.24	>1	Higher increase in symptom score in asthmatics but not significant compared to filtered air. EDRF estimated to be >1.	History†, exercise-induced bronchospasm, atopy‡	No	(Koenig et al. 1985)
0.24, 0.36	40	Treadmill for 10 min at the end of exposure. 32.5 L/min.	10/10	R _T , FEV ₁	0.24	0.24	1	Small, but significant changes in RT and FEV ₁ , no effect on other lung parameters.	History†, exercise-induced bronchospasm, atopy‡	No	(Koenig et al. 1987)
0.16, 0.24, 0.36	180	Intermittent exercise for 10 min every 30 min to at least quadruple minute ventilation.	30/30	-	>0.36	>0.36	-		Fulfilled two of these; History†, spirometry, carbachol	No	(Frampton et al. 1995)
0.16, 0.24, 0.36	180	Intermittent exercise for 10 min every 30 min at a workload that quadrupled the expired volume of ventilation/minute (60-200 watts).	30/30	SGaw	>0.36	>0.36	-		History†, physician‡, carbachol challenge, bronchodilator, allergy‡	No	(Utell et al. 1994)
0.74	120	15 min every 30 min to increase min ventilation 2-2.5-fold.	4/5	-	>0.74	>0.74	-		History of hyperreactivity to inhaled irritants†	Not stated	(Bell et al 1977)

0.4	360	30 min rest and moderate exercise periods. Cycle ergometer with adjusted minute ventilation of 5L/min/L vital capacity.	5/5	-	>0.4	>0.4	-	Levels of inflammatory markers in BAL (IL-8, PMN, IL-6) more increased in asthmatics. EDRF estimated to be >1.	History†, physician¶, methacholine challenge, atopy‡	No	(Basha et al 1994)
				Inflammatory markers	>0.4	0.4	>1				
0.25, 0.5	180	Intermittent exercise. Cycle ergometer for 15-min intervals (6 in total). Adjusted workload to achieve min ventilation of 14 l/(min*m²).	21/15	FEV ₁ , VC	0.5	0.5	1	EDRF estimated to be 1.	Methacholine challenge, allergy‡	No (3 months without)	(Holz et al 1999)
				IL-8 in BAL	0.5	0.5	1				
				Neutrophils and eosinophils in BAL	0.5	>0.5	<1				
				Lower respiratory tract symptoms	0.5	0.5	1				
0.32	456	Seven 50-min periods of light exercise on treadmill or bicycle, 14 L/min (asthmatics)	13/17	FEV ₁ , FEV ₁ /FVC	>0.32	0.32	>1	Increase in LRT symptom score in both groups. Wheezing more	History†, physician¶, atopy‡	Yes, 6/17 subjects	(Horstman et al 1995)

			and 15 L/min, followed by 10 min rest.		Symptoms	0.32	0.32	1	common among asthmatics than healthy (9/17 vs 0/13). No effects from filtered air exposure. EDRF estimated to be >1.			
0.24, 0.48	90	Intermittent moderate exercise. 15 min rest and exercise intervals. Treadmill. 23 L/min	8/10	-	>0.48	>0.48	-	Neutrophil and epithelial cell counts in nasal lavage increased in asthmatics. EDRF estimated to be >1.	Methacholine challenge, asymptomatic	Yes, 1/10 subjects	(McBride et al 1994)	
				Inflammatory markers	>0.48	0.48	>1					
0.5, 0.8	180, 120	Bicycle every 15 min. 25-45 l/min.	38/12	-	>0.8	>0.8	-		Physician¶, asymptomatic	Not stated	(Magnussen et al 1994)	
0.4	120	Moderate exercise on bicycle ergometer in 15 min intervals. 20 l/m ² body surface.	15/15	Inflammatory markers	>0.4	0.4	>1	ENA-78, IL- 8, IL-5, GM- CSF and IL- 10 in bronchial biopsies increased in asthmatics. EDRF estimated to be >1.	GINA- criteria, atopy‡	No	(Bosson et al 2003)	
0.8	120	Bicycle ergometer 20 l min/m ² body surface area for 15-min periods.	6/6	FEV ₁	0.8	0.8	1	Neutrophil count in induced sputum increased in both groups. EDRF	Diagnostic criteria.	No	(Hilterman et al 1995)	

					Symptoms	0.8	0.8	1	estimated to be 1.			
					Inflammatory markers	0.8	0.8	1				
	0.8	120	Four 15-min exercise periods. 30-40L/min	24/11	FEV ₁ , FVC	0.8	0.8	1	Sputum neutrophil and macrophage counts, IL-1β, IL-8, IL-6 and IL-5, but not eosinophil count and IL-10, in induced sputum increased among asthmatics. EDRF estimated to be >1.	Physician¶, methacholine challenge, atopy‡	No	(Hernandez et al 2010b)
					Inflammatory markers	>0.8	0.8	>1				
	0.4	240	Intermittent exercise. 50 W. 20 min every 30 minutes.	-	FEV ₁	0.4	0.4	1	Neutrophil and macrophage counts in induced sputum increased in both groups. EDRF estimated to be 1.	American Thoracic Society*	No (8 weeks without)	(Nightingale et al 1999)
					Inflammatory markers	0.4	0.4	1				
	0.24	60, 40, 30	Rest	10/10	-	>0.24	>0.24	-	No effect on lung function parameters other than RT. EDRF estimated to be 1.	Physician¶, methacholine challenge, exercise challenge, allergy‡	No (only bronchodilators regularly)	(Koenig et al.1988b)
	0.24, 0.36	60, 40, 30	moderate exercise for the last 10 min	10/10	R _T	0.36	0.36	1				
Sodium bisulfate	0.1, 1	16	Rest		FEV ₁	>1	>1	-	Only	Carbachol	No	(Utell et al

				16/17					uncommon effect parameters were affected. No effects on, e.g., FEV ₁ and SGaw. Overall EDRF: inconclusive.	<i>challenge</i>		(1982)
					Flow at 40% and 60% of TLC on MEFV and PEFV curves	1	1	1				
	0.1, 0.450, 1	16	Rest	14/17	-	>1	>1	-		<i>Carbachol challenge</i>	No	(Utell et al 1984)
Sodium nitrate	7	16	Rest	10/11	-	>7	>7	-		<i>Carbachol challenge</i>	No	(Utell et al 1979)
	1, 2, 3	10	Rest	5/5	-	>3	>3	-	Overall EDRF: inconclusive.	<i>Not stated</i>	<i>Not stated</i>	(Sackner et al 1981)
	3	10	Rest	6/6	-	>3	>3	-				
Sulfur dioxide, overall assessment									Five out of 8 studies have EDRF values >1, with two studies >2. Only non- informative study has an EDRF of 1. The study by Sheppard et al. (1980) suggests that the EDRF may be above 5, since effects were seen in asthmatics even at the lowest concentration tested. The overall EDRF was estimated to be >2.			

Sulfur dioxide	0.715, 1.43, 2.145, 2.86	40	Bicycle. 450 kp*m/min during the first 10 min. Ventilation 35 L/min.	10/10	FEV ₁ , MEF _{40%}	>2.86	2.145	>1.25	Asthmatics reported lower respiratory symptoms more often starting at 2.145 mg/m ³ (not analyze statistically). V _{max50%} marginally, but significantly increased in asthmatics at 0.715 but not 1 min post-exposure at 1.43 mg/m ³ . V _{max50%} clearly increased in asthmatics post-exposure to 1.43 mg/m ³ . LRT symptom score higher in asthmatics, with tendency (not significant) to increase with exposure level. No effects from filtered air exposure. EDRF estimated to be >2.	American Thoracic Society*, 8/10 had allergy†	No	(Schacter et al. 1984, Witek et al. 1985b)
					Raw	>2.86	2.86	>1				
					V _{max50%}	>2.86	1.43	>2				
	1.43	10 (tidal breathing) + 10 (hyperventilation)	10 min isocapnic hyperventilation at 30 L/min.	12/46	SRaw	>1.43	1.43	>1	Other lung parameters and symptoms not measured.	American Thoracic Society*, 23/46 had allergy†	Yes, 16/46 subjects	(Magnusson et al. 1990)

									The difference between exposure to SO ₂ and filtered air was statistically significant.			
2.86, 8.58, 14.3	10	Rest	7/7	SRaw	14.3	2.86	5	No other lung parameters were measured. More frequent LRT symptoms in asthmatics (3/7 vs 0/7).	History†, physician¶, allergy‡	No	(Sheppard et al 1980)	
0.715, 1.43, 2.145, 2.86	30	Moderate exercise for 10 min. 450 kp*m/min on a cycle ergometer.	15/15	FEV ₁ , Raw, MEF _{40%}	>2.86	2.145	>1.25	No effects from filtered air exposure.	American Thoracic Society*	Not stated	(Witek et al. 1986)	
0.57, 1.14, 1.72	60	Alternating 10 min exercise. Ergometer. Oronasal breathing. 40 L/min.	24/16	-	>1.72	>1.72	-	No effect on lung functions (SRaw, FEV ₁). Higher LRT symptom score in both groups at all exposure levels, but increased significantly more among asthmatics. EDRF estimated to be >1.	History†, methacholine challenge, allergy‡	No	(Linn et al 1987)	
22.88	5	Rest	11/4	Raw, SGaw	22.88	22.88	1	All 4 asthmatics	History†, allergy‡	Yes	(Snashall et al 1982)	

									and 2 of the 11 healthy subjects experienced mild chest tightness. EDRF estimated to be >1.			
	0.57	60	Rest	12/12	-	>0.57	>0.57	-		History†, physician¶	Yes, some of them	(Tunnicliffe et al 2001, 2003)
	1.43	180	Rest	40/40	MMEF	>1.43	1.43	>1	No significant changes in other lung function parameters (FEV ₁ , VC, FRC, FVC, Raw, R _v) or symptoms.	History†, free from attacks last 3 months	Not stated	(Jaeger et al 1979)
Sulfuric acid, overall assessment									Five studies have EDRF values >1, whereas eight were inconclusive. The overall EDRF is estimated to be >1.			
Sulfuric acid	0.38, 1.06, 1.5	60	Alternating 10-min exercise with rest. 50 L/min	21/21	FEV ₁ , FVC	>1.5	1.06	>1.42	Significantly higher symptoms score in the lower respiratory for asthmatics, not seen for healthy. No effects from filtered air exposure.	History†, physician¶, methacholine challenge, 20/21 had allergy‡	Not stated	(Avol et al. 1988b)

0.150, 0.680	60	Alternating 10-min exercise with rest.	6/6	SRaw	>0.680	0.680	>1	Significantly greater response after 0.680 mg/m ³ compar ed to filtered air and 0.150 mg/m ³ .	Not stated	Not stated	(Linn et al 1986b)
0.1, 1	16	Rest	16/17	FEV ₁ , SGaw	>1	1	>1	EDRF estimated to be >1.	Carbachol challenge	No	(Utell et al 1982)
				60% TLC on MEFV, 40- 60% TLC on PEFV	1	1	1				
0.1, 0.450, 1	16	Rest	14/17	FEV ₁	>1	1	>1	EDRF estimated to be >1.	Carbachol challenge	No	(Utell et al 1984)
				FEF _{40-60%}	1	>1	<1				
				SGaw	>1	0.45	>2.2				
0.1	356	Six 50-min periods. 29 L/min.	15/30	-	>0.1	>0.1	-	No significant effects on lung function (FEV ₁ , SRaw) or symptoms.	History†, physician¶, methacholine challenge	Yes (some used inhaled, none oral)	(Linn et al. 1994)
0.1	120	15 min every 30 min on bicycle. 150- 300 kg m/min. Doubled minute volume of ventilation	6/6	-	>0.1	>0.1	-	No significant effects on lung function (FEV ₁ , FVC, FEF _{25-75%} , TLC, R _V , R _T) or symptoms.	History†, physician¶, mild to more severe asthma	Yes (oral if needed)	(Avol et al. 1979)
0.1	180	10 min every 30 min to at	30/30	-	>0.1	>0.1	-	No significant effects on	Fulfilled two of these;	No	(Frampton et al. 1995)

		least quadruple minute ventilation.							lung function (FEV ₁ , SGaw, FVC) or symptoms.	History†, spirometry, carbachol challenge		
0.1	60	Alternating 10-min on bicycle with rest. 50 L/min.	15/15	-		>0.1	>0.1	-	No significant effects on lung function (FEV ₁ , SRaw, FVC) or symptoms.	History†, physician¶, methacholine challenge or bronchodilator	Not stated	(Anderson et al. 1992)
0.5, 1, 2	60	Alternating 10-min exercise with rest. 50 L/min.	22/22	PEFR		>2	2	-	No significant effects on other lung function parameters (FEV ₁ , FVC, Vtg, SRaw). LRT symptom scores increased in both groups. Effects on FEV ₁ , PEFR and SRaw from filtered air exposure. EDRF estimated to be 1.	History†, physician¶, allergy‡	No	(Avol et al 1988a)
				Symptoms		2	2	1				
0.07	40	Light exercise on a treadmill for the last 10 min of exposure.	8/9	-		>0.07	>0.07	-	No significant effects on lung function (FEV ₁ , FVC, R _T).	History†, methacholine challenge	Not stated	(Koenig et al. 1993)
0.01, 0.1, 1	10	Rest	5/5, 6/6, 12/12	-		>1	>1	-	No significant effects on lung function (FEV ₁ , VC, R _T , ERV, R _V , TLC, PEFR, V _{max} 50-75%, Raw, SGaw) or symptoms.	Relatively free from symptoms	Yes, 6/7 subjects	(Sackner et al. 1978)

	0.075, 0.1, 0.35, 0.45, 1	16, 30, 120, 240	16 min, all conc: rest, 30 min, 0.35 mg/m ³ : 10 min exercise 120 min, 0.075 mg/m ³ : 4*10min exercise, 240 min, 0.1, 0.45 mg/m ³ : 3*10 min exercise	14/17	FEV ₁ , SGaw	>1	1	>1	Increased airway reactivity to carbachol in both groups at 0.45 mg/m ³ 24 h later. Statistically significant changes compared to both baseline and control exposures (NaCl).	Not stated	Not stated	(Utell et al. 1991)
	0.1	180	10 min every 30 min. Quadrupled the expired volume of ventilation/min (60-200 watts).	30/30	-	>0.1	>0.1	-	No significant effects on lung function (FEV ₁ , FVC or SGaw) or symptoms.	History†, physician¶, carbachol challenge and bronchodilator, allergy‡	No	(Utell et al. 1994)
	0.2, 2	60	Rest	12/12	-	>2	>2	-	No significant effects on lung function (FEV ₁ , FVC, MMEF) or symptoms.	History†, physician¶	Yes, some of them	(Tunnicliffe et al 2003)
Tear gas	5-442	8-120 sec	Rest	-/33	-	Not applicable	Not applicable	-	Time to incapacitation similar among healthy and asthmatics. No lung function measurements. More chest symptoms among asthmatics. Overall EDF: inconclusive	History†, Normal X-ray	Not stated	(Gutentag et al. 1960)

2,4-/2,6-toluenediisocyanate	0.071, 0.142	120	Rest	10/15	-	>0.142	>0.142	-	No significant changes in FEV ₁ , IGV, SRaw, Raw, VC or symptoms at group level. However, 3 asthmatics experienced chest tightness, 2 cough, 2 decreased FEV ₁ , and 4 marked increase in SRaw. No such effects among healthy subjects. Overall EDRF estimated to be >1.	History†, acetylcholine challenge	Not stated	(Baur 1985)
Zinc ammoniumsulfate	0.02	120	Alternating 15 min bicycle ergometer with 15 min rest. Doubling ventilation volume/min. 150-300 kg m/min depending on individual tolerance.	21/19	FEV ₁ , FEF _{50%} , TLC	0.02	0.02	1	FEV ₁ judged to be the most relevant effect. Overall EDRF estimated to be 1.	History†, physician¶, 13/19 had allergy‡	Yes, 4/19 subjects	(Linn et al 1981)
					R _V , R _T , TLC	>0.02	0.02	>1				
					FEV ₂ , FEF _{75%} , FEV ₁ /FVC, CC/TLC	0.02	>0.02	<1				

Mixtures												
Carbon black (0.5 µm) and Sulfuric acid (0.5 µm)	0.25 + 0.1	60	Heavy exercise. Alternating 10-min on bicycle ergometers with 10 min rest. 50 L/min.	15/15	-	>tested dose	>tested dose	-	Overall EDRF: inconclusive	History†, physician¶, methacholine challenge or bronchodilator	Not stated	(Anderson et al. 1992)
Diesel particles in ambient air (indoor, Sweden)	0.1 PM ₁₀ + urban air (1.7 ppm CO, 0.6 ppm NO, 0.2 ppm NO ₂ , 1.4 ppm HC, 0.2 ppm CH ₂ O)	120	Moderate exercise. Alternating 15-min on bicycle with 15 min rest.	25/15	SRaw	0.1	0.1	1	Levels of IL-10 significantly increased in asthmatics. Neutrophils, lymphocytes and IL-8 were significantly increased in healthy subjects. Overall EDRF estimated to be 1.	National Institutes of Health - criteria, methacholine challenge, allergy‡	No	(Holgate et al 2003) (Stenfors et al 2004)
					Inflammatory markers	0.1	0.1	1				
Environmental tobacco smoke	side stream cigarette smoke for 1 h	60	Rest	10/10	FEV ₁ , FVC, FEF _{25-75%}	Not applicable	Not applicable	-	Markedly impaired lung function effects among asthmatics but not among healthy in Dahms study. No effects on either group in Magnusson study. Overall EDRF estimated to	History†, physician¶, methacholine challenge	Not stated	(Dahms et al 1981)
	side stream cigarette smoke for 1 h	60	Rest	16/18	-	Not applicable	Not applicable	-		History†, allergy‡	Yes, 9/18 subjects.	(Magnusson et al 1992)

									be >1.			
Nitrogen dioxide and Sulfur dioxide	healthy: 0.94 +1.43 asthma: 0.94+0.86	120	Intermittent exercise. Alternating 15-min on bicycle ergometers with 15 min rest. 150-400 kg-m/min.	24/19	-	>tested dose	>tested dose	-	No effects on lung function in either group. Lower respiratory tract symptoms, headache and fatigue similar in healthy and asthmatics. Exposure to sulfur dioxide lower for asthmatics. Overall EDF: inconclusive.	History†, physician¶, allergy‡	Yes (if needed)	(Linn et al 1980)
					Symptoms	=tested dose	=tested dose	1				
Ozone in ambient air	ambient 0.33, 0.31 (Los Angeles)	60	Moderate continuous exercise. 38L/min	48/50	FVC	0.33	0.33	1	Lower-respiratory tract symptom score increased more in asthmatics. EDF estimated to be >1.	Physician¶	Not stated	(Avol et al 1983)
					FEV ₁	>0.33	0.33	>1				
					Symptoms	>0.33	>0.33	-				
Ozone and Limonene	0.04-0.074 and 98% pure 35-36 ppb	180	Rest	38/33	Symptoms	>0.074	>0.074		Overall EDF: inconclusive	Physician¶, GINA - criteria	Not stated	(Fadeyi et al 2014)
Ozone and Nitrogen dioxide	0.24+0.56	60	Moderate exercise. 32.8 ±6 L/min	12/12	-	>tested dose	>tested dose	-	Overall EDF: inconclusive.	Physician¶, methacholine challenge,	No (only bronchodilators)	(Koenig et al 1988a)

										exercise challenge	regularly	
Ozone and Sulfur dioxide	0.64+1.057	120	Alternating 15-min exercise with 15 min rest to increase min ventilation 2 to 2 ½ times.	4/4	FEV ₁	>tested dose	=tested dose	>1	Overall EDRF estimated to be >1.	History of hyperreactivity to inhaled irritants†	Not stated	(Bell et al 1977)
Ozone, Sulfur dioxide and Sulfuric acid	0.29 SO ₂ +0.1 H ₂ SO ₄ +0.2 O ₃	240	Alternating 15-min on bicycle ergometers with 15min rest	15/5	-	>tested dose	>tested dose	-	Children aged 9-12. No effects on lung function or symptoms in either group. Overall EDRF: inconclusive.	History†, physician¶	No	(Linn et al 1997)
Ozone and Sulfuric acid	0.24+0.1	390	Six 50-min exercise periods per exposure day. 29 L/min	15/30	FEV ₁ , SRaw	=tested dose	=tested dose	1	Respiratory and irritant symptoms similar in both groups. Overall EDRF estimated to be 1.	History†, physician¶, methacholine challenge	Yes (some used inhaled, no oral)	(Linn et al. 1994)
					Symptoms	=tested dose	=tested dose	1				
PM _{2.5} in urban air	0.174 (Los Angeles suburb)	120	Alternating 15-min on a pedal crank device with 15 min rest. 15-20 l/min/m ² body surface area.	12/12	-	>0.174	>0.174	-	No effects on lung function, inflammatory markers or symptoms in either group. Overall EDRF: inconclusive.	History†, physician¶, methacholine challenge, atopy‡	No	(Gong et al 2003)
	0.157 (Los Angeles suburb)	120	Alternating 15-min on a pedal crank device with 15 min rest. 15-20 l/min/m ² body	4/12	-	>0.157	>0.157	-		Physician¶, methacholine challenge	No	(Gong et al 2004)

			surface area.								
			Intermittent exercise. Alternating 15-min exercise with 15 min rest. 15-20 l/min/m ² body surface area.								
0.013-0.277 (Los Angeles suburb)	120			17/4	-	>0.013-0.277	>0.013-0.277	-		Physician¶, atopic‡	No (Gong et al 2008)

* According to the criteria established by the American Thoracic Society.

† Self-reported history of asthma.

‡Allergy or atopy diagnosed by a physician or self-reported.

¶Asthma diagnosed by a physician

§The following conversion factors from ppm to mg/m³ were used: ammonia 1 ppm = 0.71 mg/m³, chlorine 1 ppm = 2.9 mg/m³, formaldehyde 1 ppm = 1.25 mg/m³, nitric oxide 1 ppm = 1.23 mg/m³, nitrogen dioxide 1 ppm = 1.88 mg/m³, ozone 1 ppm = 2 mg/m³, sulfur dioxide 1 ppm = 2.86 mg/m³, 2,4-toluenediisocyanate 1 ppm = 7.12 mg/m³.

Abbreviations

C _L	Pulmonary compliance
ENA-78	Neutrophil chemokine
ERV	Expiratory reserve volume; the maximal volume of air that can be exhaled from the end-expiratory tidal position (FRC-R _V).
FEF _{25-75%}	Forced expiratory flow related to 25-75% of the FVC curve. Equal to V _{max} _{25-75%} at TLC.
FEV ₁	Forced expiratory volume in 1 second. Volume of air forcibly expired in the first second with a maximal effort
FEV ₁ /FVC	Ratio
FRC	Functional residual capacity: the volume of air in the lungs following a tidal volume exhalation = ERV + R _V
FRV	Functional residual volume
FVC	Forced vital capacity: the total volume that can be forcefully expired with a maximal effort
GM-CSF	Granulocyte-macrophage colony stimulating factor
IC	Inspiratory capacity: the maximal volume of air that can be inhaled from the tidal volume end-expiratory level (TLC-FRC)
IGV	Intrathoracic gas volume
IL-8	Interleukin-8
MEF _{40%}	Maximal expiratory flow at 40% of FVC
MEFV	Maximal expiratory flow volume. The subject inspired maximally to total lung capacity (TLC) and then forcefully expired to RV to obtain MEFV.
MMEF	Maximal mid-expiratory flow between 25% and 75% of TLC. Equal to MMFR.
MPO	Myeloperoxidase
NAR	Nasal airway resistance
PC ₂₀ FEV ₁	Provocative concentration required to produce a 20% reduction in FEV ₁
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PEFV	Partial expiratory flow volume (expiratory flow versus lung volume)

PMN	Polymorphonuclear neutrophils
Raw	Airway resistance
R _L	Pulmonary resistance
R _T	Total respiratory resistance
R _V	Residual volume: the volume of air that remains in the lungs after maximal exhalation (TLC-VC)
SGaw	Specific airway conductance
SRaw	Specific airway resistance
TGV	Thoracic gas volume
TLC	Total lung capacity: the total volume of air in the lungs after complete inhalation: the sum of all compartments (IC + FRC or IRV + VT + ERV + RV)
TNF- α	Tumour necrosis factor
VC	Vital capacity: the maximal volume of air that can be exhaled starting from maximal inspiration, TLC can be measured either as slow vital capacity (SVC) or forced vital capacity (FVC)
V _{isov}	Volume of isoflow
V _{max50%}	Maximal flow at 50% of FVC
Vtg	Volume of thoracic gas

Appendix B: Comparative concentration*time and response analyses

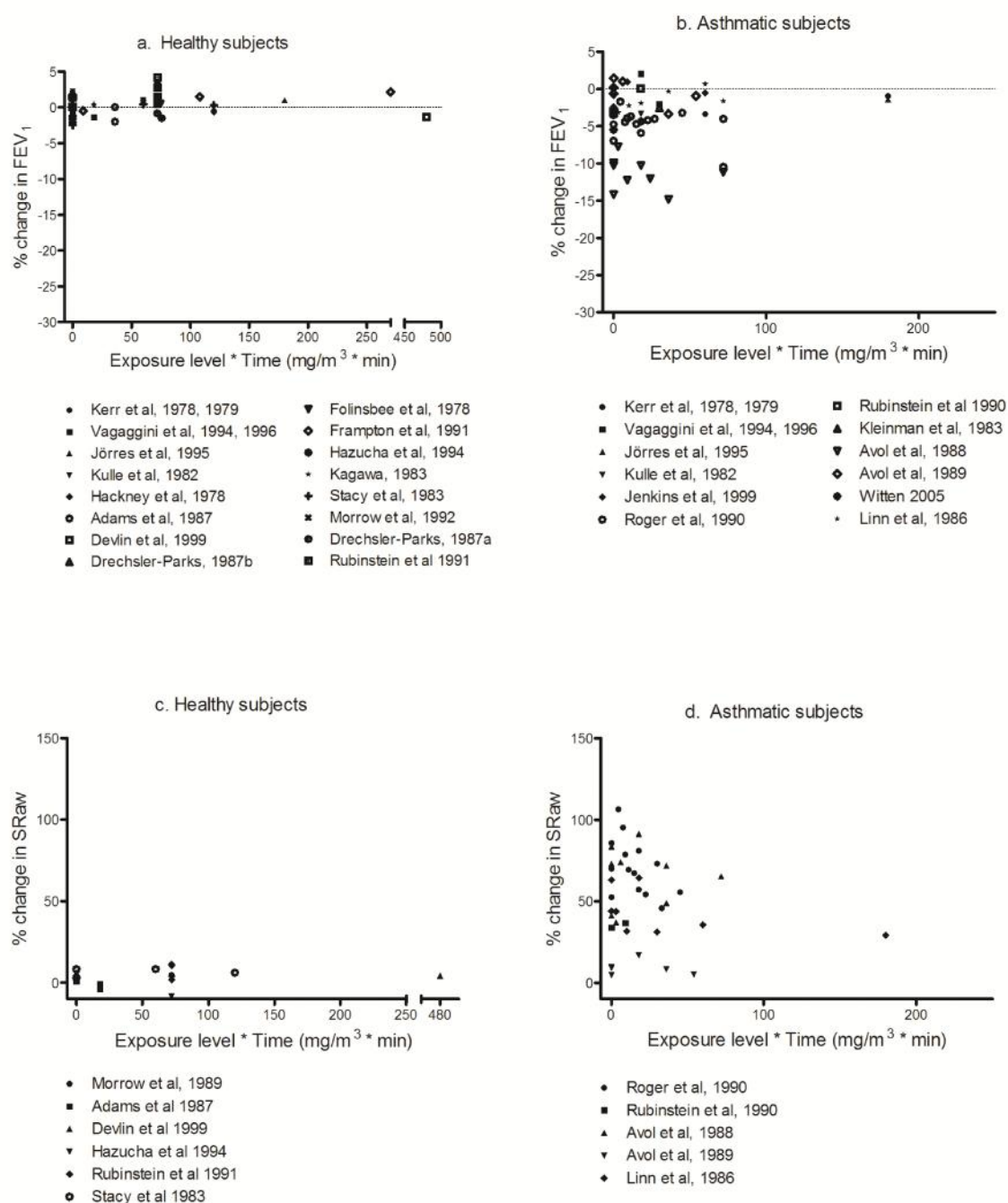


Figure 1. Percentage changes in forced expiratory volume in 1 second (FEV₁) and in specific airway resistance (SRaw) in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to nitrogen dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

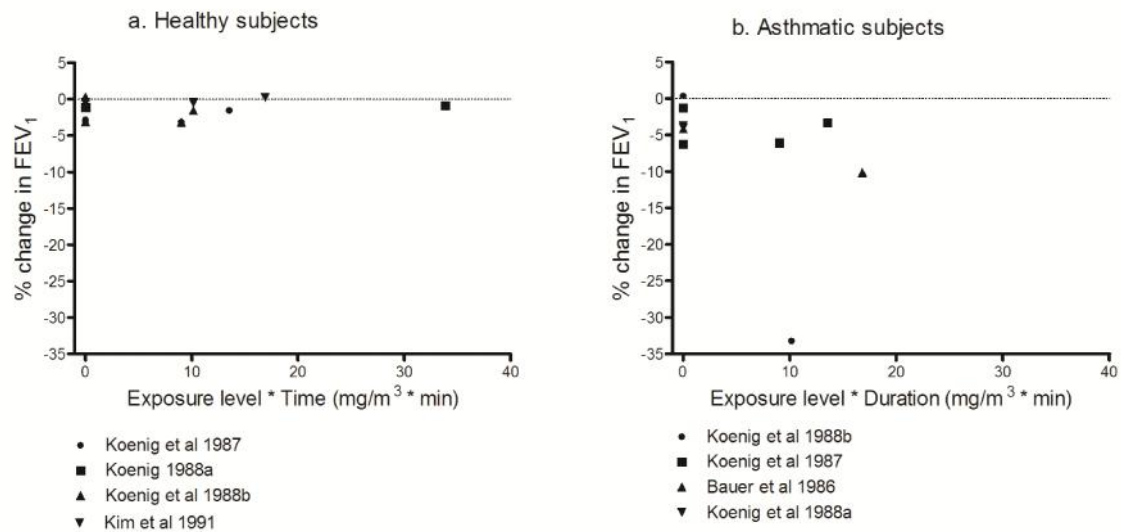


Figure 2. Percentage change in forced expiratory volume in 1 second (FEV₁) in healthy and asthmatic subjects following exposure by inhalation (mouth-only breathing) to nitrogen dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

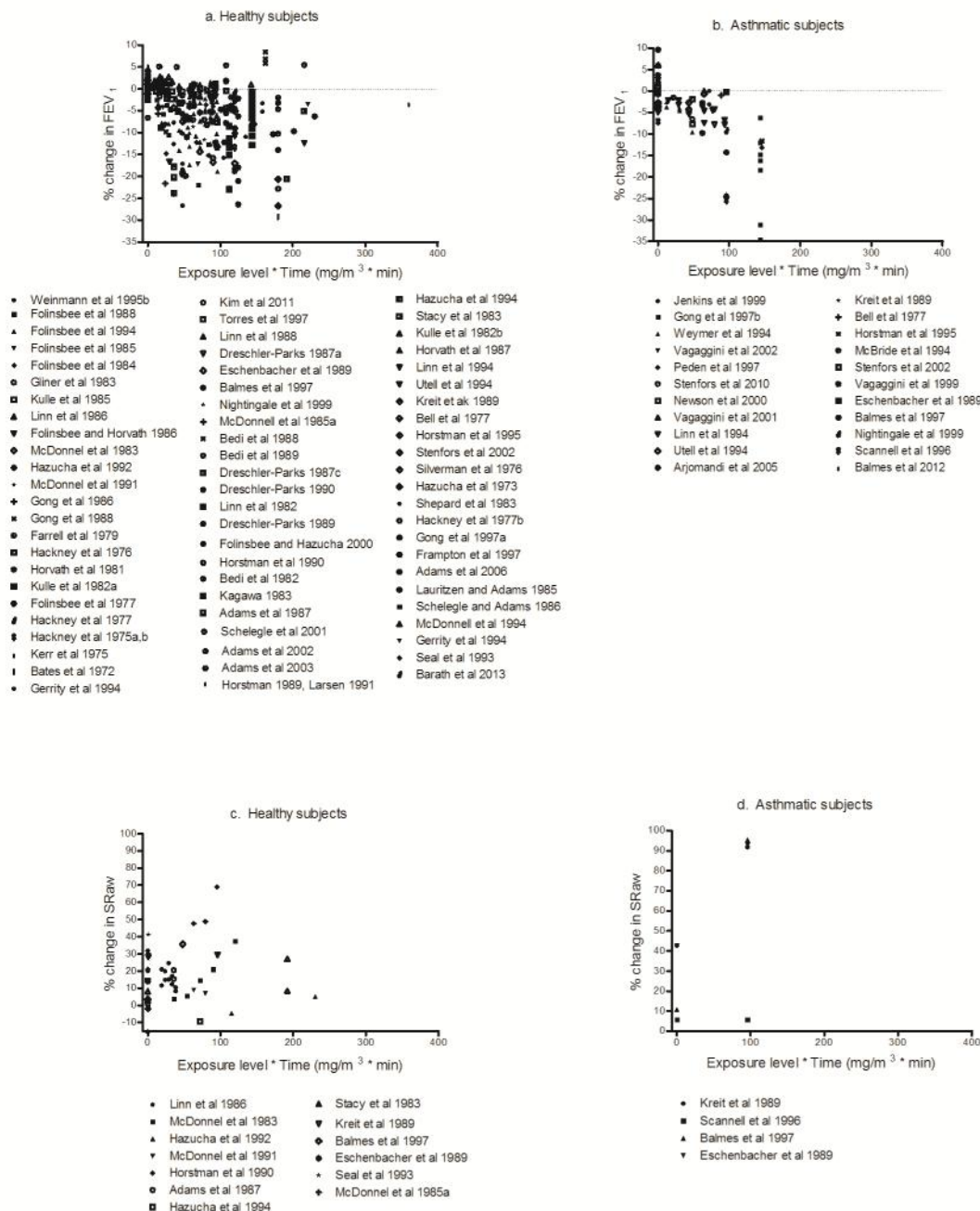


Figure 3. Percentage changes in forced expiratory volume in 1 second (FEV_1) and in specific airway resistance (SRaw) in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to ozone during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

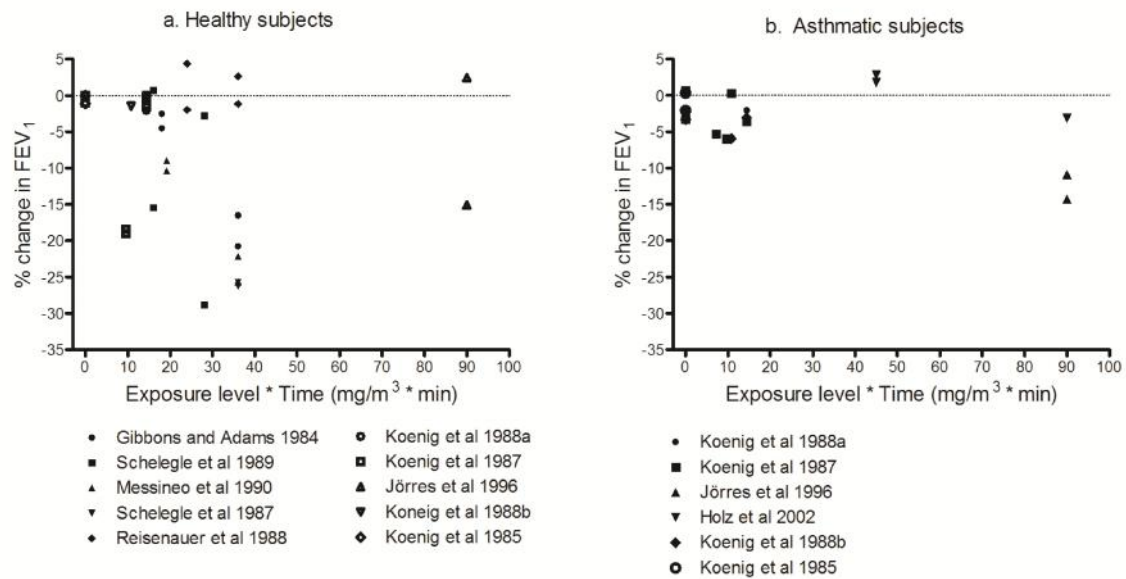


Figure 4. Percentage change in forced expiratory volume in 1 second (FEV₁) in healthy and asthmatic subjects following exposure by inhalation (mouth-only breathing) to ozone during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

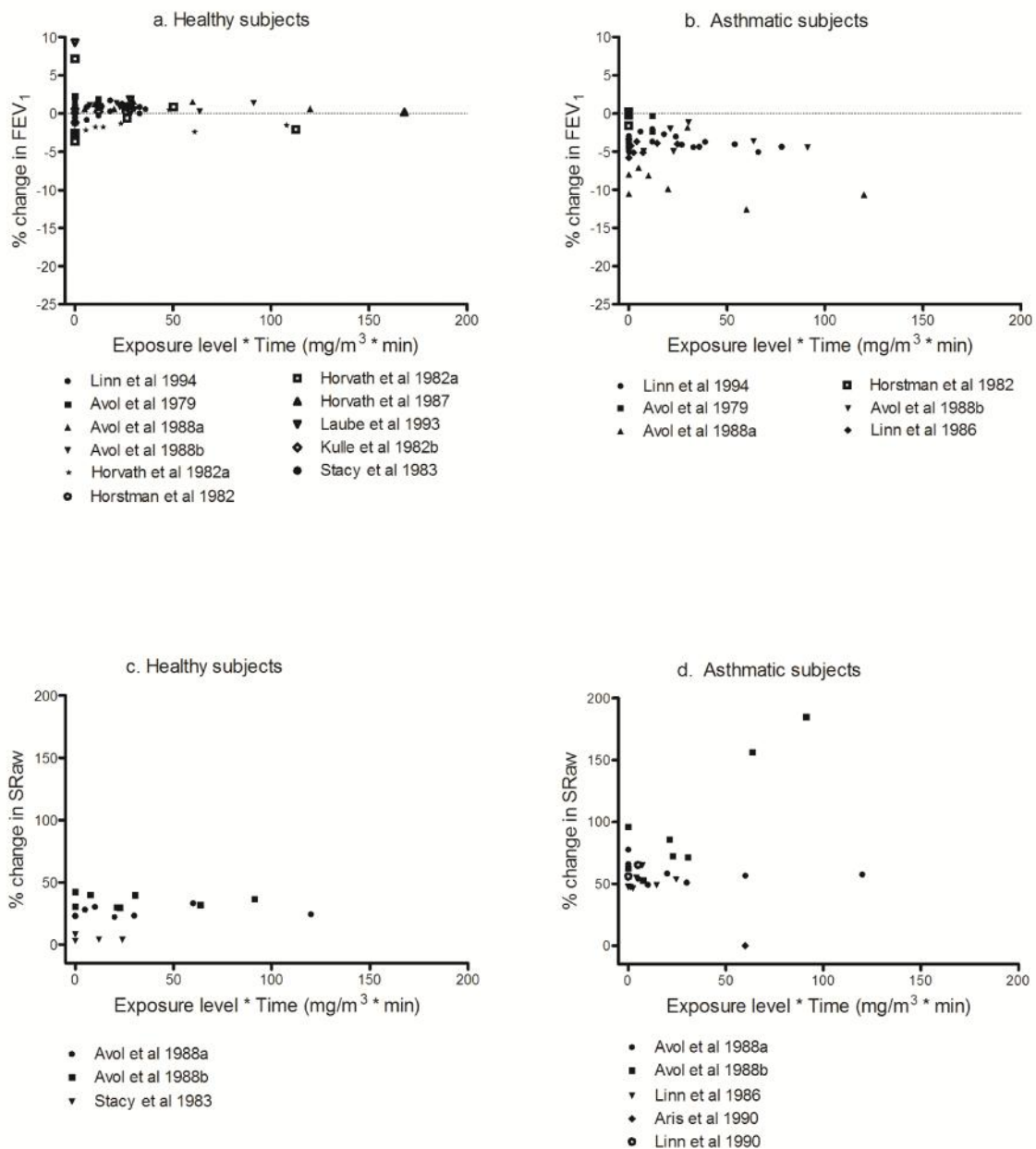


Figure 5. Percentage changes in forced expiratory volume in 1 second (FEV₁) and in specific airway resistance (SRaw) in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to sulfuric acid during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

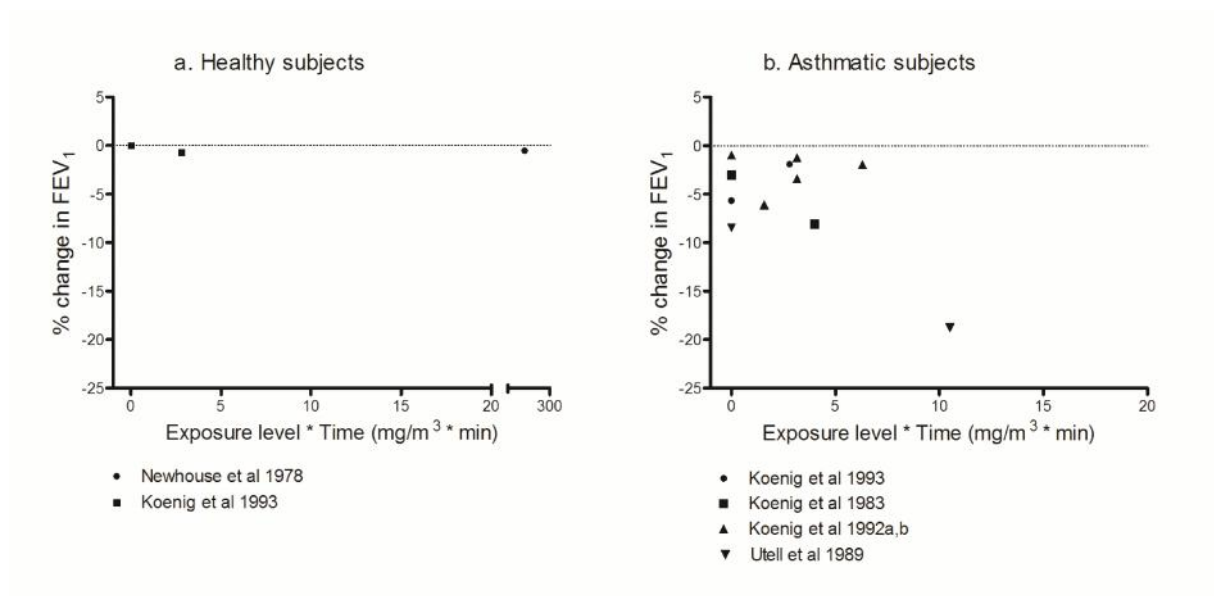


Figure 6. Percentage change in forced expiratory volume in 1 second (FEV₁) in healthy and asthmatic subjects following exposure by inhalation (mouth-only breathing) to sulfuric acid during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

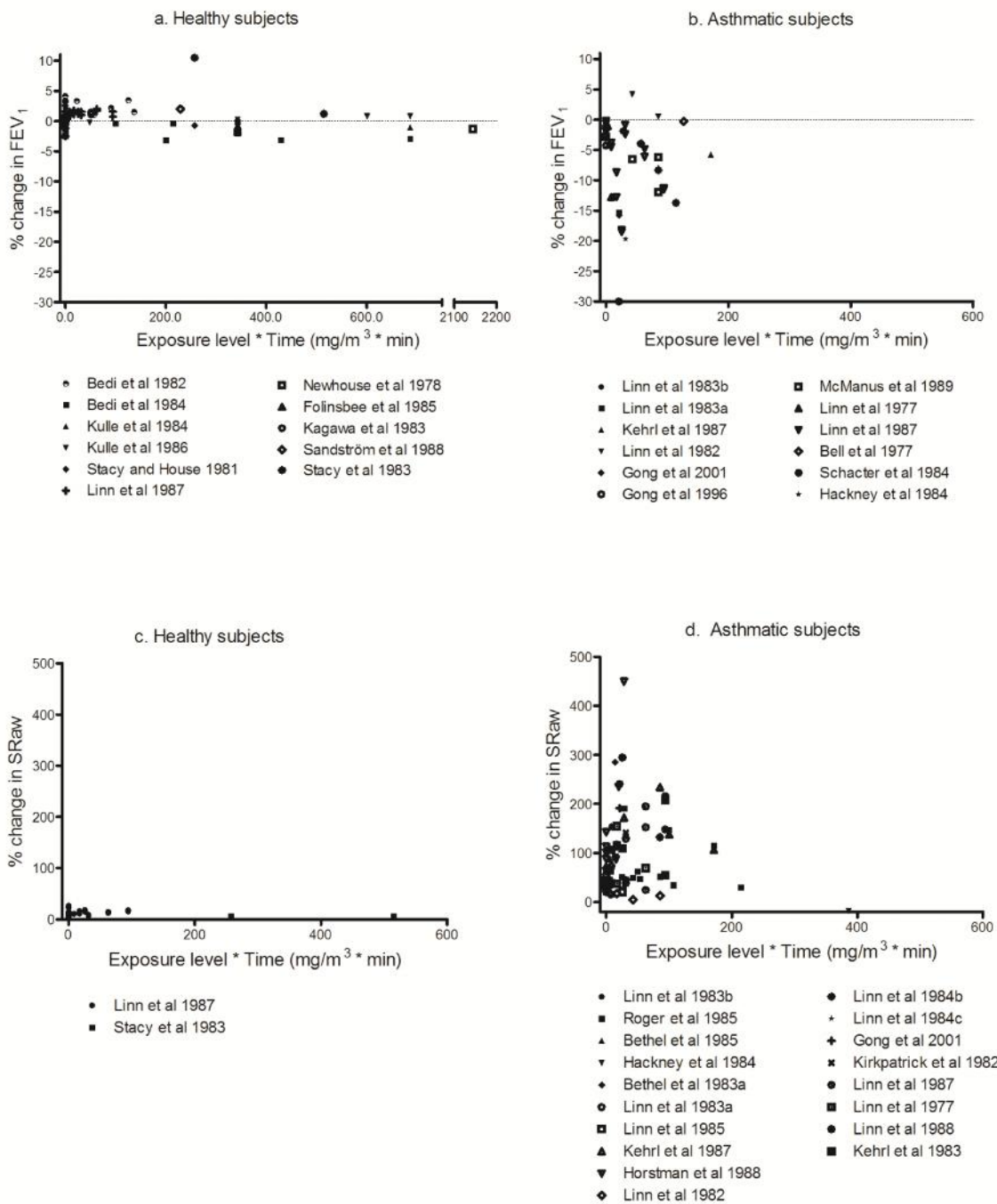


Figure 7. Percentage changes in forced expiratory volume in 1 second (FEV₁) and in specific airway resistance (SRaw) in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to sulfur dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

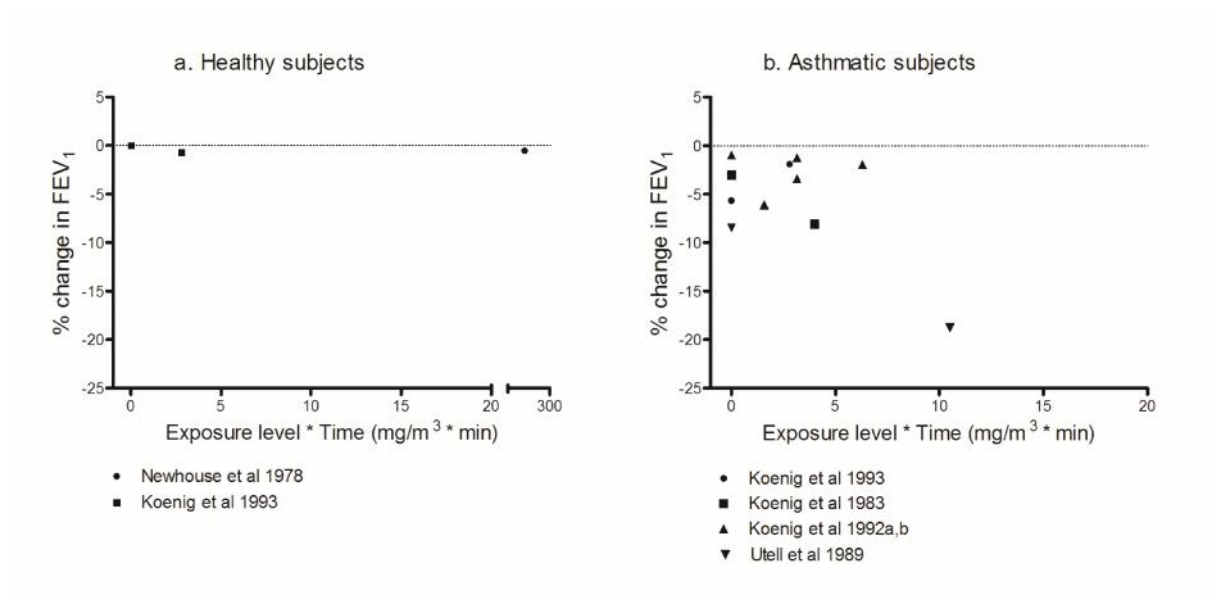


Figure 8. Percentage change in forced expiratory volume in 1 second (FEV₁) in healthy and asthmatic subjects following exposure by inhalation (mouth-only breathing) to sulfur dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

Appendix C: Studies included in Table 3 (n=103).

Acetaldehyde

Myou, S., Fujimara, M., Nishi, K., Ohka, T., Matsuda, T. (1993). Aerosolized acetaldehyde induces histamine-mediated bronchoconstriction in asthmatics. *Am Rev of Respir Dis.* 14 148: 940-943.

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

Prieto, L., Sanchez Toril, F., Gutierrez, V. and Marin, M. J. (2002a). Airway responsiveness to inhaled acetaldehyde in subjects with allergic rhinitis: relationship to metacholine responsiveness. *Respir* 69(2):129-135.

Ammonia

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

Sigurdarson, S. T., O'Shaughnessy, P. T., Watt, J. A., Kline, J.N. (2004). Experimental human exposure to inhaled grain dust and ammonia: Towards a model of concentrated animal feeding operations. *Am J Ind Med* 46(4):345-348

Ammonium bisulfate

Avol E. L., Jones M. P., Bailey R. M., Chang, N. M., Kleinman, M. T., Linn W. S., Bell K. A., Hackney J. D. (1979). Controlled exposures of human volunteers to sulfate aerosols. Health effects and aerosol characterization. *Am Rev Respir Dis.* 120(2):319-327.

Tunncliffe, W. S., Harrison, R. M., Kelly, F. J., Dunster, C., Ayres, J. G. (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:e15

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

Utell, M. J., Morrow, P. E., Hyde, R. W. (1982). Comparison of Normal and Asthmatic Subjects Responses to Sulfate Pollutant Aerosols. *Ann. Occup. Hyg.* 26:691-697

Ammonium nitrate

Sackner, M.A., Ford, D. (1981). Effects of breathing nitrate aerosols in high concentrations for 10 minutes on pulmonary function in normal and asthmatic adults, and preliminary results in normal exposed to nitric acid fumes. *Am Rev Resp Dis.* 123:151

Ammonium sulfate

Avol, E. L., Jones, M. P., Bailey, R. M., Chang, N. M., Kleinman, M.T., Linn, W.S., Bell, K.A., Hackney, J.D. (1979). Controlled exposures of human volunteers to sulfate aerosols. Health effects and aerosol characterization. *Am Rev Respir Dis.* 120(2):319-327.

Koenig, J. Q., Dumler, K., Rebolledo, V., Williams, P. V., Pierson, W. E. (1993). Respiratory effects of inhaled sulfuric acid on senior asthmatics and nonasthmatics. *Arch Environ Health* 48(3):171-175

Utell, M. J., Morrow, P. E., Hyde, R. W. (1982). Comparison of Normal and Asthmatic Subjects Responses to Sulfate Pollutant Aerosols. *Ann. Occup. Hyg.* 26:691-697

Carbon aerosols

Anderson, K. R., Avol, E. L., Edwards, S. A., Shamoo, D. A., Peng, R.-C., Linn, W. S., Hackney, J. D. (1992). Controlled exposures of volunteers to respirable carbon and sulfuric acid. *J. Air Waste Manage. Assoc.* 42:770-776

Pietropaoli, A. P., Frampton, M. W., Hyde, R. W., Morrow, P. E., Oberdörster, G., Cox, C., Speers, D. M., Frasier, L. M., Chalupa, D. C., Huang, L.-S., Utell, M. J. (2004). Pulmonary function, diffusion capacity, and inflammation in healthy and asthmatic subjects exposed to ultrafine particles. *Inhal toxicol.* 16(1):59-72

Same as Pietropaoli et. al (2004): Frampton, M. W., Utell, M.J., Zareba, W., Oberdörster,, G., Cox, C., Huang, L. S., Morrow, P. E., Lee, F. E., Chalupa, D., Frasier, L. M., Speers, D. M., Stewart, J. (2004). Effects of exposure to ultrafine carbon particles in healthy subjects and subjects with asthma. *Research Report (Health Effects Institute)* 126:1-47; discussion 49-63

Chlorine

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

Ferric sulfate

Kleinman, M. T., Linn, W. S., Bailey, R. M., Anderson, K. R., Whynot, J. D., Medway, D. A., Hackney, J. D. (1981). Human exposure to ferric sulfate aerosol: effects on pulmonary function and respiratory symptoms. *Am. Ind. Hyg. Assoc J.* 42(4):298-304

Formaldehyde

Green, D. J., Sauder, L. R., Kulle, T. J. and Bascom. R. (1987). Acute response to 3.0 ppm formaldehyde in exercising healthy nonsmokers and asthmatics. *Am. Rev. Respir. Dis.* 135:1261-1266.

Kulle, T.J., Green, D.J. and Sauder. L.R. (1986). Acute pulmonary effects of 3.0 ppm formaldehyde in exercising healthy nonsmokers and asthmatics. *Amer. Rev. Respir. Dis.* 133:A355.

Witek, T. J., Schacter, E. N., Tosun, T., Leaderer, B. P. and Beck. G. J. (1986). Controlled human studies on the pulmonary effects of indoor air pollution: experiences with sulfur dioxide and formaldehyde. *Environ. Intl.* 12:129-135.

Nitrogen oxide

Höglman, M., Frostell, C. G., Hedenström, H. and Hedenstierna. G. (1993a). Inhalation of nitric oxide modulates adult human bronchial tone. *Am. Rev. Respir. Dis.* 148:1474-1478.

Nitrogen dioxide

Ahmed, T., Danta, I., Dougherty, R. L., Schreck, R., Sackner, M. A. (1983). Effect of NO₂ (0.1 ppm) on specific bronchial reactivity to ragweed antigen in subjects with allergic asthma. *Am Rev Res Dis* 127: Suppl: 160

Bylin, G., Lindvall, T., Rehn, T., Sundin, B. (1985). Effects of short term exposure to ambient nitrogen dioxide concentrations on human bronchial reactivity and lung function, *Eur. J. Resp. Dis.*, 66: 205-217.

Hazucha, M. J., Ginsberg, J. F., McDonnell, W. F., Haak, E. D., Pimmel, R. L., House, D. L., Bromberg, P. A. (1982). Changes in bronchial reactivity, of asthmatics and normals following exposure to 0.1 ppm NO₂. In: Schneider T, Grant L, eds. Air Pollution by Nitrogen Oxides. Amsterdam, Elsevier.

Hazucha, M.J., Ginsberg, J.F., McDonnell, W.F., Haak, E.D., Jr., Pimmel, R.L., Salaam, S.A., House, D.E., Bromberg, P.A. (1983). Effects of 0.1 ppm nitrogen dioxide on airways of normal and asthmatic subjects. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 54:730-739.

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

Kerr, H. D., Kulle, T. J., McIlhany, M. L., Swidersky, P. (1978). Effects of nitrogen dioxide on pulmonary function in human subjects. An environmental chamber study. *Report: ISS EPA/600/1-78/025*; Order no. PB-281 186, 20 pp.

Same study as Kerr et al 1978 and Kulle et al 1982: Kerr, H. D., Kulle, T. J., McIlhany, M. L., Swidersky, P. (1979). Effects of nitrogen dioxide on pulmonary function in human subjects: An environmental chamber study. *Environ. Research* 19:392-404.

Koenig, J. Q., Covert, D. S., Morgan, M. S., Horike, M., Horike, N., Marshall, S. G., Pierson, W. E. (1985). Acute effects of 0.12 ppm ozone or 0.12 ppm nitrogen dioxide on pulmonary function in healthy and asthmatic adolescents. *Am. Rev. Respir. Dis.* 132:648-651.

Koenig, J. Q., Covert, D. S., Marshall, S. G., van Belle, G., Pierson, W. E. (1987). The effects of ozone and nitrogen dioxide on pulmonary function in healthy and in asthmatic adolescents. *Am. Rev. Respir. Dis.* 136:1152-1157.

Koenig JQ, Covert DS, Smith MS, Van Belle G, Pierson WE. (1988a). The pulmonary effects of ozone and nitrogen dioxide alone and combined in healthy and asthmatic adolescent subjects. *Toxicol Ind Health.* 4(4):521-532.

Koenig J. Q., Pierson W. E., Covert D. S., Marshall S. G., Morgan M. S., van Belle G. (1988b). The effects of ozone and nitrogen dioxide on lung function in healthy and asthmatic adolescents. *Res Rep Health Eff Inst.* (14):5-24.

Same as Kerr et al 1978, 1979: Kulle, T. J. (1982). Effects of nitrogen dioxide on pulmonary function in normal healthy humans and subjects with asthma and chronic disease. *Stud Environ Sci* 21:477-486

Linn, W. S., Hackney, J. D. (1983). Short-term human respiratory effects of nitrogen dioxide: determination of quantitative dose-response profiles. Phase 1. Exposure of healthy volunteers to 4 ppm NO₂. *NTIS order no. PB84-132299*. 30 pp.

Same as Linn et al 1983, 1985: Linn, W. S., Hackney, J. D. (1984). Short-term human respiratory effects of nitrogen dioxide: determination of quantitative dose-response profiles. Phase 2. Exposure of asthmatic volunteers to 4 ppm NO₂. *NTIS order no. PB85-104388*. 31 pp.

Same as Linn et al 1983, 1984: Linn, W. S., Solomon, J. C., Trim, S. C., Spier, C. E., Shamoo, D. A., Venet, T. G., Avol, E. L., Hackney, J. D. (1985a) Effects of exposure to 4 ppm nitrogen dioxide in healthy and asthmatic volunteers. *Arch Environ Health*. 40(4):234-239.

Magnussen, H., Nowak, D., Jorres, R. (1994). Experimental effects of air pollutants on healthy probands and asthmatic subjects. *Pneumologie*. 48(2):85-88.

Morrow, P. E., Utell, M. J. (1989). Responses of susceptible subpopulations to nitrogen dioxide. Cambridge, MA: Research Rept. *Health Effects Inst.*, report no. 23.

Vagaggini, B., Paggiaro, P. L., Giannini, D., Franco, A. D., Cianchetti, S., Carnevali, S., Taccola, M., Bacci, E., Bancalari, L., Dente, F. L., Giuntini, C. (1994). Effects of short-term exposure to NO₂ (0.3-1 ppm) on the hypertonic saline induced sputum in normal, asthmatic and rhinitic subjects (Italian). *Arch Sci Lav* 10:655-660

Same study as Vagaggini et al 1994: Vagaggini, B., Paggiaro, P. L., Giannini, D., Di Franco, A., Cianchetti, S., Carnevali, S., Taccola, M., Bacci, E., Bancalari, L., Dente, F. L., Giuntini, C. (1996). Effect of short-term NO₂ exposure on induced sputum in normal, asthmatic and COPD subjects. *Eur. Respir. J.* 9:1852-1857

Ozone

Arjomandi, M., Witten, A., Abbritti, E., Reintjes, K., Schmidlin, I., Zhai, W., Solomon, C., Balmes, J. (2005). Repeated exposure to ozone increases alveolar macrophage recruitment into asthmatic airways. *Am J Respir Crit Care Med*. 172:427-432

Same study as Arjomandi et al 2005: Christian, D. L., Chen, L. L., Scannell, C. H., Ferrando, R. E., Welch, B. S., Balmes, J. R. (1998). Ozone-induced inflammation is attenuated with multiday exposure. *Am J Respir Crit Care Med* 158:532-537

Balmes, J. R., Aris, R. M., Chen, L. L., Scannell, C., Tager, I.B., Finkbeiner, W., Christian, D., Kelly, T., Hearne, P. Q., Ferrando, R., Welch, B. (1997). Effects of ozone on normal and potentially sensitive human subjects. Part 1: Airway inflammation and responsiveness to ozone in normal and asthmatic subjects. *Res Rep Health Eff Inst*. 78:1-37; Discussion 81-99

Basha, M. A., Gross, K. B., Gwizdala, C. J., Haidar, A. H., Popovich, J. JR. (1994). Bronchoalveolar lavage neutrophilia in asthmatic and healthy volunteers after controlled exposure to ozone and filtered purified air. *Chest*. 106:1757-1765

Bell, K. A., Linn, W. S., Hazucha, M., Hackney, J. D., Bates D. V. (1977). Respiratory Effects of Exposure to Ozone Plus Sulfur Dioxide in Southern Californians and Eastern Canadians. *Am. Ind. Hyg. Assoc. J.* 38:696-706.

Bosson, J., Stenfors, N., Bucht, A., Helleday, R., Purazar, J., Holgate, S. T., Kelly, F. J., Sandström, T., Wilson, S., Frew, A. J. Blomberg, A. (2003). Ozone-induced bronchial epithelial cytokine expression differs between healthy and asthmatic subjects. *Clin Exp Allergy*. 33 (6):777-82

Eschenbacher, W. L., Ying, R. L. Kreit, J. W Gross, K. B. (1989). Ozone-Induced Lung Function Changes in Normal and Asthmatic Subjects and the Effect of Indomethacin, *Studies in Environmental Science*, 35:493-499

Esther, C. R. Jr., Peden, D. B., Alexis, N. E., Hernandez, M. L. (2011). Airway purinergic responses in healthy, atopic nonasthmatic, and atopic asthmatic subjects exposed to ozone. *Inhal Toxicol*. 23(6):324-30.

Frampton, M. W., Morrow, P. E., Cox, C., Levi, P. C., Condemi, J. J., Speers, D., Gibb, F. R. Utell, M. J. (1995). Sulfuric acid aerosol followed by ozone exposure in healthy and asthmatic subjects. *Environ. Res*. 69: 1-14

Hernandez, M. L., Lay, J. C., Harris, B., Esther, C. R. Jr., Brickey, W. J., Bromberg, P. A., Diaz-Sanchez, D., Devlin, R. B., Kleeberger, S. R., Alexis, N. E., Peden, D. B. (2010). Atopic asthmatic subjects but not atopic subjects without asthma have enhanced inflammatory response to ozone. *J Allergy Clin Immunol*. 126(3):537-44.e1.

Hilterman, T. J., Stolk, J., Hiemstra, P. S., Fokkens, P. H., Rombout, P. J., Sont, J. K., Sterk, P. J., Dijkman, J. H. (1995). Effect of ozone exposure on maximal airway narrowing in non-asthmatic and asthmatic subjects. *Clinical Science*. 89:619-624

Holz, O., Jörres, R. A., Timm, P., Mücke, M., Richter, K., Koschyk, S., Magnussen, H. (1999). Ozone-induced Airway Inflammatory Changes Differ between Individuals and Are Reproducible *Am J Respir Crit Care Med*. 159:776-784

Horstman, D.H., Ball, B. A., Brown, J., Gerrity, T., Folinsbee, L. J. (1995). Comparison of pulmonary responses of asthmatic and nonasthmatic subjects performing light exercise while exposed to a low level of ozone. *Toxicology and industrial health*. 11(4):369-385

Jörres, R., Nowak, D., Magnussen, H. (1996). The effect of ozone exposure on allergen responsiveness in subjects with asthma or rhinitis. *Am J Respir Crit Care Med*. 153:56-64

Koenig, J. Q., Covert, D. S., Morgan, M. S., Horike, M., Horike, N., Marshall, S. G., Pierson, W. E. (1985). Acute effects of 0.12 ppm ozone or 0.12 ppm nitrogen dioxide on pulmonary function in healthy and asthmatic adolescents. *Am. Rev. Respir. Dis*. 132:648-651.

Koenig, J. Q., Covert, D. S., Marshall, S. G., van Belle, G., Pierson, W. E. (1987). The effects of ozone and nitrogen dioxide on pulmonary function in healthy and in asthmatic adolescents. *Am. Rev. Respir. Dis*. 136:1152-1157.

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

Koenig, J. Q., Pierson, W. E., Covert, D.S., Marshall, S.G., Morgan, M.S., van Belle G. (1988b). The effects of ozone and nitrogen dioxide on lung function in healthy and asthmatic adolescents. *Res Rep Health Eff Inst.* Jan;(14):5-24.

Kreit, J. W., Gross, K. B., Moore, T. B., Lorenzen, T. J., D'arcy, J., Eschenbacher, W. L. (1989). Ozone-induced changes in pulmonary function and bronchial responsiveness in asthmatics. *J Appl Physiol.* 66(1):217-222

Linn, W. S., Shamoo, D. A., Anderson, K. R., Peng, R.-C., Avol, E. L., Hackney, J.D. (1994). Effects of prolonged, repeated exposure to ozone, sulfuric acid, and their combination in healthy and asthmatic volunteers. *Am. J. Respir. Crit. Care Med.* 150:431-440

Magnussen, H., Nowak, D., Jorres, R. (1994). Experimental effects of air pollutants on healthy probands and asthmatic subjects. *Pneumologie.* 48(2):85-88.

McBride, D. E., Koenig, J. Q., Luchtel, D. L., Williams, P. V., Hendersson, W. L. JR. (1994). Inflammatory effects of ozone in the upper airways of subjects with asthma. *Am J Respir Crit Care Med.* 149:1192-1197

Nightingale, J.A., Rogers, D.F. and Barnes, P.J. (1999). Effect of inhaled ozone on exhaled nitric oxide pulmonary function, and induced sputum in normal and asthmatic subjects. *Thorax*, 54:1061-1069

Scannell, C., Chen, L., Aris, R. M., Tager, I., Christian, D., Ferrando, R., Welch, B., Kelly, T., Balmes, J. R. (1996). Greater ozone-induced inflammatory responses in subjects with asthma. *Am J Respir Crit Care Med.* 154: 24-29

Stenfors N, Pourazar J, Blomberg A, Krishna MT, Mudway I, Helleday R, Kelly FJ, Frew AJ and Sandström T. (2002). Effect of ozone on bronchial mucosal inflammation in asthmatic and healthy subjects. *Respir Med.* 96(5):352-8

Utell, M. J., Frampton, M. W., Morrow, P. E., Cox, C., Levy, P. C., Speers, D. M., Gibb, F.R. (1994). Oxidant and acid aerosol exposure in healthy subjects and subjects with asthma. Part II: Effects of sequential sulfuric acid and ozone exposures on the pulmonary function of healthy subjects and subjects with asthma. *Res. Rep. Health Eff. Inst.* 70:37-93

Sodium bisulfate

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

Utell, M. J., Morrow, P. E., Hyde, R. W. (1982). Comparison of Normal and Asthmatic Subjects Responses to Sulfate Pollutant Aerosols. *Ann. Occup. Hyg.* 26:691-697

Sodium nitrate

Sackner, M. A., Ford, D. (1981). Effects of breathing nitrate aerosols in high concentrations for 10 minutes on pulmonary function in normal and asthmatic adults, and preliminary results in normal exposed to nitric acid fumes. *Am Rev Resp Dis.* 123:151

Utell, M. J., Swinburne, A. J., Hyde, R. W., Speers, D. M., Gibb, F. R., Morrow, P. E. (1979). Airway reactivity to nitrates in normal and mild asthmatic subjects. *J. Applied. Physiol.* 46(1): 189-196

Sulfur dioxide

Jaeger, M. J., Tribble, D., Wittig, H. J. (1979). Effect of 0.5 ppm sulfur dioxide on the respiratory function of normal and asthmatic subjects. *Lung*. 156:119-127

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

Magnussen, H., Jorres, R., Wagner, H. M., G. von Nieding. (1990). Relationship between the airway response to inhaled sulfur dioxide, isocapnic hyperventilation, and histamine in asthmatic subjects. *Int. Arch. Occup. Environ. Health* 62(7):485-491.

Witek, T.J., Schachter, E. N., Beck, G. J., Cain, W., Colice, G., Leaderer, B. P. (1985b). Respiratory symptoms associated with sulfur dioxide exposure *Int. Arch. Occup. Environ. Health*, 55(2):179-183

Same as Witek 1985b: Schachter, E. N., Witek, T. J., Beck, G. J., Hosein, H. B., Colice, G., Leaderer, B. P., Cain, W. (1984). Airway effects of low concentrations of sulfur dioxide: Dose response characteristics. *Arch. Environ. Health* 39(1):34-42.

Sheppard, D., Wong, W. S., Uehara, C. F., Nadel, J. A., Boushey, H. A. (1980). Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Resp Dis*. 122:873-878.

Snashall, P. D., Baldwin, C. (1982). Mechanisms of sulfur dioxide induced bronchoconstriction in normal and asthmatic man. *Thorax* 37:118-123.

Tunnicliffe, W. S., Hilton, M. F., Harrison, R. M., Ayres J. G. (2001). The effect of sulphur dioxide exposure on indices of heart rate variability in normal and asthmatic adults. *Eur Respir J*. 17:604-608.

Same as Tunnicliffe et al 2001: Tunnicliffe, W. S., Harrison, R. M. Kelly F. J., Duster, C. Ayers, J. G. (2003). The effect of sulphurous air pollutant exposure on symptoms, lung function, exhaled nitric oxide, and nasal epithelial lining fluid antioxidant concentration in normal and asthmatic adults. *Occup. Environ. Med*. 60:15.

Witek, T. J., Schacter, E. N., Tosun, T., Leaderer, B. P., Beck, G. J. (1986). Controlled human studies on the pulmonary effects of indoor air pollution: experiences with sulfur dioxide and formaldehyde. *Environ. Intl*. 12:129-135.

Sulfuric acid

Anderson, K. R., Avol, E. L., Edwards, S. A., Shamoo, D. A., Peng, R.-C., Linn, W. S., Hackney, J. D. (1992). Controlled exposures of volunteers to respirable carbon and sulfuric acid. *J. Air Waste Manage. Assoc*. 42:770-776

Avol, E. L., Jones, M. P., Bailey, R. M., Chang, N. M., Kleinman, M. T., Linn, W. S., Bell, K. A., Hackney, J. D. (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., Linn, W. S., Whiteman, J. D., Whynot, J. D., Anderson, K. R., Hackney, J. D. (1988a). Short-term respiratory effects of sulfuric acid in fog: a laboratory study of healthy and asthmatic volunteers. *JAPCA* 38:258-263

Avol, E. L., Linn, W. S., Whynot, J. D., Anderson, K. R., Shamoo, D. A., Valencia, L. M., Little, D. E., Hackney, J. D. (1988b). Respiratory dose-response study of normal and asthmatic volunteers exposed to sulfuric acid aerosol in the sub-micrometer size range. *Toxicol. Ind. Health* 4(2):173-184

Frampton, M. W., Morrow, P. E., Cox, C., Levi, P. C., Condemi, J. J., Speers, D., Gibb, F. R., Utell, M. J. (1995). Sulfuric acid aerosol followed by ozone exposure in healthy and asthmatic subjects. *Environ. Res.* 69:1-14

Koenig, J. Q., Dumler, K., Rebolledo, V., Williams, P. V., Pierson, W. E. (1993). Respiratory effects of inhaled sulfuric acid on senior asthmatics and nonasthmatics. *Arch. Environ. Health* 48(3):171-175

Linn, W. S., Avol, E. L., Shamoo, D. A., Anderson, K. R., Whynot, J. D., Hackney, J. D. (1986b). Respiratory effects of "acid fog" exposure in normal and asthmatic volunteers. *Am Rev Respir Dis*, 133 (4) Suppl:A214

Linn, W. S., Shamoo, D. A., Anderson, K. R., Peng, R.-C., Avol, E. L., Hackney, J. D. (1994). Effects of prolonged, repeated exposure to ozone, sulfuric acid, and their combination in healthy and asthmatic volunteers. *Am. J. Respir. Crit. Care Med.* 150:431-440

Sackner, M. A., Ford, D., Fernandez, J., Ciple, J., Perez, D., Kwoka, M., Reinhart, M., Michaelson, E. D., Schreck, R., Wanner, A. (1978). Effects of sulfuric acid aerosol on cardiopulmonary function of dogs, sheep and humans. *Am. Rev. Resp. Dis.* 118:497

Tunnicliffe, W. S., Harrison, R. M., Kelly, F. J., Dunster, C., Ayres, J. G. (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:e15

Utell, M. J., Morrow, P. E., Hyde, R. W. (1982). Comparison of Normal and Asthmatic Subjects Responses to Sulfate Pollutant Aerosols. *Ann. Occup. Hyg.* 26:691-697

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

Utell, M. J., Frampton, M. W., Morrow, P. E. (1991). Air pollution and asthma: clinical studies with sulfuric acid aerosols. *Allergy Proc.* 12:385-388

Utell, M. J., Frampton, M. W., Morrow, P. E., Cox, C., Levy, P. C., Speers, D. M., Gibb, F. R. (1994). Oxidant and acid aerosol exposure in healthy subjects and subjects with asthma. Part II: Effects of sequential sulfuric acid and ozone exposures on the pulmonary function of healthy subjects and subjects with asthma. *Res. Rep. Health Eff. Inst.* 70:37-93

Tear gas (o-chlorobenzylidenemalonitrile)

Gutentag, P. J., Hart, J., Owens, E. J., Punte, C. L. (1960). The evaluation of CS aerosol as a riot control agent in man. Technical Report CWLR 2365, April 1960, U.S. Army Chemical Warfare Laboratories, Army Chemical Center.

Toluenediisocyanate

Baur, X. (1985) Isocyanate hypersensitivity. Final report to the International Isocyanate Institute III File No. 10349; III Project E-AB-19, Munich, Germany.

Zinc ammonium sulfate

Linn, W. S., Kleinman, M. T., Bailey, R. M., Medway, D. A., Spier, C. E., Whynot, J. D., Anderson, K. R., Hackney, J. D. (1981). Human respiratory responses to an aerosol containing zinc ammonium sulfate. *Environ Res.* 25:404-414

Mixtures

Carbon black (0.5 µm) and sulfuric acid (0.5µm)

Anderson, K. R., Avol, E. L., Edwards, S. A., Shamoo, D. A., Peng, R.-C., Linn, W. S., Hackney, J. D. (1992). Controlled exposures of volunteers to respirable carbon and sulfuric acid. *J. Air Waste Manage. Assoc.* 42:770-776

Diesel particles in ambient air (indoor, Sweden)

Stenfors, N., Nordenhäll, C., Salvi, S. S., Mudway, I., Söderberg, M., Blomberg, A., Helleday, R., Levin, J.-O., Holgate, S. T., Kelly, F.J., Frew, A. J., Sandström, T. (2004). Different airway inflammatory responses in asthmatic and healthy humans exposed to diesel. *Eur. Respir. J.* 23:82-86

Same as Stenfors et al 2004: Holgate, S.T., Sandström, T., Frew, A. J., Stenfors, N., Nordenhäll, C., Salvi, S. (2003). Health effects of acute exposure to air pollution, Part 1: Healthy and asthmatic subjects exposed to diesel exhaust. *Health effects institute research report* 112:67 pages

Environmental tobacco smoke

Dahms, T. E., Bolin, J. F., Slavin, R. G. (1981). Passive smoking. Effects on bronchial asthma. *Chest.* 80(5):530-534

Magnussen, H., Jörres, R., Oldigs, M. (1992). Effect of one hour of passive cigarette smoking on lung function and airway responsiveness in adults and children with asthma. *The clinical investigator*, 70 (3-4):368-371

Nitrogen dioxide and sulfur dioxide

Linn, W. S., Jones, M. P., Bailey, R. M., Kleinman, M. T., Spier, C. E., Fischer, D. A., Hackney, J. D. (1980). Respiratory effects of mixed nitrogen dioxide and sulfur dioxide in human volunteers under simulated ambient exposure conditions, *Environmental Research* 22(2):431-438

Ozone in ambient air

Avol, E. L., Linn, W. S., Shamoo, D. A., Venet, T. G., Hackney, J. D. (1983). Acute respiratory effects of Los Angeles smog in continuously exercising adults. *J Air Pollut Control Assoc.* 33(11):1055-1060.

Ozone and limonene

Fadeyi, M. O., Tham, K. W., Wu, W.Y. (2014). Impact of sthma, exposure period, and filters on human responses during exposure to ozone and its initiated chemistry products. *Indoor air*. doi: 10.1111/ina.12161 (e-pub ahead of print)

Ozone and nitrogen dioxide

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

Ozone and sulfur dioxide

Bell, K. A., Linn, W. S., Hazucha, M., Hackney, J. D., Bates, D. V. (1977). Respiratory Effects of Exposure to Ozone Plus Sulfur Dioxide in Southern Californians and Eastern Canadians. *Am. Ind. Hyg. Assoc. J*. 38:696-706.

Ozone, sulfur dioxide and sulfuric acid

Linn, W. S., Gong, H. G. Jr., 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* 52:179-187.

Ozone and sulfuric acid

Linn, W. S., Shamoo, D. A., Anderson, K. R., Peng, R.-C., Avol, E. L., Hackney, J. D. (1994). Effects of prolonged, repeated exposure to ozone, sulfuric acid, and their combination in healthy and asthmatic volunteers. *Am. J. Respir. Crit. Care Med*. 150:431-440

PM2.5 in urban air

Gong, H., Linn, W. S., Clark, K. W., Anderson, K. R., Sioutas, C., Alexis, N. E., Cascio, W. E., Devlin, R. B. (2008). Exposures of healthy and asthmatic volunteers to concentrated ambient ultrafine particles in Los Angeles. *Inhal toxicol*, 20:533-545

Gong, H., Linn, W. S., Terrell, S. L., Clark, K. W., Geller, M. D., Anderson, K. R., Cascio, W. E., Sioutas, C. (2004). Altered heart-rate variability in asthmatic and healthy volunteers exposed to concentrated ambient coarse particles, *Inhal toxicol*, 16: 335-343

Gong, H., Linn, W. S., Sioutas, C., Terrell, S. L., Clark, K. W., Anderson, K. R., Terrell, L. L. (2003). Controlled exposures of healthy and asthmatic volunteers to concentrated ambient fine particles in Los Angeles. *Inhal toxicol*, 15:305-325

Appendix D. The studies concerning nitrogen dioxide, ozone, sulfuric acid and sulfur dioxide (n=476).

Studies with only healthy subjects:

Nitrogen dioxide

Adams, W. C., Brookes, K. A., Schelegle, E. S. (1987). Effects of NO₂ alone and in combination with O₃ on young men and women. *J Appl Physiol.* 62(4):1698-704

Azadniv, M., Utell, M. J., Morrow, P. E., Gibb, F. R., Nichols, J., Roberts, N. J., Speers, D. M., Torres, A., Tsai, Y., Abraham, M. K., Voter, K. Z., Frampton, M. W. (1998). Effects of nitrogen dioxide exposure on human host defense *Inhalat Toxicol*, 10(6):585-601(17)

Blomberg, A., Krishna, M. T., Bocchino, V., Biscione, G. L., Shute, J. K., Kelly, F. J., Frew, A. J., Holgate, S. T., Sandström, T. (1997). The inflammatory effects of 2 ppm NO₂ on the airways of healthy subjects. *Am J Respir Crit Care Med.* 156(2 Pt 1):418-24.

Blomberg, A., Krishna, M. T., Helleday, R., Söderberg, M., Ledin, M. C., Kelly, F. J., Frew, A. J., Holgate, S. T., Sandström, T. (1999). Persistent airway inflammation but accommodated antioxidant and lung function responses after repeated daily exposure to nitrogen dioxide. *Am J Respir Crit Care Med.* 159(2):536-43.

Devlin RB, Horstman DP, Gerrity TR, Becker S, Madden MC, Biscardi F, Hatch GE, Koren HS. (1999). Inflammatory response in humans exposed to 2.0 ppm nitrogen dioxide. *Inhal Toxicol.* 11(2):89-109.

Drechsler-Parks, D. M. (1987a). Effect of nitrogen dioxide, ozone, and peroxyacetyl nitrate on metabolic and pulmonary function. *Res Rep Health Eff Inst.* (6):1-37

Drechsler-Parks, D. M., Bedi, J. F., Horvath, S. M. (1987b). Pulmonary function responses of older men and women to NO₂. *Environ Res.* 44(2):206-212.

Folinsbee, L. J., Horvath, S. M., Bedi, J. ., Delehunt, J. C. (1978). Effect of 0.62 ppm NO₂ on cardiopulmonary function in young male nonsmokers. *Environ. Res.* 15:199-205.

Frampton, M. W., Morrow, P. E., Cox, C., Gibb, R., Speers, D. M., Utell, M. (1991). Effects of nitrogen dioxide exposure on pulmonary function and airway reactivity in normal humans. *Am Rev Respir Dis* 143:522-527.

Frampton, M. W., Boscia, J., Roberts, N. J. Jr., Azadniv, M., Torres, A., Cox, C., Morrow, P. E., Nichols, J., Chalupa, D., Frasier, L. M., Gibb, F. R., Speers, D. M., Tsai, Y., Utell, M. J. (2002). Nitrogen dioxide exposure: effects on airway and blood cells. *Am J Physiol Lung Cell Mol Physiol.* 282(1):L155-165.

Same study as Kulle 1988: Goings, S. A., Kulle, T. J., Bascom, R., Sauder, L. R., Green, D. J., Hebel, J. R., Clements, M. L. (1989). Effect of nitrogen dioxide exposure on susceptibility to influenza A virus infection in healthy adults. *Am Rev Respir Dis.* 139(5):1075-1081.

Same study as Kulle 1988: Gong, H. Jr., Linn, W. S., Clark, K. W., Anderson, K. R., Geller, M. D., Sioutas, C. (2005). Respiratory responses to exposures with fine particulates and nitrogen dioxide in the elderly with and without COPD. *Inhal Toxicol.* 17(3):123-132.

Hackney, J. D., Thiede, F. C., Linn, W. S., Pedersen, E. E., Spier, C. E., Law, D. C., Fischer, D. A. (1978). Experimental studies on human health effects of air pollutants. IV. Short-term physiological and clinical effects of nitrogen dioxide exposure. *Arch Environ Health*. 33(4):176-180.

Hazucha, M. J., Folinsbee, L. J. Seal, E., Bromberg, P.A. (1994). Lung function response of healthy women after sequential exposures to NO₂ and O₃. *Am. J. Respir. Crit. Care Med.* 150:642-647.

Helleday, R., Sandström, T., Stjernberg, N. (1994). Differences in bronchoalveolar cell response to nitrogen dioxide exposure between smokers and nonsmokers. *Eur Respir J*. 7(7):1213-1220.

Helleday, R., Huberman, D., Blomberg, A., Stjernberg, N., Sandström, T. (1995). Nitrogen dioxide exposure impairs the frequency of the mucociliary activity in healthy subjects. *Eur Respir J*. 8(10):1664-1668.

Huang, Y-C.T., Rappold, A. G., Graff, D. W., Ghio, A. J., Devlin, R. B. (2012). Synergistic effects of exposure to concentrated ambient fine pollution particles and nitrogen dioxide in humans. *Inhal. Toxicol.* 24(12):790-797

Kagawa, J. J. (1983). Respiratory effect of two-hour exposure with intermittent exercise to ozone, sulfur dioxide and nitrogen dioxide alone and in combination in normal subjects. *Am. Ind. Hyg. Assoc.* 44(1): 14-20.

Kelly FJ, Blomberg A, Frew A, Holgate ST, Sandstrom T. (1996). Antioxidant kinetics in lung lavage fluid following exposure of humans to nitrogen dioxide. *Am J Respir Crit Care Med.* 154(6 Pt 1):1700-1705.

Kim, S. U., Koenig, J. Q., Pierson, W. E., Hanley, Q. S. (1991). Acute pulmonary effects of nitrogen dioxide exposure during exercise in competitive athletes. *Chest*. 99(4):815-819.

Kulle, T. J., Clements M. L. (1988). Susceptibility to virus infection with exposure to nitrogen dioxide. *Res Rep Health Eff Inst.* (15):5-21

Mohsenin, V., Gee, J. B. L. (1987). Acute effect of nitrogen dioxide exposure on the functional activity of alpha-1-protease inhibitor in bronchoalveolar lavage fluid of normal subjects. *Am. Rev. Respir. Dis.* 136:646-650.

Mohsenin, V. (1988). Airway responses to 2.0 ppm nitrogen dioxide in normal subjects. *Arch Environ Health*. 43(3):242-246.

Morrow, P. E., Utell, M. J., Bauer, M. A., Smeglin, A. M., Frampton, M. W., Cox, C., Speers, D. M., Gibb, F. R. (1992). Pulmonary performance of elderly normal subjects and subjects with chronic obstructive pulmonary disease exposed to 0.3 ppm nitrogen dioxide. *Am Rev Respir Dis.* 145(2 Pt 1):291-300

Pathmanathan, S, Krishna, M., Blomberg, A., Helleday, R., Kelly, F., Sandstrom, T., Holgate, S., Wilson, S., Frew, A. (2003). Repeated daily exposure to 2 ppm nitrogen dioxide

upregulates the expression of IL-5, IL-10, IL-13, and ICAM-1 in the bronchial epithelium of healthy human airways. *Occup Environ Med.* 60(11): 892–896

Posin, C., Buckley, R. D., Clark, K., Hackney, J. D., Jones, M. P., Patterson, J. V. (1978). Nitrogen dioxide inhalation and human blood biochemistry. *Arch Environ Health.* 33(6):318-324

Rubinstein, I., Reiss, T. F., Bigby, B. G., Stites, D. P., Boushey, H. A. Jr. (1991). Effects of 0.60 PPM nitrogen dioxide on circulating and bronchoalveolar lavage lymphocyte phenotypes in healthy subjects. *Environ Res.* 55(1):18-30.

Sandström, T., Stjernberg, N., Eklund, A., Ledin, M. C., Bjermer, L., Kolmodin-Hedman, B., Lindström, K., Rosenhall, L., Angström, T. (1991). Inflammatory cell response in bronchoalveolar lavage fluid after nitrogen dioxide exposure of healthy subjects: a dose-response study. *Eur Respir J.* 4(3):332-339.

Sandström, T., Helleday, R., Bjermer, L., Stjernberg, N. (1992) Effects of repeated exposure to 4 ppm nitrogen dioxide on bronchoalveolar lymphocyte subsets and macrophages in healthy men. *Eur Respir J.* 5(9):1092-1096.

Stacy, R. W., Seal, E. Jr., House, D. E., Green, J., Roger, L. J., Raggio, L. (1983). A survey of effects of gaseous and aerosol pollutants on pulmonary function of normal males. *Arch Environ Health.* 38(2):104-115

Toyama, T., Tsunoda, T., Nakaza, M., Higashi, T., Nakadate, T. (1981). [Airway response to short-term inhalation of NO₂, O₃ and their mixture in healthy men (Authors translation)] *Sangyo Igaku.* 23(3):285-293.

von Niding, G., Krekeler, H., Fuchs, R., Wagner, M., Koppenhagen, K. (1973). Studies of the acute effects of NO₂ on lung function: influence on diffusion, perfusion and ventilation in the lungs. *Int Arch Arbeitsmed.* 31(1):61-72.

Von Niding, G., Wagner, H. M., Casper, H., Beuthan, A., Smidt, U. (1980). Effect of experimental and occupational exposure to NO₂ in sensitive and normal subjects. In nitrogen Oxides and Their Effects on Health, ed. S.D. Lee, Ann Arbor Michigan: *Ann Arbor Science*, 215-331

von Niding, G., Wagner, H. M., Krekeler, H., Löllgen, H., Fries, W., Beuthan, A. (1979). Controlled studies of human exposure to single and combined action of NO₂, O₃, and SO₂. *Int Arch Occup Environ Health.* 15:43(3):195-210.

Yokoyama, E. (1968). Effects of acute controlled exposure to NO₂ on mechanics of breathing in healthy subjects. *Bull Inst Public Health.* 17(4):337-346.

Ozone

Adams, W. C. (2002). Comparison of chamber and face-mask 6.6-hr exposures to ozone on pulmonary function and symptoms responses. *Inhalation Toxicol.* 14: 745-764.

Adams, W. C. (2003a). Comparison of chamber and face mask 6.6-hr exposure to 0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. *Inhalation Toxicol.* 15:265-281.

Adams, W. C. (2006). Comparison of chamber 6.6 h exposures to 0.04-0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. *Inhalation Toxicol.* 18:127-136.

Adams, W. C., Savin, W. M., Christo, A. E. (1981). Detection of ozone toxicity during continuous exercise via the effective dose concept. *J Appl Physiol.* 51(2):415-422

Adams, W. C., Schelegle, E. S. (1983). Ozone and high ventilation effects on pulmonary function and endurance performance. *J Appl Physiol.* 55(3):805-812.

Adams, W. C., Brookes, K. A., Schelegle, E.S. (1987). Effects of NO₂ alone and in combination with O₃ on young men and women. *J Appl Physiol.* 62(4):1698-1704

Alexis, N. E., Lay J. C., Hazucha, M., Harris, B., Hernandez, M.L., Bromberg, P.A., Kehrl, H., Diaz-Sanchez, D., Kim, C., Devlin, R. B., Peden, D. B. (2010). Low-level ozone exposure induces airways inflammation and modifies cell surface phenotypes in healthy humans. *Inhal Toxicol.* 22(7):593-600.

Avol, E. L., Linn, W. S., Shamoo, D. A., Spier, C. E., Valencia, L. M., Venet, T. G., Trim, S. C., Hackney, J. D. (1987). Short-term respiratory effects of photochemical oxidant exposure in exercising children. *JAPCA.* 37(2):158-162.

Avol, E. L., Linn, W. S., Peng, R. C., Valencia, G., Little, D., Hackney, J. D. (1988). Laboratory study of asthmatic volunteers exposed to nitrogen dioxide and to ambient air pollution. *Am Ind Hyg Assoc J.* 49(4):143-149

Avol, E. L., Linn, W. S., Shamoo, D. A., Valencia, L. M., Anzar, U. T., Venet, T. G., Hackney, J. D. (1985). Respiratory effects of photochemical oxidant air pollution in exercising adolescents. *Am Rev Respir Dis.* 132(3):619-622.

Avol, E. L., Linn, W. S., Venet, T. G., Shamoo, D. A., Hackney, J. D. (1984). Comparative respiratory effects of ozone and ambient oxidant pollution exposure during heavy exercise. *J Air Pollut Control Assoc.* 34(8):804-809.

Balmes, J. R., Chen, L. L., Scannell, C., Tager, I., Christian, D., Hearne, P. Q., Kelly, T., Aris, R. M. (1996). Ozone-induced decrements in FEV₁ and FVC do not correlate with measures of inflammation. *Am J Respir Crit Care Med.* 153(3):904-909.

Barath, S., Mills, N. L., Ädelroth, E., Olin, A-C., Blomberg, A. (2013). Diesel exhaust but not ozone increases fraction of exhaled nitric oxide in a randomized controlled experimental exposure study of healthy human subjects. *Environ. Health* 12:36

Bates, D. V., Bell, G. M., Burnham, C. D., Hazucha, M., Mantha, J., Pengelly, L. D., Silverman, F. (1972). Short-term effects of ozone on the lung. *J Appl Physiol.* 32(2):176-181.

Bates, D. V., Hazucha, M. J. (1973). The short-term effects of ozone on the human lung. In: proceedings of the conference on health effects of air pollutants. *Washington, DC: US Govt. Printing office.* pp 507-540

Bedi, J. F., Horvath, S. M., Folinsbee, L. J. (1982). Human exposure to sulfur dioxide and ozone in a high temperature-humidity environment. *Am Ind Hyg Assoc J.* 43(1):26-30.

Bedi, J.F., Horvath, S.M., Drechsler-Parks, D.M. (1989). Adaptation by older individuals repeatedly exposed to 0.45 parts per million ozone for two hours. *JAPCA.* 39(2):194-199.

Bedi, J. F., Horvath, S. M. (1987). Longitudinal case study of pulmonary function response to ozone. *The American journal of medicine,* 82(4):860.

Bedi, J. F., Horvath, S. M., Drechsler-Parks, D. M. (1988). Reproducibility of the pulmonary function response of older men and women to a 2-hour ozone exposure. *JAPCA.* 38(8):1016-1019.

Bennett, W. D., Hazucha, M. J., Folinsbee, L. J., Bromberg, P. A., Kissling, G. E., London, S. J. (2007). Acute pulmonary function response to ozone in young adults as a function of body mass index. *Inhal Toxicol.* 19(14):1147-1154.

Bromberg, P. A., Koren, H. S. (1995). Ozone-induced human respiratory dysfunction and disease. *Toxicol Lett.* 82-83:307-316

Bush, M. L., Asplund, P. T., Miles, K.A., Ben-Jebria, A., Ultman, J.S.. (1996). Longitudinal distribution of O₃ absorption in the lung: gender differences and intersubject variability. *J. Appl. Physiol* 81:1651-1657

Devlin, R. B., McDonnell, W. F., Becker, S., Madden, M. C., McGee, M. P., Perez, R., Hatch, G., House, D. E., Koren, H. S. (1996). Time-dependent changes of inflammatory mediators in the lungs of humans exposed to 0.4 ppm ozone for 2 hr: a comparison of mediators found in bronchoalveolar lavage fluid 1 and 18 hr after exposure. *Toxicol Appl Pharmacol.* 138(1):176-185.

Drechsler-Parks, D. M. (1987a). Effect of nitrogen dioxide, ozone, and peroxyacetyl nitrate on metabolic and pulmonary function. *Res Rep Health Eff Inst.* (6):1-37

Drechsler-Parks, D. M., Horvath, S. M., Bedi, J. F. (1990). The "effective dose" concept in older adults exposed to ozone. *Exp Gerontol.* 25(2):107-115

Drechsler-Parks, D. M., Bedi, J. F., Horvath, S. M. (1987c). Pulmonary function responses of older men and women to ozone exposure. *Exp Gerontol.* 22(2):91-101.

Drechsler-Parks, D. M., Bedi, J. F., Horvath, S. M. (1989). Pulmonary function responses of young and older adults to mixtures of O₃, NO₂ and PAN. *Toxicol Ind Health.* 5(3):505-517.

Drechsler-Parks, D. M. (1995b). Cardiac output effects of O₃ and NO₂ exposure in healthy older adults. *Toxicol Ind Health.* 11(1):99-109.

Farrell, B. P., Kerr, H. D., Kulle, T. J., Sauder, L. R., Young, J. L. (1979). Adaptation in human subjects to the effects of inhaled ozone after repeated exposure. *Am Rev Respir Dis.* 119(5):725-730.

Folinsbee, L. J., McDonnell, W. F., Horstman, D. H. (1988). Pulmonary function and symptom responses after 6.6-hr exposure to 0.12 ppm ozone with moderate exercise. *JAPCA* 38: 28-35.

Folinsbee, L. J., Horstman, D. H., Kehrl, H. R., Harder, S., Abdul-Salaam, S., Ives, P. J. (1994). Respiratory responses to repeated prolonged exposure to 0.12 ppm ozone. *Am. J. Respir. Crit. Care Med.* 149: 98-105.

Folinsbee, L. J., Bedi, J. F., Horvath S. M. (1980). Respiratory responses in humans repeatedly exposed to low concentrations of ozone. *Am Rev Respir Dis.* 121(3):431-9.
Folinsbee LJ, Horvath SM. (1986). Persistence of the acute effects of ozone exposure. *Aviat Space Environ Med.* 57(12 Pt 1):1136-1143.

Folinsbee, L. J., Bedi, J. F., Horvath, S. M. (1984). Pulmonary function changes after 1 h continuous heavy exercise in 0.21 ppm ozone. *J Appl Physiol.* 57(4):984-988.

Folinsbee, L. J., Horvath, S. M., Raven, P. B., Bedi, J. F., Morton, A. R., Drinkwater, B. L., Bolduan, N. W., Gliner, J. A. (1977a). Influence of exercise and heat stress on pulmonary function during ozone exposure. *J Appl Physiol.* 43(3):409-413.

Folinsbee LJ, Silverman F, Shepard RJ. (1977b). Decrease of maximum work performance following ozone exposure. *J Appl Physiol.* 42(4):531-536.

Folinsbee, L. J., Bedi, J. F., Horvath, S. M. (1985). Pulmonary response to threshold levels of sulfur dioxide (1.0 ppm) and ozone (0.3 ppm). *J Appl Physiol.* 58(6):1783-1787.

Folinsbee, L. J., Silverman, F., Shephard, R. J. (1975). Exercise responses following ozone exposure. *J Appl Physiol.* 38(6):996-1001.

Folinsbee, L. J., Drinkwater, B.L., Bedi J.F., Horvath, S.M. (1978). The influence of exercise on the pulmonary function changes due to exposure to low concentration of ozone. In: environmental stress: Individual human adaptations, edited by L.J. Folinsbee, J.A. Wagner, J.F. Borgia, B.L. Drinkwater, J.A. Gliner, and J.F. Bedi, New York: Academic, 125-145

Folinsbee, L. J., Horstman, D. H., Kehrl, H. R., Harder, S., Abdul-Salaam, S., Ives, P. J. (1994). Respiratory responses to repeated prolonged exposure to 0.12 ppm ozone. *Am J Respir Crit Care Med.* 149(1):98-105.

Folinsbee, L. J., Horstman, D. H., Kehrl, H. R. (1991). Effects of single and repeated prolonged low-level ozone exposure in man. *Society for Occupational and Environmental Health on Health effects of air pollution: Impact of clean air legislation*, 42-43.

Folinsbee, L. J., Hazucha, M. J. (2000). Time course of response to ozone exposure in healthy adult females. *Inhal Toxicol.* 12(3):151-167.

- Foster, W. M., Silver, J. A., Groth, M. L. (1993). Exposure to ozone alters regional function and particle dosimetry in the human lung. *J. Appl. Physiol.* 75: 1938-1945.
- Foster, W. M., Weinmann, G. G., Menkes, E., Macri, K. (1997). Acute exposure of humans to ozone impairs small airway function. *Ann. Occup. Hyg.* 41(suppl. 1): 659-666.
- Foster, W. M., Brown, R. H., Macri, K., Mitchell, C. S. (2000). Bronchial reactivity of healthy subjects: 18-20 h postexposure to ozone. *J Appl Physiol.* 89(5):1804-1810
- Frampton, M. W., Morow, P. E., Gibb, F. R., Speers, D. M., Gavras, J. B., Utell, M. J. (1993). Airways responsiveness to ozone in smokers and nonsmokers. *Am. Rev. Respir. Dis.* 147:A636.
- Frampton, M. W., Morrow, P. E. Torres, A. Cox, C. Voter, K. Z., Utell, M. J. (1997). Ozone responsiveness in smokers and nonsmokers. *Am. J. Respir. Crit. Care Med.* 155:116-121.
- Frampton, M. W., Morrow, P. E., Torres, A., Voter, K. Z., Whitin, J. C., Cox, C., Speers, D. M., Tsai Y., Utell, M. J. (1997b). Effects of ozone on normal and potentially sensitive human subjects. Part II: Airway inflammation and responsiveness to ozone in nonsmokers and smokers. *Res Rep Health Eff Inst.* (78):39-72; discussion 81-99.
- Gerrity, T. R., McDonnell, W. F., House, D. E. (1994). The relationship between delivered ozone dose and functional responses in humans. *Toxicol Appl Pharmacol.* 124(2):275-283.
- Gibbons, S. I., Adams, W. C. (1984). Combined effects of ozone exposure and ambient heat on exercising females. *J Appl Physiol.* 57(2):450-456.
- Gliner, J. A., Horvath, S. M., Folinsbee, L. J. (1983). Preexposure to low ozone concentrations does not diminish the pulmonary function response on exposure to higher ozone concentrations. *Am Rev Respir Dis.* 127(1):51-55.
- Gong, H. Jr., Bradley, P. W., Simmons, M. S., Tashkin, D. P. (1986). Impaired exercise performance and pulmonary function in elite cyclists during low-level ozone exposure in a hot environment. *Am Rev Respir Dis.* 134(4):726-733.
- Gong, H. Jr., Bedi, J. F., Horvath, S. M. (1988). Inhaled albuterol does not protect against ozone toxicity in nonasthmatic athletes. *Arch Environ Health.* 43(1):46-53.
- Gong, H., Shamoo, D. A., Anderson, K. R., Linn, W.S. (1997). Responses of older men with and without chronic obstructive pulmonary disease to prolonged ozone exposure. *Arch Environ Health* 52:18-25.
- Haak, E. D., Hazucha, M.J., Stacy, R. W., House, D.E., Hetcham, B.T., Seal, E., Roger L.J., Knelson, J.H. (1984). Pulmonary effects in healthy young men of four sequential exposures to ozone. *Cincinnati, OH: EPA, (Publ. EPA-600/X-84-033)*
- Hackney, J. D., Linn, W. S., Mohler, J. G., Collier, C. R. (1977b). Adaptation to short-term respiratory effects of ozone in men exposed repeatedly. *J Appl Physiol.* 43(1):82-85.

Hackney, J. D., Linn, W. S., Mohler, J. G., Pedersen, E. E., Breisacher, P., Russo, A. (1975a). Experimental studies on human health effects of air pollutants. II. Four-hour exposure to ozone alone and in combination with other pollutant gases. *Arch Environ Health*. 30(8):379-384.

Same study as 1975a: Hackney, J. D., Linn, W. S., Law, D. C., Karuza, S. K., Greenberg, H, Buckley, R. D., Pedersen, E. E. (1975b). Experimental studies on human health effects of air pollutants. III. Two-hour exposure to ozone alone and in combination with other pollutant gases. *Arch Environ Health*. 30(8):385-390.

Hackney, J. D., Linn, W. S., Karuza, S. K., Buckley, R. D., Law, D. C., Bates, D. V., Hazucha, M., Pengelly, D., Silverman, F. (1977). Effects of ozone exposure in Canadians and Southern Californians. Evidence for adaptation? *Arch Environ Health*. 32(3):110-116.

Hackney, J. D., Linn, W. S., Buckley, R. D., Hislop, H. J. (1976). Studies in adaption to ambient oxidant air pollution: effects of ozone exposure in Los Angeles residents vs. new arrivals. *Environ Health Perspect*. 18:141-146.

Hatch, G.E., McKee, J., Brown, J., McDonnell, W., Seal, E., Soukup, J., Slade, R., Crissman, K., Devlin, R. (2013). Biomarkers of dose and effect of inhaled ozone in resting versus exercising human subjects: comparison with resting rats. *Biomarker insights*, 8:53-67

Hazucha, M. J., Folinsbee, L. J., Bromberg, P. A. (2003). Distribution and reproducibility of spirometric response to ozone by gender and age. *J Appl Physiol*. 95(5):1917-1925.

Hazucha, M. (1981). Assessment of ozone induced hyperreactivity by histamine in normal healthy subjects. In: proceedings of the research planning workshop on health effects of oxidants, edited by Northrop, *Cincinnati, OH: EPA, (Publ. EPA-600/9-81-001)* p. 314-327.

Hazucha, M. J. (1973). Effects of ozone and sulfur dioxide on pulmonary function in man (PhD thesis). *Montreal, Canada: McGill Univ*.

Hazucha, M., Parent, C., Bates, D.V.. (1977). Development of ozone tolerance in man. In: Proceedings of the international conference on photochemical oxidant pollution and its control, edited by B. Dimitriades. *Cincinnati, OH: EPA, (Publ., EPA-600/3-77-001a)* 1, 527-541.

Hazucha, M. J., Folinsbee, L.J., Seal, E., Bromberg, P.A. (1994). Lung function response of healthy women after sequential exposures to NO₂ and O₃. *Am. J. Respir. Crit. Care Med*. 150:642-647.

Hazucha, M. J., Folinsbee, L. J., Seal, E. Jr. (1992). Effects of steady-state and variable ozone concentration profiles on pulmonary function. *Am. Rev. Respir. Dis*. 146: 1487-1493.

Hazucha, M. J., Bates, D. V., Bromberg, P. A. (1989). Mechanism of action of ozone on the human lung. *J Appl Physiol*. 67(4):1535-1541.

Hazucha, M., Silverman, F., Parent, C., Field, S., Bates, D. V. (1973b). Pulmonary function in man after short-term exposure to ozone. *Arch Environ Health*. 27(3):183-188.

Hernandez, M. L., Harris, B., Lay, J. C., Bromberg, P. A., Diaz-Sanchez, D., Devlin, R. B., Kleeberger, S. R., Alexis, N. E., Peden, D. B. (2010a). Comparative airway inflammatory response of normal volunteers to ozone and lipopolysaccharide challenge. *Inhal Toxicol.* 22(8):648-656.

Holtzman, M. J., Cunningham, J. H., Sheller, J. R., Irsigler, G. B., Nadel, J. A., Boushey, H. A. (1979). Effect of ozone on bronchial reactivity in atopic and nonatopic subjects. *Am Rev Respir Dis.* 120(5):1059-1067.

Horstman, D. H., Folinsbee, L. J., Ives, P. J., Abdul-Salaam, S., McDonnell, W. F. (1990). Ozone concentration and pulmonary response relationships for 6.6-hr exposures with five hrs of moderate exercise to 0.08, 0.10, and 0.12 ppm. *Am. Rev. Respir. Dis.* 142: 1158-1163.

Horstman, D., McDonnell, W., Folinsbee, L. J., Abdul-Salaam, S., Ives, P. (1989). Changes in pulmonary function and airway reactivity due to prolonged exposure to typical ambient ozone (O_3) levels. Atmospheric Ozone Research and Its Policy Implications, Schneider, T., Lee, S.D., Wolters, G.J.R., Grant, L.D. Eds., Elsevier, New York, pp 755-762

Horvath, S. M., Gliner, J. A., Folinsbee, L. J. (1981). Adaptation to ozone: duration of effect. *Am Rev Respir Dis.* 123(5):496-499.

Horvath, S. M., Gliner, J. A., Matsen-Twisdale, J. A. (1979). Pulmonary function and maximum exercise responses following acute ozone exposure. *Aviat Space Environ Med.* 50(9):901-905.

Horvath, S. M., Folinsbee, L. J., Bedi, J. F. (1987). Combined effect of ozone and sulfuric acid on pulmonary function in man. *Am Ind Hyg Assoc J.* 48(2):94-98.

Kagawa, J., Tsuru, K. (1979). Respiratory effects of 2-hour exposure to ozone and nitrogen dioxide alone and in combination in normal subjects performing intermittent exercise (authors translation). *Nippon Kyou Shikkan, Gakkai Zasshi* 17:765-774

Kagawa, J. (1983). Respiratory effect of two-hour exposure with intermittent exercise to ozone, sulfur dioxide and nitrogen dioxide alone and in combination in normal subjects. *Am. Ind. Hyg. Assoc.* 44(1):14-20.

Kagawa, J. (1984). Exposure-effect relationship of selected pulmonary function measurements in subjects exposed to ozone. *Int Arch Occup Environ Health.* 53(4):345-358.

Kerr, H. D., Kulle, T. J., McIlhany, M. L., Swidersky, P. (1975). Effects of ozone on pulmonary function in normal subjects. An environmental-chamber study. *Am Rev Respir Dis.* 111(6):763-773.

Ketcham, B., Lassiter, S., Haak, E., Knelson, J. H. (1977). Effects of ozone plus moderate exercise on pulmonary function in healthy young men. In: proceedings of the international conference on photochemical oxidants pollution and its control, edited by B. Dimitriadis. Cincinnati, OH: EPA, (Publ. EPA-600/3-77-001a) 1:495-504

Kim, C. S., Alexis, N. E., Rappold, A. G., Kehrl, H., Hazucha, M. J., Lay, J. C., Schmitt, M. T., Case, M., Devlin, R. B., Peden, D. B., Diaz-Sanchez, D. (2011). Lung function and

inflammatory responses in healthy young adults exposed to 0.06 ppm ozone for 6.6 hours. *Am J Respir Crit Care Med.* 183(9):1215-1221.

Koren, H. S., Devlin, R. B., Graham, D. E., Mann, R., McGee, M. P., Horstman, D. H., Kozumbo, W. J., Becker, S., House, D. E., McDonnell, W. F., Bromberg, P. A. (1989). Ozone-induced inflammation in the lower airways of human subjects. *Am Rev Respir Dis.* 139(2):407-415.

Koren, H. S., Devlin, R. B., Becker, S., Perez, R., McDonnell, W. F. (1991). Time-dependent changes of markers associated with inflammation in the lungs of humans exposed to ambient levels of ozone. *Toxicol Pathol.* 19(4 Pt 1):406-411.

Kulle, T. J., Sauder, L. R., Hebel, J. R., Chatham, M. D. (1985). Ozone response relationships in healthy nonsmokers. *Am Rev Respir Dis.* 132(1):36-41.

Kulle, T. J., Sauder, L. R., Kerr, H. D., Farrell, B. P., Bermel, M. S., Smith, D. M. (1982a). Duration of pulmonary function adaptation to ozone in humans. *Am Ind Hyg Assoc J.* 43(11):832-837.

Kulle, T. J., Kerr, H. D., Farrell, B. P., Sauder, L. R., Bermel, M. S. (1982b). Pulmonary function and bronchial reactivity in human subjects with exposure to ozone and respirable sulfuric acid aerosol. *Am Rev Respir Dis.* 126(6):996-1000.

Uses data from Horstman 89: Larsen, R. I., McDonnell, W. F., Horstman, D. H., Folinsbee, L. J. (1991). An air quality data analysis system for interrelating effects, standards, and needed source reductions: Part 11. A lognormal model relating human lung function decrease to O₃ exposure. *J Air Waste Manage Assoc.* 41(4):455-459.

Lauritzen, S. K., Adams, W. C. (1985). Ozone inhalation effects consequent to continuous exercise in females: comparison to males. *J Appl Physiol.* 59(5):1601-1606.

Lay, J. C., Alexis, N. E., Kleeberger, S. R., Roubey, R. A., Harris, B. D., Bromberg, P. A., Hazucha, M. J., Devlin, R. B., Peden, D. B. (2007). Ozone enhances markers of innate immunity and antigen presentation on airway monocytes in healthy individuals. *J Allergy Clin Immunol.* 120(3):719-722.

Linder, J., Herren, D., Monn, C., Wanner, H. U. (1988). [Effect of ozone on physical performance]. [Article in German] *Schweiz Z Sportmed.* 36(1):5-10.

Linn, W. S., Avol, E. L., Shamoo, D. A., Peng, R. C., Valencia, L. M., Little, D. E., Hackney, J. D. (1988). Repeated laboratory ozone exposures of volunteer Los Angeles residents: an apparent seasonal variation in response. *Toxicol Ind Health.* 4(4):505-520.

Linn, W. S., Medway, D. A., Anzar, U. T., Valencia, L. M., Spier, C. E., Tsao, F. S., Fischer, D. A., Hackney, J. D. (1982). Persistence of adaptation to ozone in volunteers exposed repeatedly for six weeks. *Am Rev Respir Dis.* 125(5):491-495.

Linn, W.S., Fischer, D.A., Medway, D.A., Anzar, U.T., Spier, C.E., Balencia, L.M., Venet, T.G., Hackney, J.D. (1982). Short-term respiratory effects of 0.12 ppm ozone exposure in volunteers with chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* 125:658-663.

Linn, W. S., Avol, E. L., Shamoo, D. A., Spier, C. E., Valencia, L. M., Venet, T. G., Fischer, D. A., Hackney, J. D. (1986). A dose-response study of healthy, heavily exercising men exposed to ozone at concentrations near the ambient air quality standard. *Toxicol Ind Health*. 2(1):99-112.

Liu, L. J., Olson, M. P., Allen, G. A., Koutrakis, P., McDonnell, W. F., Gerrity, T. R. (1994). Evaluation of the harvard ozone passive sampler on human subjects indoors. *Environ Sci Technol*. 28(5):915-923.

McDonnell, W. F., Kehrl, H. R., Abdul-Salaam, S., Ives, P. J., Folinsbee, L. J., Devlin, R. B., O'Neil, J. J., Horstman, D. H. (1991). Respiratory response of humans exposed to low levels of ozone for 6.6 hours. *Arch Environ Health*. 46(3):145-150.

McDonnell, W. F., Stewart, P. W., Andreoni, S., Seal, E., Jr., Kehrl, H. R., Horstman, D. H., Folinsbee, L. J., Smith, M. V. (1997). Prediction of ozone-induced FEV1 changes: effects of concentration, duration, and ventilation. *Am. J. Respir. Crit. Care Med*. 156:715-722.

McDonnell, W. F., Horstman, D. H., Hazucha, M. J., Seal, E. Jr., Haak, E. D., Salaam, S. A., House, D. E. (1983). Pulmonary effects of ozone exposure during exercise: dose-response characteristics. *J Appl Physiol*. 54(5):1345-1352.

McDonnell, W. F. 3rd, Horstman, D. H., Abdul-Salaam, S., House, D. E. (1985a). Reproducibility of individual responses to ozone exposure. *Am Rev Respir Dis*. 131(1):36-40.

McDonnell, W. F. 3rd, Chapman, R. S., Leigh, M. W., Strope, G. L., Collier, A. M. (1985b). Respiratory responses of vigorously exercising children to 0.12 ppm ozone exposure. *Am Rev Respir Dis*. 132(4):875-879.

McDonnell, W.F., Horstman, D. H., Abdul-Salaam, S., Raggio, L. J., Green J. A. (1987). The respiratory responses of subjects with allergic rhinitis to ozone exposure and their relationship to nonspecific airway reactivity. *Toxicol Ind Health*. 3(4):507-517.

McDonnell, W. F., Stewart, P. W., Smith, M. V. (2007). The temporal dynamics of ozone-induced FEV1 changes in humans: an exposure-response model. *Inhal Toxicol*. 19(6-7):483-494.

McDonnell, W. F., Stewart, P. W., Smith, M. V., Pan, W. K., Pan, J. (1999). Ozone-induced respiratory symptoms: exposure-response models and association with lung function. *Eur Respir J*. 14(4):845-853.

McDonnell, W. F., Stewart, P. W., Andreoni, S., Smith, M. V. (1995). Proportion of moderately exercising individuals responding to low-level, multi-hour ozone exposure. *Am J Respir Crit Care Med*. 152(2):589-596.

McDonnell, W.F, Smith, M. V. (1994). Description of acute ozone response as a function of exposure rate and total inhaled dose. *J Appl Physiol*. 76(6):2776-2784.

Messineo, T. D., Adams, W. C. (1990). Ozone inhalation effects in females varying widely in lung size: comparison with males. *J Appl Physiol*. 69(1):96-103.

Reeser, W. H., Lee, G. M., Taylor, A., Wang, L., Arnold, S. F., Ultman, J. S., Ben-Jebria, A. (2005). Uptake of ozone in human lungs and its relationship to local physiological response. *Inhal Toxicol.* 17(13):699-707

Reisenauer, C. S., Koenig, J. Q., McManus, M. S., Smith, M. S., Kusic, G., Pierson, W. E. (1988). Pulmonary response to ozone exposures in healthy individuals aged 55 years or greater. *JAPCA.* 38(1):51-55.

Schelegle, E. S., Adams, W. C. (1986). Reduced exercise time in competitive simulations consequent to low level ozone exposure. *Med Sci Sports Exerc.* 18(4):408-414.

Schelegle, E. S., Adams, W. C., Siefkin, A. D. (1987). Indomethacin pretreatment reduces ozone-induced pulmonary function decrements in human subjects. *Am Rev Respir Dis.* 136:1350-1354

Schelegle, E. S., Morales, C. A., Walby, W. F., Marion, S., Allen, R. P. (2009). 6.6-hour of ozone concentrations from 60 to 87 parts per billion in healthy humans. *Am J Respir Crit Care Med.* 180(3):265-272.

Schelegle, E. S., Walby, W. F., Adams, W. C. (2007). Time course of ozone-induced changes in breathing pattern in healthy exercising humans. *J Appl Physiol.* 102(2):688-697.

Schelegle, E. S., Adams, W. C., Giri, S. N., Siefkin, A. D. (1989). Acute ozone exposure increases plasma prostaglandin F₂ alpha in ozone-sensitive human subjects. *Am Rev Respir Dis.* 140(1):211-216.

Schelegle, E. S., Eldridge, M. W., Cross, C. E., Walby, W. F., Adams, W. C. (2001). Differential effects of airway anesthesia on ozone-induced pulmonary responses in human subjects. *Am J Respir Crit Care Med.* 163(5):1121-1127.

Seal, E., McDonnell, W.F., House, D.E. (1996). Effects of age, socioeconomic status, and menstrual cycle on pulmonary response to ozone. *Arch. Environ. Health* 51:132-137.

Seal, E. Jr., McDonnell, W. F., House, D. E., Salaam, S. A., Dewitt, P. J., Butler, S. O, Green J., Raggio, L. (1993). The pulmonary response of white and black adults to six concentrations of ozone. *Am Rev Respir Dis.* 147(4):804-810.

Seltzer, J., Bigby, B. G., Stulbarg, M., Holtzman, M. J., Nadel, J. A., Ueki, I. F., Leikauf, GD, Goetzel, E. J., Boushey, H. A. (1986). O₃-induced change in bronchial reactivity to methacholine and airway inflammation in humans. *J Appl Physiol.* 60(4):1321-1326.

Shephard, R. J., Urch, B., Silverman, F., Corey, P. N. (1983). Interaction of ozone and cigarette smoke exposure. *Environ Res.* 31(1):125-137.

Silverman, F., Shephard, R.J., Folinsbee, L. (1977). Effect of physical activity on lung responses to acute ozone exposure. In proceedings of the 4th international clean air congress, edited by S. Kasuga, N Suzuki, T.Yamada, G.Kimura, K.Imagaki and M. Onoi. *Tokyo, Publ. JUAPPA*, 15-19

Stacy, R. W., Seal, E. Jr., House, D. E., Green, J., Roger, L. J., Raggio, L. (1983). A survey of effects of gaseous and aerosol pollutants on pulmonary function of normal males. *Arch Environ Health*. 38(2):104-115.

Torres, A., Utell, M. J., Morow, P. E., Voter, K. Z., Whitin, J. C., Cox, C., Looney, R. J., Speers, D. M., Tsai, Y., Frampton, M. W. (1997). Airway inflammation in smokers and nonsmokers with varying responsiveness to ozone. *Am J Respir Crit Care Med*. 156(3 Pt 1):728-736.

Toyama, T., Tsunoda, T., Nakaza, M., Higashi, T., Nakadate, T. (1981). [Airway response to short-term inhalation of NO₂, O₃ and their mixture in healthy men (Authors translation)] *Sangyo Igaku*. 23(3):285-293.

Ultman, J. S., Ben-Jebria, A., Arnold, S. F. (2004). Uptake distribution of ozone in human lungs: intersubject variability in physiologic response. *Boston, MA: Health Effects Institute*.

von Niding, G., Wagner, H. M., Krekeler, H., Löllgen, H., Fries, W., Beuthan, A. (1979). Controlled studies of human exposure to single and combined action of NO₂, O₃, and SO₂. *Int Arch Occup Environ Health*. 43(3):195-210.

Weinmann, G., Weidenbach-Gerbase, G., Foster, W.M., Zacur, H., Frank, R. (1995a). Evidence for ozone-induced small-airway dysfunction: Lack of menstrual cycle and gender effects. *Am. J. Respir. Crit. Care Med*. 152:988-996.

Weinmann, G. G., Bowes, S.M., Gerbase, M. W., Kimball, A. W., Frank, R. (1995b). Response to acute ozone exposure in healthy men. Results of a screening procedure. *Am J Respir Crit Care Med*. 151(1):33-40.

Sulfur dioxide

Amdur, M. O., Melvin, W. W. Jr., Drinker, P. (1953). Effects of inhalation of sulphur dioxide by man. *Lancet*. 265(6789):758-759.

Andersen, I. B., Lundqvist, G.R., Jensen, P.L., Proctor, D.F. (1974). Human response to controlled levels of sulfur dioxide. *Arch. Environ. Health* 28(1):31-39.

Bedi, J. F., Horvath, S. M., Folinsbee, L. J. (1982). Human exposure to sulfur dioxide and ozone in a high temperature-humidity environment. *Am Ind Hyg Assoc J*. 43(1):26-30.

Bedi, J. F., Folinsbee, L. J., Horvath, S.M. (1984). Pulmonary function effects of 1.0 and 2.0 ppm sulphur dioxide exposure in active young male non-smokers. *J. Air Pollut. Control Assoc*. 34: 1117-1121.

Carson, J. L., Collier, A. M., Hu, S, Smith, C.A., Stewart, P. (1987). The appearance of compound cilia in the nasal mucosa of normal human subjects following acute, in vivo exposure to sulfur dioxide. *Environ Res*. 42(1):155-165.

Douglas, R. B., Coe, J. E. (1987). The relative sensitivity of the human eye and lung to irritant gases. *Ann Occup Hyg*. 31(2):265-267.

Folinsbee, L. J., Bedi, J. F., Horvath, S. M. (1985). Pulmonary response to threshold levels of sulfur dioxide (1.0 ppm) and ozone (0.3 ppm). *J Appl Physiol.* 58(6):1783-1787.

Frank, N. R., Amdur, M. O., Worcester, J., Whittenberger, J. L. (1962). Effects of acute controlled exposure to SO₂ on respiratory mechanics in healthy male adults. *J Appl Physiol.* 17:252-258

Frank, N. R., Amdur, M.O., Whittenberger, J. L. (1964). A comparison of the acute effects of SO₂ administered alone or in combination with NaCl particles in the respiratory mechanics of healthy adults. *Air Water Pollut.* 8:125-133.

Frank, N. R. (1964b). Studies on the effects of acute exposure to sulphur dioxide in human subjects. *Proceedings of the royal society of medicine.* 1029-1033

Islam, M. S., Neuhaan, H. F., Gryegowski, E., Oberanscheidt, J. (1992). Bronchomotoric effect of low concentration of sulphur dioxide in young healthy volunteers. *Fresenius Envir Bull* 1:541-546

Islam, M. S., Oberbarnscheidt, J., Schlipkötter, H. W. (1994). Non-specific airway responsiveness to hyperventilation of low doses of sulfur dioxide and cold air of non-smoking healthy volunteers of different ages. *Zentralbl Hyg Umweltmed.* 195(5-6):556-566.

Kagawa, J. J. (1983). Respiratory effect of two-hour exposure with intermittent exercise to ozone, sulfur dioxide and nitrogen dioxide alone and in combination in normal subjects. *Am. Ind. Hyg. Assoc.* 44(1):14-20.

Koenig, J. Q, Pierson, W. E., Horike, M., Frank, R. (1982a). Bronchoconstrictor responses to sulfur dioxide or sulfur dioxide plus sodium chloride droplets in allergic, nonasthmatic adolescent. *J Allergy Clin Immunol.* 69(4):339-344.

Koenig, J. Q., Pierson, W. E., Horike, M., Frank, R. (1982b). Effects of inhaled sulfur dioxide (SO₂) on pulmonary function in healthy adolescents: exposure to SO₂ alone or SO₂ + sodium chloride droplet aerosol during rest and exercise. *Arch Environ Health.* 37(1):5-9.

Koenig, J. Q., Marshall, S. G., Horike, M., Shapiro, G. G., Furukawa, C. T., Bierman, C. W., Pierson, W. E. (1987). The effects of albuterol on sulfur dioxide-induced bronchoconstriction in allergic adolescents. *J Allergy Clin Immunol.* 79(1):54-58.

Kreisman, H., Mitchell, C. A., Hosein, H. R., Bouhuys, A. (1976). Effect of low concentrations of sulfur dioxide on respiratory function in man. *Lung.* 29:154(1):25-34.

Kulle, T. J., Sauder, L. R., Shanty, F., Kerr, H. D., Farrell, B.P., Miller, W.R., Milman, J.H. (1984). Sulfur dioxide and ammonium sulfate effects on pulmonary function and bronchial reactivity in human subjects. *Am Ind. Hyg. Assoc. J.* 45(3): 156-161.

Kulle, T. J., Sauder, L. R., Hebel, J. R., Miller, W. R., Green, D. J. (1986). Shanty F. Pulmonary effects of sulfur dioxide and respirable carbon aerosol. *Environ Res.* 41(1):239-250.

Lawther, P. J., Macfarlane, A. J., Waller, R. E., Brooks, A. G. (1975). Pulmonary function and sulphur dioxide, some preliminary findings. *Environ Res.* 10(3):355-367

Nadel, J. A., Tamplin, B, Tokiwa, Y. (1965). Mechanism of bronchoconstriction during inhalation of sulfur dioxide; reflex involving vagus nerve. *Arch Environ Health.* 10:175-178

Newhouse, M. T., Wolff, R. K., Dolovich, M., Obminski, G. (1978). Effect of TLV levels of SO₂ and H₂ SO₄ on bronchial clearance in exercising man. *Arch Environ Health.* 33(1):24-32.

Nowak, D., Jörres, R., Berger, J., Claussen, M., Magnussen, H. (1997). Airway responsiveness to sulfur dioxide in an adult population sample. *Am J Respir Crit Care Med.* 156(4 Pt 1):1151-1156.

Randinelli, R. C., Koenig, J. Q., Marshall, S. G. (1987). The effects of sulfur dioxide on pulmonary function in healthy nonsmoking male subjects aged 55 years and older. *Am Ind Hyg Assoc J.* 48(4):299-303.

Sandström, T., Kolmodin-Hedman, B., Stjernberg, N., Andersson, M. C., Löfvenius, G. (1988). Challenge test for sulfur dioxide--symptom and lung function measurements. *Scand J Work Environ Health.* 14 Suppl 1:77-79

Sandström, T., Stjernberg, N., Andersson, M. C., Kolmodin-Hedman, B., Lindström, K., Rosenhall, L. (1989a). Cell response in bronchoalveolar lavage fluid after sulfur dioxide exposure. *Scand J Work Environ Health.* 15(2):142-146.

Sandström T, Stjernberg N, Andersson MC, Kolmodin-Hedman B, Lundgren R, Rosenhall L, Angström T. (1989b). Cell response in bronchoalveolar lavage fluid after exposure to sulfur dioxide: a time-response study. *Am Rev Respir Dis.* 140(6):1828-1831.

Sandström, T., Stjernberg, N., Andersson, M. C., Kolmodin-Hedman, B., Lundgren, R., Angström, T. (1989c). Is the short term limit value for sulphur dioxide exposure safe? Effects of controlled chamber exposure investigated with bronchoalveolar lavage. *Br J Ind Med.* 46(3):200-203.

Sim, V. M., Pattle, R. E. (1957). Effect of possible smog irritants on human subjects. *J Am Med Assoc.* 165(15):1908-1913.

Snell, R. E., Luchsinger, P. C.. (1969). Effects of sulfur dioxide on expiratory flow rates and total respiratory resistance in normal human subjects. *Arch Environ Health.* 18(4):693-698.

Speizer, F. E., Frank, N. R. (1966). A comparison of changes in pulmonary flow resistance in healthy volunteers acutely exposed to SO₂ by mouth and by nose. *Br J Ind Med* 23(1):75-79.

Stacy, R.W., House, D., Friedman, M., Hazucha, M., Green, J., Raggio, L., Roger, L.J. (1981). Effects of 0.75 ppm sulfur dioxide on pulmonary function parameters of normal human subjects. *Arch. Environ. Health* 36(4):172-178.

Stacy, R. W., Seal, E. Jr., House, D. E., Green, J., Roger, L. J., Raggio, L. (1983). A survey of effects of gaseous and aerosol pollutants on pulmonary function of normal males. *Arch Environ Health*. 38(2):104-115.

von Nieding, G., Wagner, H. M., Krekeler, H., Löllgen, H., Fries, W., Beuthan, A. (1979). Controlled studies of human exposure to single and combined action of NO₂, O₃, and SO₂. *Int Arch Occup Environ Health*. 43(3):195-210.

Weir, F.W., Bromberg, P.A. (1974). Effects of sulfur dioxide on healthy and peripheral airway impaired subjects. *Recent Advances Assessment Health Effects Environmental Pollutants*, 4, 1989-2004.

Sulfuric acid

Amdur, M.O., Silverman, L., Drinker, P. (1952). Inhalation of sulfuric mist by human subjects. *Ind. Hyg. Occ. Med.* 6: 305-313

Bowes, S. M., Francis, M., Laube, B.L., Frank, R. (1995). Acute exposure to acid fog: Influence of breathing pattern on effective dose. *Am. Ind. Hyg. Assoc. J.* 56:143-150

Chaney, S., Blomquist, W. Muller, K., DeWitt P. (1980a). Biochemical effects of sulfuric acid mist inhalation by human subjects while at rest. *Arch. Environ. Health* 35:270-275

Chaney, S., Blomquist, W., Muller, K., Goldstein, G. (1980b). Biochemical changes in humans upon exposure to sulfuric acid aerosol and exercise. *Arch. Environ. Health* 35:211-216

Culp, D. J., Latchney, L. R., Frampton, M. W., Jahnke, M. R., Morrow, P. E., Utell, M. J. (1995). Composition of human airway mucins and effects after inhalation of acid aerosol. *American Journal of Physiology - Lung Cellular and Molecular Physiology*. 269(3 Pt 1):L358-370.

Horstman, D., Hazucha, M., Haak, E., Stacy, R. (1982). Effects of submicronic sulfuric acid aerosol on human pulmonary function. *Arch. Environ. Health* 37:136-141

Horvath, S. M., Folinsbee, L. J., Bedi, J. F. (1982). Effects of large (0.9 micrometers) sulfuric acid aerosols on human pulmonary function. *Environ Res* 28:123-130

Horvath, S. M., Folinsbee, L. J., Bedi, J. F. (1987). Combined effect of ozone and sulfuric acid on pulmonary function in man. *Am Ind Hyg. Assoc J* 48(2):94-98

Kulle, T. J., Kerr, H. D. Farell, B. P. Sauder, L. R., Bermel, M. S. (1982). Pulmonary function and bronchial reactivity in human subjects with exposure to ozone and respirable sulfuric acid aerosol. *Am Rev Respir Dis* 126:996-1000

Laube BL, Bowes SM 3rd, Links JM, Thomas KK, Frank R. (1993). Acute exposure to acid fog. Effects on mucociliary clearance. *Am Rev Respir Dis*. 147(5):1105-1111.

Leikauf, G., Yeates, D.B., Wales, K.A., Spektor, D. Albert, R.E., Lippmann, M. (1981). Effects of sulfuric acid aerosol on respiratory mechanics and mucociliary particle clearance in healthy nonsmoking adults. *Am. Ind. Hyg. Assoc. J.* 42:273-282

Leikauf, G. D., Spektor, D. M., Albert, R. E., Lippmann, M. (1984). Dose-dependent effects of submicrometer sulfuric acid aerosol on particle clearance from ciliated human lung airways. *Am. Ind. Hyg. Assoc. J.* 45(5):285-292

Lippmann, M., Schlesinger, R. B., Leikauf, G. (1980). Effects of sulfuric acid aerosol inhalations. *Am. J. Ind. Med.* 1:375-381

Newhouse, M. T., Wolff, R. K., Dolovich, M., Obminski, G. (1978). Effect of TLV levels of SO₂ and H₂ SO₄ on bronchial clearance in exercising man. *Arch Environ Health.* 33(1):24-32.

Sim, V. M., Pattle, R. E. (1957). Effect of possible smog irritants on human subjects. *J Am Med Assoc.* 165(15):1908-1913.

Spektor, D. M., Yen, B. M., Lippmann, M. (1989). Effect of concentration and cumulative exposure of inhaled sulfuric acid on tracheobronchial particle clearance in healthy humans. *Environ Health Perspect.* 79:167-172.

Stacy, R. W., Seal, E. Jr., House, D. E., Green, J., Roger, L. J., Raggio, L. (1983). A survey of effects of gaseous and aerosol pollutants on pulmonary function of normal males. *Arch Environ Health.* 38(2):104-115.

Utell, M. J., Morrow, P. E., Hyde, R. W. (1983). Latent development of airway hyperreactivity in human subjects after sulfuric acid aerosol exposure. *J Aerosol Sci.* 14:202-205.

Studies with only asthmatic subjects:

Nitrogen dioxide

Avol, E. L., Linn, W. S., Peng, R. C., Valencia, G., Little, D., Hackney, J. D. (1988). Laboratory study of asthmatic volunteers exposed to nitrogen dioxide and to ambient air pollution. *Am Ind Hyg Assoc J.* 49(4):143-149.

Avol, E. L., Linn, W. S., Peng, R. C., Whynot, J. D., Shamoo, D. A., Little, D. E., Smith, M. N., Hackney, J. D. (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.

Barck, C., Sandström, T., Lundahl, J., Halldén, G., Svartengren, M., Strand, V., Rak, S., Bylin, G. (2002). Ambient level of NO₂ augments the inflammatory response to inhaled allergen in asthmatics. *Respiratory Medicine* 96:907-917.

Barck, C., Lundahl, J., Halldén, G., Bylin, G. (2005a). Brief exposures to NO₂ augment the allergic inflammation in asthmatics. *Environ Res.* 97(1):58-66.

Barck, C., Lundahl, J., Holmström, M., Bylin, G. (2005b). Does nitrogen dioxide affect inflammatory markers after nasal allergen challenge? *Am J Rhinol.* 19(6):560-566.

Bauer, M. A., Utell, M. J., Morrow, P. E., Speers, D. M., 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

Bauer, M. A., Utell, M. J., Morrow, P. E., Speers, D. M., Gibb, F. R. (1986). Inhalation of 0.30 ppm nitrogen dioxide potentiates exercise-induced bronchospasm in asthmatics. *Am Rev Respir Dis.* 134(6):1203-1208.

Bylin, G., Hedenstierna, G., Lindvall, T., Sundin, B. (1988). Ambient nitrogen dioxide concentrations increase bronchial responsiveness in subjects with mild asthma. *Eur Respir J.* 1(7):606-612

Devalia, J. L., Rusznak, C., Herdman, M. J., Trigg, C. J., Tarraf, H., Davies, R. J. (1994). Effect of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. *Lancet.* 344(8938):1668-1671

Jenkins, H. S., Devalia, J. L., Mister, R. L., Bevan, A. M., Rusznak, C., Davies, R. J. (1999). The effect of exposure to ozone and nitrogen dioxide on the airway response of atopic asthmatics to inhaled allergen: dose- and time-dependent effects. *Am J Respir Crit Care Med.* 160(1):33-39.

Jörres, R., Magnussen, H. (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.

Jörres, R., Magnussen, H. (1991). Effect of 0.25 ppm nitrogen dioxide on the airway response to methacholine in asymptomatic asthmatic patients. *Lung.* 169(2):77-85.

Kleinman, M. T., Bailey, R. M., Linn, W. S., Anderson, K. R., Whynot, J. D., Shamoo, D. A., Hackney, J. D. (1983). Effects of 0.2 ppm nitrogen dioxide on pulmonary function and response to bronchoprovocation in asthmatics. *J Toxicol Environ Health.* 12(4-6):815-826.

Linn, W. S., Shamoo, D. A., Avol, E. L., Whynot, J. D., Anderson, K. R., Venet, T. G., Hackney, J. D. (1986). Dose-response study of asthmatic volunteers exposed to nitrogen dioxide during intermittent exercise. *Arch Environ Health.* 41(5):292-296.

Mohsenin, V. (1987). Airway responses to nitrogen dioxide in asthmatic subjects. *J Toxicol Environ Health.* 22(4):371-380.

Orehek, J., Grimaldi, F., Muls, E., Durand, J. P., Viala, A., Charpin, J. (1981). [Bronchial response to allergens after controlled NO₂ exposure (author's transl)].[Article in French] *Bull Eur Physiopathol Respir.* 17(6):911-915.

Riedl, M. A., Diaz-Sanchez, D., Linn, W. S., Gong, H. Jr., Clark, K. W., Effros, R. M., Miller, J. W., Cocker, D. R., Berhane, K. T. (2012). Allergic inflammation in human lower respiratory tract affected by exposure to diesel exhaust. *Resp. Rep. Health Eff. Inst.* 196:5-43; discussion 45-64

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

Rubinstein, I., Bigby, B. G., Reiss, T. F., Boushey, H. A. Jr. (1990). Short-term exposure to 0.3 ppm nitrogen dioxide does not potentiate airway responsiveness to sulfur dioxide in asthmatic subjects. *Am Rev Respir Dis.* 141(2):381-385.

Sackner, M. A., Birch, S., Friden, A., Marchette, B. (1981). Effects of breathing low levels of nitrogen dioxide for four hours on pulmonary function of asthmatic adults *Am. Rev. Resp. Dis.* 123:151

Salome, C. M., Brown, N. J., Marks, G. B., Woolcock, A. J., Johnson, G. M., Nancarrow, P. C., Quigley, S., Tiong, J. (1996). Effect of nitrogen dioxide and other combustion products on asthmatic subjects in a home-like environment. *Eur Respir J.* 9(5):910-918

Strand, V., Salomonsson, P., Lundahl, J., Bylin, G. (1996). Immediate and delayed effects of nitrogen dioxide exposure at an ambient level on bronchial responsiveness to histamine in subjects with asthma. *Eur Respir J* 9:733-740.

Strand, V., Rak, S., Svartengren, M., Bylin, G. (1997). Nitrogen dioxide exposure enhances asthmatic reaction to inhaled allergen in subjects with asthma. *Am J Respir Crit Care Med.* 155(3):881-887.

Strand, V., Svartengren, M., Rak, S., Barck, C., Bylin, G. (1998). Repeated exposure to an ambient level of NO₂ enhances asthmatic response to a nonsymptomatic allergen dose. *Eur Respir J* 12:6-12.

Svartengren, M., Strand, V., Bylin, G., Järup, L., Pershagen, G. (2000). Short-term exposure to air pollution in a road tunnel enhances the asthmatic response to allergen. *Eur Respir J.* 15(4):716-724

Tunnicliffe, W. S., Burge, P. S., Ayres, J. G. (1994). Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. *Lancet.* 344(8939-8940):1733-1736.

Witten, A., Solomon, C., Abbritti, E., Arjomandi, M., Zhai, W., Kleinman, M., Balmes, J. (2005). Effects of nitrogen dioxide on allergic airway responses in subjects with asthma. *J Occup Environ Med.* 47(12):1250-1259.

Ozone

Balmes, J. R., Arjomandi, M., Wong, H., Holland, N. (2012). Effect of GSTM1 genotype on ozone-induced allergic airway inflammation. California air resources board contract number 03-315

Ball, B. A., Folinsbee, L. J., Peden, D. B., Kehrl, H. R. (1996). Allergen bronchoprovocation of patients with mild allergic asthma after ozone exposure. *J Allergy Clin Immunol.* 98(3):563-572.

Bartoli, M. L., Vagaggini, B., Malagrino, L., Bacci, E., Cianchetti, S., Dente, F. L., Novelli, F., Costa, F., Paggiaro, P. (2013). Baseline airway inflammation may be a determinant of the response to ozone exposure in asthmatic patients. *Inhal. toxicol.* 25(3):127-133

- Fernandes, A. L., Molfino, N. A., McClean, P. A., Silverman, F., Tarlo, S., Raizenne, M., Slutsky, A. S., Zamel, N. (1994). The effect of pre-exposure to 0.12 ppm of ozone on exercise-induced asthma. *Chest*. 106(4):1077-1082.
- Gong, H. Jr., McManus, M. S., Linn, W. S. (1997b). Attenuated response to repeated daily ozone exposures in asthmatic subjects. *Arch Environ Health*. 52(1):34-41.
- Hanania, N. A., Tarlo, S. M., Silverman, F., Urch, B., Senathirajah, N., Zamel, N., Corey, P. (1998). Effect of exposure to low levels of ozone on the response to inhaled allergen in allergic asthmatic patients. *Chest*. 114(3):752-756.
- Hiltermann, T. J., Peters, E. A., Alberts, B., Kwikkers, K., Borggreven, P. A., Hiemstra, P. S., Dijkman, J. H., van Bree, L. A., Stolk, J. (1998). Ozone-induced airway hyperresponsiveness in patients with asthma: role of neutrophil-derived serine proteinases. *Free Radic Biol Med*. 24(6):952-958.
- Hiltermann, J. T., Lapperre, T. S., van Bree, L., Steerenberg, P. A., Brahim, J. J., Sont, J. K., Sterk, P. J., Hiemstra, P. S., Stolk, J. (1999). Ozone-induced inflammation assessed in sputum and bronchial lavage fluid from asthmatics: a new noninvasive tool in epidemiologic studies on air pollution and asthma. *Free Radic Biol Med*. 27(11-12):1448-1454.
- Holz, O., Mücke, M., Paasch, K., Böhme, S., Timm, P., Richter, K., Magnussen, H., Jörres, R. A. (2002). Repeated ozone exposures enhance bronchial allergen responses in subjects with rhinitis or asthma. *Clin Exp Allergy*. 32(5):681-689.
- Jenkins, H. S., Devalia, J. L., Mister, R. L., Bevan, A. M., Rusznak, C., Davies, R. J. (1999). The effect of exposure to ozone and nitrogen dioxide on the airway response of atopic asthmatics to inhaled allergen: dose- and time-dependent effects. *Am J Respir Crit Care Med*. 160(1):33-39.
- Kehrl, H. R., Peden, D. B., Ball, B., Folinsbee, L. J., Horstman, D. (1999). Increased specific airway reactivity of persons with mild allergic asthma after 7.6 hours of exposure to 0.16 ppm ozone. *J Allergy Clin Immunol*. 104(6):1198-1204.
- Linn, W. S., Buckley, R. D., Spier, C. E., Blessey, R. L., Jones, M. P., Fischer, D. A., Hackney, J. D. (1978). Health effects of ozone exposure in asthmatics. *Am Rev Respir Dis*. 117(5):835-843.
- Linn, W. S., Anderson, K. R., Shamoo, D. A., Edwards, S. A., Webb, T. L., Hackney, J. D., Gong, H. Jr. (1995). Controlled exposures of young asthmatics to mixed oxidant gases and acid aerosol. *Am J Respir Crit Care Med*. 152(3):885-891.
- Molfino, N. A., Wright, S. C., Katz, I., Tarlo, S., Silverman, F., McClean, P. A., Szalai, J. P., Raizenne, M., Slutsky, A. S., Zamel, N. (1991). Effect of low concentrations of ozone on inhaled allergen responses in asthmatic subjects. *Lancet*. 27:338(8761):199-203.
- Newson, E. J., Krishna, M. T., Lau, L. C., Howarth, P. H., Holgate, S. T., Frew, A. J. (2000). Effects of short-term exposure to 0.2 ppm ozone on biomarkers of inflammation in sputum, exhaled nitric oxide, and lung function in subjects with mild atopic asthma. *J Occup Environ Med*. 42(3):270-277.

Peden, D. B., Boehlecke, B., Horstman, D., Devlin, R. (1997). Prolonged acute exposure to 0.16 ppm ozone induces eosinophilic airway inflammation in asthmatic subjects with allergies. *J Allergy Clin Immunol.* 1100(6 Pt 1):802-808.

Silverman, F. (1979). Asthma and respiratory irritants (ozone). *Environ Health Perspect.* 29:131-136.

Stenfors, N., Bosson, J., Helleday, R., Behndig, A. F., Pourazar, J., Törnqvist, H., Kelly, F. J., Frew, A. J., Sandström, T., Mudway, I. S., Blomberg, A. (2010). Ozone exposure enhances mast-cell inflammation in asthmatic airways despite inhaled corticosteroid therapy. *Inhal Toxicol.* 22(2):133-139.

Vagaggini, B., Carnevali, S., Macchioni P, Taccola, M., Fornai, E., Bacci, E., Bartoli, M. L., Cianchetti S, Dente FL, Di Franco A, Giannini D, Paggiaro PL. (1999). Airway inflammatory response to ozone in subjects with different asthma severity. *Eur Respir J.* 13(2):274-280.

Vagaggini, B., Taccola, M., Conti, I., Carnevali, S., Cianchetti, S., Bartoli, M. L., Bacci, E., Dente, F. L., Di Franco, A., Giannini, D., Paggiaro, P. L. (2001). Budesonide reduces neutrophilic but not functional airway response to ozone in mild asthmatics. *Am J Respir Crit Care Med.* 164(12):2172-2176.

Vagaggini, B., Taccola, M., Cianchetti, S., Carnevali, S., Bartoli, M. L., Bacci, E., Dente, F. L., Di Franco, A., Giannini, D., Paggiaro, P. L. (2002). Ozone exposure increases eosinophilic airway response induced by previous allergen challenge. *Am J Respir Crit Care Med.* 15:166(8):1073-1077.

Weymer, A. R., Gong, H. Jr., Lyness, A., Linn, W. S. (1994). Pre-exposure to ozone does not enhance or produce exercise-induced asthma. *Am J Respir Crit Care Med.* 149(6):1413-1419.

Sulfur dioxide

Balmes, J. R., Fine, J. M., Sheppard, D. (1987). Symptomatic bronchoconstriction after short-term inhalation of sulfur dioxide. *Am Rev Respir Dis.* 136(5):1117-1121.

Balmes, J. R., Fine, J. M., Gordon, T., Sheppard, D. (1989). Potential bronchoconstrictor stimuli in acid fog. *Environ Health Perspect.* 79:163-166.

Bell, K. A., Linn, W. S., Hazucha, M., Hackney, J. D., Bates, D. V. (1977). Respiratory Effects of Exposure to Ozone Plus Sulfur Dioxide in Southern Californians and Eastern Canadians. *Am. Ind. Hyg. Assoc. J.* 38:696-706.

Bethel, R. A., Epstein, J., Sheppard, D., Nadel, J. A., Boushey, H. A. (1983a) Sulfur dioxide-induced bronchoconstriction in freely breathing, exercising, asthmatic subjects. *Am Rev Respir Dis.* 128(6):987-990.

Bethel, R. A., Erle, D. J., Epstein, J., Sheppard, D., Nadel, J. A., Boushey, H. A. (1983b). Effect of exercise rate and route of inhalation on sulfur-dioxide-induced bronchoconstriction in asthmatic subjects. *Am Rev Respir Dis.* 128(4):592-596.

Bethel, R. A., Sheppard, D., Epstein, J., Tam, E., Nadel, J. A., Boushey, H. A. (1984). Interaction of sulfur dioxide and dry cold air in causing bronchoconstriction in asthmatic subjects. *J Appl Physiol Respirat Environ Exercise Physiol.* 57:419-423.

Bethel, R. A., Sheppard, D., Geffroy, B., Tam, E., Nadel, J. A., Boushey, H. A. (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.

Bigby, B., Boushey, H. (1993). Effects of nedocromil sodium on the bronchomotor response to sulfur dioxide in asthmatic patients. *J Allergy Clin Immunol.* 92(1 Pt 2):195-197.

Devalia, J. L., Rusznak, C., Herdman, M. J., Trigg, C. J., Davies, R. J., Tarraf, H. (1994). Effect of nitrogen dioxide and sulfur dioxide on airway response of mild asthmatic patients to allergen inhalation. *Lancet* 344: 1668-1671.

Field, P. I., Simmul, R., Bell, S.C., Allen, D. H., Berend, N. (1996). Evidence for opioid modulation and generation of prostaglandins in sulphur dioxide (SO₂)-induced bronchoconstriction. *Thorax* 51:159-163.

Gong, H. Jr., Lachenbruch, P. A., Harber, P., Linn, W. S. (1995). Comparative short-term health responses to sulfur dioxide exposure and other common stresses in a panel of asthmatics. *Toxicol Ind Health.* 11(5):467-487.

Gong, H. Jr., Linn, W. S., Shamoo, D. A., Anderson, K. R., Nugent, C. A., Clark, K. W., Lin, A. E. (1996). Effect of inhaled salmeterol on sulfur dioxide-induced bronchoconstriction in asthmatic subjects. *Chest.* 110(5):1229-1235.

Gong, H. Jr., Linn, W. S., Terrell, S. L., Anderson, K. R., Clark, K. W. (2001). Anti-inflammatory and lung function effects of montelukast in asthmatic volunteers exposed to sulfur dioxide. *Chest.* 119(2):402-408.

Hackney, J. D., Linn, W. S., Bailey, R. M., Spier, C. E., Valencia, L. M. (1984). Time course of exercise-induced bronchoconstriction in asthmatics exposed to sulfur dioxide. *Environ Res.* 34(2):321-327.

Heath, S. K., Koenig, J. Q., Morgan, M. S., Checkoway, H., Hanley, Q. S., Rebolledo, V. (1994). Effects of sulfur dioxide exposure on African-American and Caucasian asthmatics. *Environ Res.* 66(1):1-11.

Horstman, D., Roger, L. J., Kehrl, H., Hazucha M. (1986). Airway sensitivity of asthmatics to sulfur dioxide. *Toxicol Ind Health.* 2(3):289-298.

Horstman, D. H., Seal, E. Jr., Folinsbee, L. J., Ives, P., Roger, L. J. (1988). The relationship between exposure duration and sulfur dioxide-induced bronchoconstriction in asthmatic subjects. *Am Ind Hyg Assoc J.* 49(1):38-47.

Jörres, R., Magnussen, H. (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.

Kehrl, H. R., Roger, L. J., Hazucha, M. J., Horstman, D. H. (1983). Pulmonary responses of young male adult asthmatics to SO₂ with moderate exercise. *Am. Rev. Resp. Dis.* 127:A160

- Kehrl, H. R., Roger, L. J., Hazucha, M. J., Horstman, D. H. (1987). Differing response of asthmatics to sulfur dioxide exposure with continuous and intermittent exercise. *Am Rev Respir Dis.* 135(2):350-355.
- Kirkpatrick, M. B., Sheppard, D., Nadel, J. A., Boushey, H. A. (1982). Effect of the oronasal breathing route on sulfur dioxide-induced bronchoconstriction in exercising asthmatic subjects. *Am Rev Respir Dis.* 125(6):627-631.
- Koenig, J. Q., Pierson, W. E., Frank, R. (1980). Acute effects of inhaled SO₂ plus NaCl droplet aerosol on pulmonary function in asthmatic adolescents. *Environ Res.* 22(1):145-153. No abstract available.
- Koenig, J. Q., Pierson, W. E., Horike, M., Frank, R. (1981). Effects of SO₂ plus NaCl aerosol combined with moderate exercise on pulmonary function in asthmatic adolescents. *Environ Res.* 25(2):340-348.
- Koenig, J. Q., Pierson, W. E., Horike, M. (1983). The effects of inhaled sulfuric acid on pulmonary function in adolescent asthmatics. *Am Rev Respir Dis.* 128(2):221-225.
- Koenig, J. Q., Morgan, M. S., Horike, M., Pierson, W. E. (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., Marshall, S. G., Horike, M., Shapiro, G. G., Furukawa, C. T., Bierman, C. W., Pierson, W. E. (1987). The effects of albuterol on sulfur dioxide-induced bronchoconstriction in allergic adolescents. *J Allergy Clin Immunol.* 79(1):54-58.
- Koenig, J. Q., Marshall, S. G., van Belle, G., McManus, M. S., Bierman, C. W., Shapiro, G. G., Furukawa, C. T., Pierson, W. E. (1988). Therapeutic range cromolyn dose-response inhibition and complete obliteration of SO₂-induced bronchoconstriction in atopic adolescents. *J Allergy Clin Immunol.* 81(5 Pt 1):897-901.
- 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.
- Koenig, J. Q., Covert, D. S., Hanley, Q. S., Van Belle, G., Pierson, W. E. (1990). Prior exposure to ozone potentiates subsequent responses to sulfur dioxide in adolescent asthmatic subjects. *Am Rev Respir Dis* 141:377-380.
- Koenig, J. Q., Dumler, K., Rebolledo, V., Williams, P. V., Pierson, W. E. (1995). Theophylline mitigates the bronchoconstrictor effects of sulfur dioxide in subjects with asthma. *J Allergy Clin Immunol.* 89(4):789-794.
- Lazarus, S. C., Wong, H. H., Watts, M. J., Boushey, H. A., Lavins, B. J., Minkwitz, M. C. (1997). The leukotriene receptor antagonist zafirlukast inhibits sulfur dioxide-induced bronchoconstriction in patients with asthma. *Am J Respir Crit Care Med* 156:1725-1730.
- Linn, W. S., Venet, T. G., Shamoo, D. A., Valencia, L. M., Anzar, U. T., Spier, C. E., Hackney, J. D. (1977). Respiratory effects of sulfur dioxide in heavily exercising asthmatics. *Am Ind Hyg Assoc J* 38:696-706.

- Linn, W. S., Bailey, R. M., Shamoo, D. A., Venet, T. G., Wightman, L. H., Hackney, J. D. (1982). Respiratory responses of young adult asthmatics to sulfur dioxide exposure under simulated ambient conditions. *Environ Res.* 29(1):220-232.
- Linn, W. S., Shamoo, D. A., Spier, C. E., Valencia, L. M., Anzar, U. T., Venet, T. G., Hackney, J. D. (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., Venet, T. G., Shamoo, D. A., Valencia, L. M., Anzar, U. T., Spier, C. E., Hackney, J. D. (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., Avol, E. L., Shamoo, D. A., Venet, T. G., Anderson, K. R., Whynot, J. D., Hackney, J. D. (1984a). Asthmatics' responses to 6-hr sulfur dioxide exposures on two successive days. *Arch Environ Health*. 39(4):313-319.
- Linn, W. S., Shamoo, D. A., Venet, T. G., Bailey, R. M., Wightman, L. H., Hackney, J. D. (1984b). Comparative effects of sulfur dioxide exposures at 5 degrees C and 22 degrees C in exercising asthmatics. *Am Rev Respir Dis*. 129(2):234-239.
- Linn, W. S., Shamoo, D. A., Venet, T. G., Spier, C. E., Valencia, L. M., Anzar, U. T., Hackney, J. D. (1984c). Combined effect of sulfur dioxide and cold in exercising asthmatics. *Arch Environ Health*. 39(5):339-346
- Linn, W. S., Shamoo, D. A., Anderson, K. R., Whynot, J. D., Avol, E. L., Hackney, J. D. (1985). Effects of heat and humidity on the responses of exercising asthmatics to sulfur dioxide exposure. *Am Rev Respir Dis*. 131(2):221-225.
- Linn, W. S., Avol, E. L., Shamoo, D. A., Peng, R. C., Spier, C. E., Smith, M. N., Hackney, J. D. (1988). Effect of metaproterenol sulfate on mild asthmatics' response to sulfur dioxide exposure and exercise. *Arch Environ Health*. 43(6):399-406.
- Linn, W. S., Shamoo, D. A., Peng, R. C., Clark, K. W., Avol, E. L., Hackney, J. D. (1990). Responses to sulfur dioxide and exercise by medication-dependent asthmatics: effect of varying medication levels. *Arch Environ Health*. 45(1):24-30.
- McManus, M. S., Koenig, J. Q., Altman, L. C., Pierson, W. E. (1989). Pulmonary effects of sulfur dioxide exposure and ipratropium bromide pretreatment in adults with nonallergic asthma. *J Allergy Clin Immunol*. 83(3):619-626.
- Myers, D. J., Bigby, B. G., Boushey, H. A. (1986a). The inhibition of sulfur dioxide-induced bronchoconstriction in asthmatic subjects by cromolyn is dose dependent. *Am Rev Respir Dis*. 133(6):1150-1153.
- Myers, D. J., Bigby, B. G., Calvayrac, P., Sheppard, D., Boushey, H. A. (1986b). Interaction of cromolyn and a muscarinic antagonist in inhibiting bronchial reactivity to sulfur dioxide and to eucapnic hyperpnea alone. *Am Rev Respir Dis*. 133(6):1154-1158.
- Roger, L. J., Kehrl, H. R., Hazucha, M., Horstman, D. H. (1985). Bronchoconstriction in asthmatics exposed to sulfur dioxide during repeated exercise, *J Appl Physiol*, 59(3):784-791.

Rubinstein, I., Bigby, B. G., Reiss, T. F., Boushey, H. A. Jr. (1990). Short-term exposure to 0.3 ppm nitrogen dioxide does not potentiate airway responsiveness to sulfur dioxide in asthmatic subjects. *Am Rev Respir Dis.* 141(2):381-385.

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

Sheppard, D., Nadel, J. A., Boushey, H. A. (1981b). Inhibition of sulfur dioxide-induced bronchoconstriction by disodium cromoglycate in asthmatic subjects. *Am Rev Respir Dis.* 124(3):257-259

Sheppard, D., Epstein, J., Bethel, R. A., Nadel, J. A., Boushey, H. A. (1983). Tolerance to sulfur dioxide-induced bronchoconstriction in subjects with asthma. *Environ Res.* 30(2):412-419.

Sheppard, D., Eschenbacher, W. L., Boushey, H. A., Bethel, R. A. (1984). Magnitude of the interaction between the bronchomotor effects of sulfur dioxide and those of dry (cold) air. *Am Rev Respir Dis.* 130(1):52-55.

Tam, E. K., Liu, J., Bigby, B. G., Boushey, H. A. (1988). Sulfur dioxide does not acutely increase nasal symptoms or nasal resistance in subjects with rhinitis or in subjects with bronchial responsiveness to sulfur dioxide. *Am Rev Respir Dis.* Dec;138(6):1559-64. Erratum in: *Am Rev Respir Dis* 139(6):1579.

Trenga, C. A., Koenig, J. Q., Williams, P. V. (1999). Sulphur dioxide sensitivity and plasma antioxidants in adult subjects with asthma. *Occup Environ Med.* 56(8):544-547.

Wiebicke, W., Jörres, R., Magnussen, H. (1990). Comparison of the effects of inhaled corticosteroids on the airway response to histamine, methacholine, hyperventilation, and sulfur dioxide in subjects with asthma. *J Allergy Clin Immunol.* 86(6 Pt 1):915-923.

Winterton, D. L., Kaufman, J., Keener, C. V., Quigley, S., Farin, F. M., Williams, P. V., Koenig, J. Q. (2001). Genetic polymorphisms as biomarkers of sensitivity to inhaled sulfur dioxide in subjects with asthma. *Ann Allergy Asthma Immunol.* 86(2):232-238.

Witek, TJ Jr, Schachter, E. N. (1985a). Airway responses to sulfur dioxide and methacholine in asthmatics. *J Occup Med.* 27(4):265-268.

Sulfuric acid

Aris, R., Christian, D., Sheppard, D., Balmes, J. R. (1990). Acid fog-induced bronchoconstriction. The role of hydroxymethanesulfonic acid. *Am Rev Respir Dis.* 141(3):546-551.

Aris, R., Christian, D., Sheppard, D., Balmes, J. R. (1991). Lack of bronchoconstrictor response to sulfuric acid aerosols and fogs. *Am Rev Respir Dis.* 143(4 Pt 1):744-750

Avol, E. L., Linn, W. S., Shamoo, D. A., Anderson, K. R., Peng, R. C., Hackney, J. D. (1990). Respiratory responses of young asthmatic volunteers in controlled exposures to sulfuric acid aerosol. *Am Rev Respir Dis.* 142(2):343-348.

Balmes, J. R., Fine, J. M., Christian, D., Gordon, T., Sheppard, D. (1988). Acidity potentiates bronchoconstriction induced by hyposmolar aerosols. *Am Rev Respir Dis* 138:35-39

Balmes, J., Fine, J. M., Christian, D., Gordon, T., Sheppard, D. (1989). Lack of bronchoconstrictor response to sulfuric acid-containing fogs in subjects with asthma. *Am Rev Respir Dis* 139 (4) Part 2:A281

Bauer, M. A., Utell, M. J. Speers, D. M., Gibb, F. R., Morrow, P. E. (1988). Effects of near ambient levels of sulfuric acid aerosol in lung function in exercising subjects with asthma and COPD *Am Rev Resp Dis* 137(4)

Hanley, Q. S., Koenig, J. Q., Larson, T. V., Anderson, T. L., van Belle, G., Rebolledo, V., Covert, D. S., Pierson, W. E. (1992). Response of young asthmatic patients to inhaled sulfuric acid. *Am Rev Respir Dis*. 145(2 Pt 1):326-331.

Jörres, R., Magnussen, H. (1992). The effect of acid aerosols on airway responsiveness in asthmatics. *J. Aero. Med.* 5(2):103-111

Koenig, J. Q., Pierson, W. E., Horike, M. (1983). The effects of inhaled sulfuric acid on pulmonary function in adolescent asthmatics. *Am Rev Respir Dis*. 128(2):221-225.

Koenig, J. Q., Morgan, M. S., Horike, M., Pierson, W. E. (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., 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.

Koenig, J. Q., Covert, D. S., Larson, T. V., Pierson, W. E. (1992a). The effect of duration of exposure on sulfuric acid-induced pulmonary function changes in asthmatic adolescent subjects: a dose-response study. *Toxicol Ind Health*. 8(5):285-296.

Same study as Koenig 1992a: Koenig, J.Q., Covert, D. S., Larson, T. V., Pierson. W. E. (1992b). The effect of duration of exposure on sulfuric acid-induced pulmonary function changes in asthmatic adolescent subjects: a dose-response study. *Am Rev Respir Dis* 145(4) Part 2:A428

Leduc, D., Fally, S., De Vuyst, P., Wollast, R., Yernault, J. C. (1995). Acute exposure to realistic acid fog: effects on respiratory function and airway responsiveness in asthmatics. *Environ Res*. 71(2):89-98.

Linn, W. S., Avol, E. L., Shamoo, D. A., Whynot, J. D., Anderson, K. R., Hackney, J. D. (1985). Respiratory responses of asthmatic volunteers in controlled exposures to sulfuric acid aerosols. *Am Rev Respir Dis*. 131(4)Suppl:A201

Linn, W. S., Avol, E. L., Shamoo, D. A., Anderson, K. R., Whynot, J. D., Hackney, J. D. (1986). Respiratory effects of "acid fog" exposure in normal and asthmatic volunteers. *Am Rev Respir Dis*, 133(4)Suppl:A214

Linn, W. S., Avol, E. L., Shamoo, D. A., Anderson, K. R., Peng, R.-C., Hackney, J. D. (1990). Respiratory response of young asthmatics to sulfuric acid aerosol. *Am Rev Respir Dis* 141(4)Part 2:A74

Linn, W. S., Anderson, K. R., Shamoo, D. A., Edwards, S. A., Webb, T. L., Hackney, J. D., Gong, H. Jr. (1995). Controlled exposures of young asthmatics to mixed oxidant gases and acid aerosol. *Am J Respir Crit Care Med*. 152(3):885-891.

Spektor, D. M., Leikauf, G. D., Albert, R. E., Lippmann, M. (1985). Effects of submicrometer sulfuric acid aerosols on mucociliary transport and respiratory mechanics in asymptomatic asthmatics. *Environ Res*. 37(1):174-191.

Tunnicliffe, W. S., Evans, D. E., Mark, D., Harrison, R. M., Ayres, J. G. (2001). The effect of exposure to sulphuric acid on the early asthmatic response to inhaled grass pollen allergen. *Eur Respir J*. 18(4):640-646.

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

Utell, M. J., Morrow, P. E., Hyde, R. W., Cox, C., Schreck, R. M. (1988). Comparison of responses and deposition following human exposures via oral or nasal inhalation of sulphuric acid aerosols. *Ann Occup Hyg*. 32:267-272

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

Studies with healthy and asthmatic subjects exposed under the same conditions (included for both healthy and asthmatic subjects, separately. Counted twice in the total number; n=476)

Nitrogen dioxide

Ahmed, T., Danta, I., Dougherty, R. L., Schreck, R., Sackner, M. A. (1983). Effect of NO₂ (0.1 ppm) on specific bronchial reactivity to ragweed antigen in subjects with allergic asthma. *Am Rev Respir Dis* 127: Suppl: 160

Bylin, G., Lindvall, T., Rehn, T., Sundin, B. (1985). Effects of short term exposure to ambient nitrogen dioxide concentrations on human bronchial reactivity and lung function, *Eur. J. Resp. Dis.*, 66: 205-217.

Hazucha, M. J., Ginsberg, J. F., McDonnell, W. F., Haak, E. D., Pimmel, R. L., House, D. L., Bromberg, P. A. (1982). Changes in bronchial reactivity, of asthmatics and normals following exposure to 0.1 ppm NO₂. In: Schneider T, Grant L, eds. Air Pollution by Nitrogen Oxides. Amsterdam, Elsevier.

Hazucha, M.J., Ginsberg, J.F., McDonnell, W.F., Haak, E.D., Jr., Pimmel, R.L., Salaam, S.A., House, D.E., Bromberg, P.A. (1983). Effects of 0.1 ppm nitrogen dioxide on airways of normal and asthmatic subjects. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol*. 54:730-739.

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

Kerr, H. D., Kulle, T. J., McIlhany, M. L., Swidersky, P. (1978). Effects of nitrogen dioxide on pulmonary function in human subjects. An environmental chamber study. *Report: ISS EPA/600/1-78/025*; Order no. PB-281 186, 20 pp.

Same study as Kerr et al 1978 and Kulle et al 1982: Kerr, H. D., Kulle, T. J., McIlhany, M. L., Swidersky, P. (1979). Effects of nitrogen dioxide on pulmonary function in human subjects: An environmental chamber study. *Environ. Research* 19:392-404.

Koenig, J. Q., Covert, D. S., Morgan, M. S., Horike, M., Horike, N., Marshall, S. G., Pierson, W. E. (1985). Acute effects of 0.12 ppm ozone or 0.12 ppm nitrogen dioxide on pulmonary function in healthy and asthmatic adolescents. *Am. Rev. Respir. Dis.* 132:648-651.

Koenig, J. Q., Covert, D. S., Marshall, S. G., van Belle, G., Pierson, W. E. (1987). The effects of ozone and nitrogen dioxide on pulmonary function in healthy and in asthmatic adolescents. *Am. Rev. Respir. Dis.* 136:1152-1157.

Koenig JQ, Covert DS, Smith MS, Van Belle G, Pierson WE. (1988a). The pulmonary effects of ozone and nitrogen dioxide alone and combined in healthy and asthmatic adolescent subjects. *Toxicol Ind Health.* 4(4):521-532.

Koenig J. Q., Pierson W. E., Covert D. S., Marshall S. G., Morgan M. S., van Belle G. (1988b). The effects of ozone and nitrogen dioxide on lung function in healthy and asthmatic adolescents. *Res Rep Health Eff Inst.* (14):5-24.

Same as Kerr et al 1978, 1979: Kulle, T. J. (1982). Effects of nitrogen dioxide on pulmonary function in normal healthy humans and subjects with asthma and chronic disease. *Stud Environ Sci* 21:477-486

Linn, W. S., Hackney, J. D. (1983). Short-term human respiratory effects of nitrogen dioxide: determination of quantitative dose-response profiles. Phase 1. Exposure of healthy volunteers to 4 ppm NO₂. *NTIS order no. PB84-132299*. 30 pp.

Same as Linn et al 1983, 1985: Linn, W. S., Hackney, J. D. (1984). Short-term human respiratory effects of nitrogen dioxide: determination of quantitative dose-response profiles. Phase 2. Exposure of asthmatic volunteers to 4 ppm NO₂. *NTIS order no. PB85-104388*. 31 pp.

Same as Linn et al 1983, 1984: Linn, W. S., Solomon, J. C., Trim, S. C., Spier, C. E., Shamoo, D. A., Venet, T. G., Avol, E. L., Hackney, J. D. (1985a) Effects of exposure to 4 ppm nitrogen dioxide in healthy and asthmatic volunteers. *Arch Environ Health.* 40(4):234-239.

Magnussen, H., Nowak, D., Jorres, R. (1994). Experimental effects of air pollutants on healthy probands and asthmatic subjects. *Pneumologie.* 48(2):85-88.

Morrow, P. E., Utell, M. J. (1989). Responses of susceptible subpopulations to nitrogen dioxide. Cambridge, MA: Research Rept. *Health Effects Inst.*, report no. 23.

Vagaggini, B., Paggiaro, P. L., Giannini, D., Franco, A. D., Cianchetti, S., Carnevali, S., Taccola, M., Bacci, E., Bancalari, L., Dente, F. L., Giuntini, C. (1994). Effects of short-term exposure to NO₂ (0.3-1 ppm) on the hypertonic saline induced sputum in normal, asthmatic and rhinitic subjects (Italian). *Arch Sci Lav* 10:655-660

Same study as Vagaggini et al 1994: Vagaggini, B., Paggiaro, P. L., Giannini, D., Di Franco, A., Cianchetti, S., Carnevali, S., Taccola, M., Bacci, E., Bancalari, L., Dente, F. L., Giuntini, C. (1996). Effect of short-term NO₂ exposure on induced sputum in normal, asthmatic and COPD subjects. *Eur. Respir. J.* 9:1852-1857

Ozone

Arjomandi, M., Witten, A., Abbritti, E., Reintjes, K., Schmidlin, I., Zhai, W., Solomon, C., Balmes, J. (2005). Repeated exposure to ozone increases alveolar macrophage recruitment into asthmatic airways. *Am j Respir Crit Care Med.* 172:427-432

Same study as Arjomandi et al 2005: Christian, D. L., Chen, L. L., Scannell, C. H., Ferrando, R. E., Welch, B. S., Balmes, J. R. (1998). Ozone-induced inflammation is attenuated with multiday exposure. *Am j Respir Crit Care Med* 158:532-537

Balmes, J. R., Aris, R. M., Chen, L. L., Scannell, C., Tager, I.B., Finkbeiner, W., Christian, D., Kelly, T., Hearne, P. Q., Ferrando, R., Welch, B. (1997). Effects of ozone on normal and potentially sensitive human subjects. Part 1: Airway inflammation and responsiveness to ozone in normal and asthmatic subjects. *Res Rep Health Eff Inst.* 78:1-37; Discussion 81-99

Basha, M. A., Gross, K. B., Gwizdala, C. J., Haidar, A. H., Popovich, J. JR. (1994). Bronchoalveolar lavage neutrophilia in asthmatic and healthy volunteers after controlled exposure to ozone and filtered purified air. *Chest.* 106:1757-1765

Bell, K. A., Linn, W. S., Hazucha, M., Hackney, J. D., Bates D. V. (1977). Respiratory Effects of Exposure to Ozone Plus Sulfur Dioxide in Southern Californians and Eastern Canadians. *Am. Ind. Hyg. Assoc. J.* 38:696-706.

Bosson, J., Stenfors, N., Bucht, A., Helleday, R., Purazar, J., Holgate, S. T., Kelly, F. J., Sandström, T., Wilson, S., Frew, A. J. Blomberg, A. (2003). Ozone-induced bronchial epithelial cytokine expression differs between healthy and asthmatic subjects. *Clin Exp Allergy.* 33 (6):777-82

Eschenbacher, W. L., Ying, R. L. Kreit, J. W Gross, K. B. (1989). Ozone-Induced Lung Function Changes in Normal and Asthmatic Subjects and the Effect of Indomethacin, *Studies in Environmental Science*, 35:493-499

Esther, C. R. Jr., Peden, D. B., Alexis, N. E., Hernandez, M. L. (2011). Airway purinergic responses in healthy, atopic nonasthmatic, and atopic asthmatic subjects exposed to ozone. *Inhal Toxicol.* 23(6):324-30.

Frampton, M. W., Morrow, P. E., Cox, C., Levi, P. C., Condemi, J. J., Speers, D., Gibb, F. R. Utell, M. J. (1995). Sulfuric acid aerosol followed by ozone exposure in healthy and asthmatic subjects. *Environ. Res.* 69: 1-14

Hernandez, M. L., Lay, J. C., Harris, B., Esther, C. R. Jr., Brickey, W. J., Bromberg, P. A., Diaz-Sanchez, D., Devlin, R. B., Kleeberger, S. R., Alexis, N. E., Peden, D. B. (2010). Atopic asthmatic subjects but not atopic subjects without asthma have enhanced inflammatory response to ozone. *J Allergy Clin Immunol.* 126(3):537-44.e1.

Hilterman, T. J., Stolk, J., Hiemstra, P. S., Fokkens, P. H., Rombout, P. J., Sont, J. K., Sterk, P. J., Dijkman, J. H. (1995). Effect of ozone exposure on maximal airway narrowing in non-asthmatic and asthmatic subjects. *Clinical Science.* 89:619-624

Holz, O., Jörres, R. A., Timm, P., Mücke, M., Richter, K., Koschyk, S., Magnussen, H. (1999). Ozone-induced Airway Inflammatory Changes Differ between Individuals and Are Reproducible *Am J Respir Crit Care Med.* 159:776-784

Horstman, D.H., Ball, B. A., Brown, J., Gerrity, T., Folinsbee, L. J. (1995). Comparison of pulmonary responses of asthmatic and nonasthmatic subjects performing light exercise while exposed to a low level of ozone. *Toxicology and industrial health.* 11(4):369-385

Jörres, R., Nowak, D., Magnussen, H. (1996). The effect of ozone exposure on allergen responsiveness in subjects with asthma or rhinitis. *Am J Respir Crit Care Med.* 153:56-64

Koenig, J. Q., Covert, D. S., Morgan, M. S., Horike, M., Horike, N., Marshall, S. G., Pierson, W. E. (1985). Acute effects of 0.12 ppm ozone or 0.12 ppm nitrogen dioxide on pulmonary function in healthy and asthmatic adolescents. *Am. Rev. Respir. Dis.* 132:648-651.

Koenig, J. Q., Covert, D. S., Marshall, S. G., van Belle, G., Pierson, W. E. (1987). The effects of ozone and nitrogen dioxide on pulmonary function in healthy and in asthmatic adolescents. *Am. Rev. Respir. Dis.* 136:1152-1157.

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

Koenig, J. Q., Pierson, W. E., Covert, D.S., Marshall, S.G., Morgan, M.S., van Belle G. (1988b). The effects of ozone and nitrogen dioxide on lung function in healthy and asthmatic adolescents. *Res Rep Health Eff Inst.* Jan;(14):5-24.

Kreit, J. W., Gross, K. B., Moore, T. B., Lorenzen, T. J., D'arcy, J., Eschenbacher, W. L. (1989). Ozone-induced changes in pulmonary function and bronchial responsiveness in asthmatics. *J Appl Physiol.* 66(1):217-222

Linn, W. S., Shamoo, D. A., Anderson, K. R., Peng, R.-C., Avol, E. L., Hackney, J.D. (1994). Effects of prolonged, repeated exposure to ozone, sulfuric acid, and their combination in healthy and asthmatic volunteers. *Am. J. Respir. Crit. Care Med.* 150:431-440

Magnussen, H., Nowak, D., Jorres, R. (1994). Experimental effects of air pollutants on healthy probands and asthmatic subjects. *Pneumologie.* 48(2):85-88.

McBride, D. E., Koenig, J. Q., Luchtel, D. L., Williams, P. V., Hendersson, W. L. JR. (1994). Inflammatory effects of ozone in the upper airways of subjects with asthma. *Am J Respir Crit Care Med.* 149:1192-1197

Nightingale, J.A., Rogers, D.F. and Barnes, P.J. (1999). Effect of inhaled ozone on exhaled nitric oxide pulmonary function, and induced sputum in normal and asthmatic subjects. *Thorax*, 54:1061-1069

Scannell, C., Chen, L., Aris, R. M., Tager, I., Christian, D., Ferrando, R., Welch, B., Kelly, T., Balmes, J. R. (1996). Greater ozone-induced inflammatory responses in subjects with asthma. *Am J Respir Crit Care Med*. 154: 24-29

Stenfors N, Pourazar J, Blomberg A, Krishna MT, Mudway I, Helleday R, Kelly FJ, Frew AJ and Sandström T. (2002). Effect of ozone on bronchial mucosal inflammation in asthmatic and healthy subjects. *Respir Med*. 96(5):352-8

Utell, M. J., Frampton, M. W., Morrow, P. E., Cox, C., Levy, P. C., Speers, D. M., Gibb, F.R. (1994). Oxidant and acid aerosol exposure in healthy subjects and subjects with asthma. Part II: Effects of sequential sulfuric acid and ozone exposures on the pulmonary function of healthy subjects and subjects with asthma. *Res. Rep. Health Eff. Inst.* 70:37-93

Sulfur dioxide

Jaeger, M. J., Tribble, D., Wittig, H. J. (1979). Effect of 0.5 ppm sulfur dioxide on the respiratory function of normal and asthmatic subjects. *Lung*. 156:119-127

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

Magnussen, H., Jorres, R., Wagner, H. M., G. von Niding. (1990). Relationship between the airway response to inhaled sulfur dioxide, isocapnic hyperventilation, and histamine in asthmatic subjects. *Int. Arch. Occup. Environ. Health* 62(7):485-491.

Witek, T.J., Schachter, E. N., Beck, G. J., Cain. W., Colice, G., Leaderer, B. P. (1985b). Respiratory symptoms associated with sulfur dioxide exposure *Int. Arch. Occup. Environ. Health*, 55(2):179-183

Same as Witek 1985b: Schachter, E. N., Witek, T. J., Beck, G. J., Hosein, H. B., Colice, G., Leaderer, B. P., Cain, W. (1984). Airway effects of low concentrations of sulfur dioxide: Dose response characteristics. *Arch. Environ. Health* 39(1):34-42.

Sheppard, D., Wong, W. S., Uehara, C. F., Nadel, J. A., Boushey, H. A. (1980). Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Resp Dis*. 122:873-878.

Snashall, P. D., Baldwin, C. (1982). Mechanisms of sulfur dioxide induced bronchoconstriction in normal and asthmatic man. *Thorax* 37:118-123.

Tunnicliffe, W. S., Hilton, M. F., Harrison, R. M., Ayres J. G. (2001). The effect of sulphur dioxide exposure on indices of heart rate variability in normal and asthmatic adults. *Eur Respir J*. 17:604-608.

Same as Tunnicliffe et al 2001: Tunnicliffe, W. S., Harrison, R. M. Kelly F. J., Duster, C. Ayers, J. G. (2003). The effect of sulphurous air pollutant exposure on symptoms, lung

function, exhaled nitric oxide, and nasal epithelial lining fluid antioxidant concentration in normal and asthmatic adults. *Occup. Environ. Med.* 60:15.

Witek, T. J., Schacter, E. N., Tosun, T., Leaderer, B. P., Beck, G. J. (1986). Controlled human studies on the pulmonary effects of indoor air pollution: experiences with sulfur dioxide and formaldehyde. *Environ. Intl.* 12:129-135.

Sulfuric acid

Anderson, K. R., Avol, E. L., Edwards, S. A., Shamoo, D. A., Peng, R.-C., Linn, W. S., Hackney, J. D. (1992). Controlled exposures of volunteers to respirable carbon and sulfuric acid. *J. Air Waste Manage. Assoc.* 42:770-776

Avol, E. L., Jones, M. P., Bailey, R. M., Chang, N. M., Kleinman, M. T., Linn, W. S., Bell, K. A., Hackney, J. D. (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., Linn, W. S., Whiteman, J. D., Whynot, J. D., Anderson, K. R., Hackney, J. D. (1988a). Short-term respiratory effects of sulfuric acid in fog: a laboratory study of healthy and asthmatic volunteers. *JAPCA* 38:258-263

Avol, E. L., Linn, W. S., Whynot, J. D., Anderson, K. R., Shamoo, D. A., Valencia, L. M., Little, D. E., Hackney, J. D. (1988b). Respiratory dose-response study of normal and asthmatic volunteers exposed to sulfuric acid aerosol in the sub-micrometer size range. *Toxicol. Ind. Health* 4(2):173-184

Frampton, M. W., Morrow, P. E., Cox, C., Levi, P. C., Condemi, J. J., Speers, D., Gibb, F. R., Utell, M. J. (1995). Sulfuric acid aerosol followed by ozone exposure in healthy and asthmatic subjects. *Environ. Res.* 69:1-14

Koenig, J. Q., Dumler, K., Rebolledo, V., Williams, P. V., Pierson, W. E. (1993). Respiratory effects of inhaled sulfuric acid on senior asthmatics and nonasthmatics. *Arch. Environ. Health* 48(3):171-175

Linn, W. S., Avol, E. L., Shamoo, D. A., Anderson, K. R., Whynot, J. D., Hackney, J. D. (1986b). Respiratory effects of "acid fog" exposure in normal and asthmatic volunteers. *Am Rev Respir Dis*, 133 (4) Suppl:A214

Linn, W. S., Shamoo, D. A., Anderson, K. R., Peng, R.-C., Avol, E. L., Hackney, J. D. (1994). Effects of prolonged, repeated exposure to ozone, sulfuric acid, and their combination in healthy and asthmatic volunteers. *Am. J. Respir. Crit. Care Med.* 150:431-440

Sackner, M. A., Ford, D., Fernandez, J., Ciple, J., Perez, D., Kwoka, M., Reinhart, M., Michaelson, E. D., Schreck, R., Wanner, A. (1978). Effects of sulfuric acid aerosol on cardiopulmonary function of dogs, sheep and humans. *Am. Rev. Resp. Dis.* 118:497

Tunnicliffe, W. S., Harrison, R. M., Kelly, F. J., Dunster, C., Ayres, J. G. (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:e15

Utell, M. J., Morrow, P. E., Hyde, R. W. (1982). Comparison of Normal and Asthmatic Subjects Responses to Sulfate Pollutant Aerosols. *Ann. Occup. Hyg.* 26:691-697

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

Utell, M. J., Frampton, M. W., Morrow, P. E. (1991). Air pollution and asthma: clinical studies with sulfuric acid aerosols. *Allergy Proc.* 12:385-388

Utell, M. J., Frampton, M. W., Morrow, P. E., Cox, C., Levy, P. C., Speers, D. M., Gibb, F. R. (1994). Oxidant and acid aerosol exposure in healthy subjects and subjects with asthma. Part II: Effects of sequential sulfuric acid and ozone exposures on the pulmonary function of healths subjects and subjects with asthma. *Res. Rep. Health Eff. Inst.* 70:37-93

Appendix E: Benchmark-concentration analysis

R version 2.15.2 (2012-10-26) -- "Trick or Treat"
Copyright (C) 2012 The R Foundation for Statistical Computing
ISBN 3-900051-07-0
Platform: x86_64-w64-mingw32/x64 (64-bit)

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Natural language support but running in an English locale

R is a collaborative project with many contributors.
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Type 'demo()' for some demos, 'help()' for on-line help, or
'help.start()' for an HTML browser interface to help.
Type 'q()' to quit R.

```
> local({pkg <- select.list(sort(.packages(all.available =  
TRUE)),graphics=TRUE)  
+ if(nchar(pkg)) library(pkg, character.only=TRUE)})  
> data<-f.scan("S02both0.txt")  
Read 1 item  
Read 1 item  
Read 3 items  
Read 3 items  
[1] "V1" "V2" "V3"  
> f.proast(data)
```

```
-----  
-----  
          WELCOME to PROAST  
version 32.2 last revisions made on 27/01/2015  
For report problems or bugs, email proast@rivm.nl  
-----  
-----  
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```

Q1: Which variable do you want to consider as independent variable?
(e.g. dose, age)

- 1: mg/m3
- 2: Sraw(%)
- 3: exp

Selection: 1

What type of response data do you want to consider?

- 1: continuous
- 2: binary
- 3: ordinal
- 4: quantal
- 5: continuous, clustered
- 6: quantal, clustered
- 7: continuous, summary data
- 8: quantal, CxT

Selection: 1

Do you want to fit a nested set of models

- 1: single model
- 2: nested set of models
- 3: nested set of models, but change settings first
- 4: selection of model 5

Selection: 2

The following responses are continuous:

- 1
- 2 Sraw(%)
- 3 exp

Give number(s) of the response(s) you want to analyse by set of models

----- > 2

Give value for CES (always positive)
type 0 if none > 0.2

Do you want to include Hill model family?

- 1: yes
- 2: no

Selection: 1

Give number of factor serving as potential covariate (e.g.sex)
type 0 if none ---

1: mg/m3
2: Sraw(%)
3: exp

Selection: 3

Which plot type do you want ?

1: x-y
2: log(x)-y
3: x-log(y)
4: log(x)-log(y)
5: sqrt(x)-y
6: sqrt(x)-log(y)
7: x-sqrt(y)
8: log(x)-sqrt(y)

Selection: 1

response: Sraw(%)

ANALYSIS WITH EXPONENTIAL MODELS

model	converged	npar	loglik
full	1	14	-22.71
full-v	1	15	-21.66
m1-	1	2	-51.99
m2-	1	3	-42.94
m2-a	1	4	-41.9
m2-b	1	4	-26.99
m2-ab	1	5	-26.14
m3-b	1	5	-26.52
m4-b	1	5	-26.78
m5-b	1	6	-26.67

selected model: m2-b

re-fitting selected model m2-b in terms of CED

m2-b	1	4	-26.99
------	---	---	--------

calculating C.I.....

calculating C.I.....

the CED (in orig. units) and the 90 % confidence interval for group 1 is:

33.729
26.404
46.682

the CED (in orig. units) and the 90 % confidence interval for group 2 is:

3.696
2.9465
4.9573

response: Sraw(%)

ANALYSIS WITH HILL MODELS

model	converged	npar	loglik
full	NA	14	-22.71

m1-	1	2	-51.99
m2-	1	3	-43.31
m2-a	1	4	-42.66
m2-b	1	4	-38.01
m2-ab	1	5	-37.92
m3-b	1	5	-27.79
m4-b	1	5	-26.78
m5-b	1	6	-26.73
m5-	1	5	-38.96

selected model: m5-b
re-fitting selected model m5-b in terms of CED
m5-b 1 6 -26.67
calculating C.I.....

calculating C.I.....

the CED (in orig. units) and the 90 % confidence interval for group
1 is:
23.29
9.5598
44.968

the CED (in orig. units) and the 90 % confidence interval for group
2 is:
2.3705
0.92393
4.9209

----- response: Sraw(%) -----
--
The lowest BMDL and highest BMDU from exponential and Hill models
are:
group: 1
9.5598 46.682
group: 2
0.9239 4.9573

started at: Tue Jan 27 15:29:32 2015
ended at: Tue Jan 27 15:29:40 2015

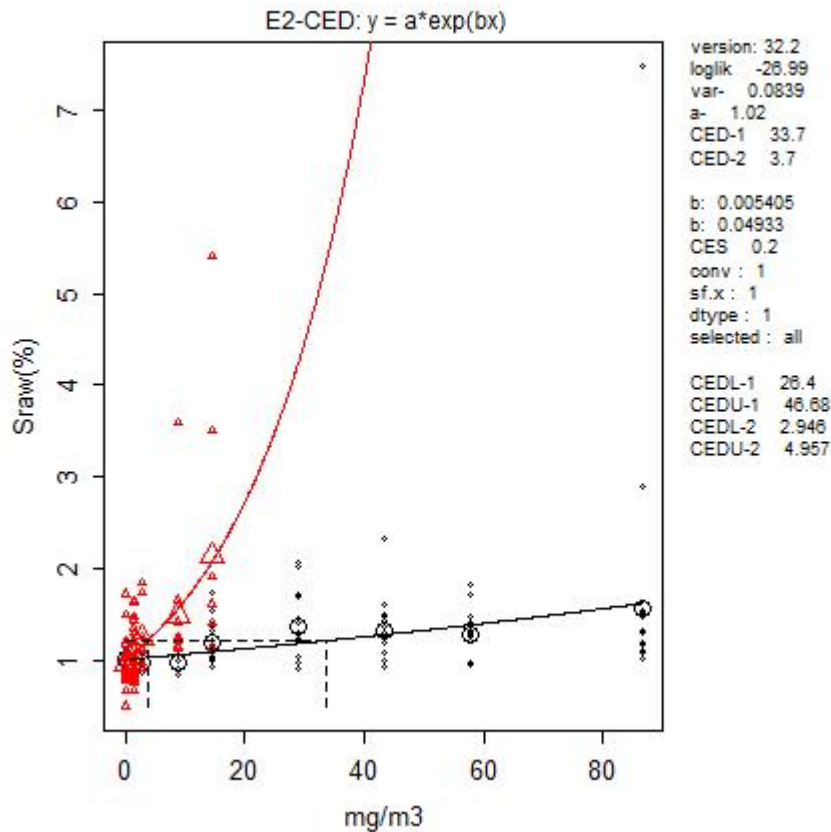


Figure 1. E2, the exponential model selected.

Human experimental studies on which the BMC analysis was based

Bethel RA, Sheppard D, Epstein J, Tam E, Nadel JA, Boushey HA. 1984. Interaction of sulfur dioxide and dry cold air in causing bronchoconstriction in asthmatic subjects. *J Appl Physiol Respirat Environ Exercise Physiol.* 57:419-423.

Jörres R, Magnussen H. (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):132-7

Lawther PJ, Macfarlane AJ, Waller RE, Brooks AG (1975) Pulmonary function and sulphur dioxide, some preliminary findings. *Environ Res.* 10(3):355-67

Sheppard D, Wong WS, Uehara CF, Nadel JA, Boushey HA. (1980). Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Resp Dis.* 122:873-878.

Appendix F: Comparative analyses of concentration-response relationships with adjustment for exercise-induced effects (by subtracting responses after control exposures to filtered air).

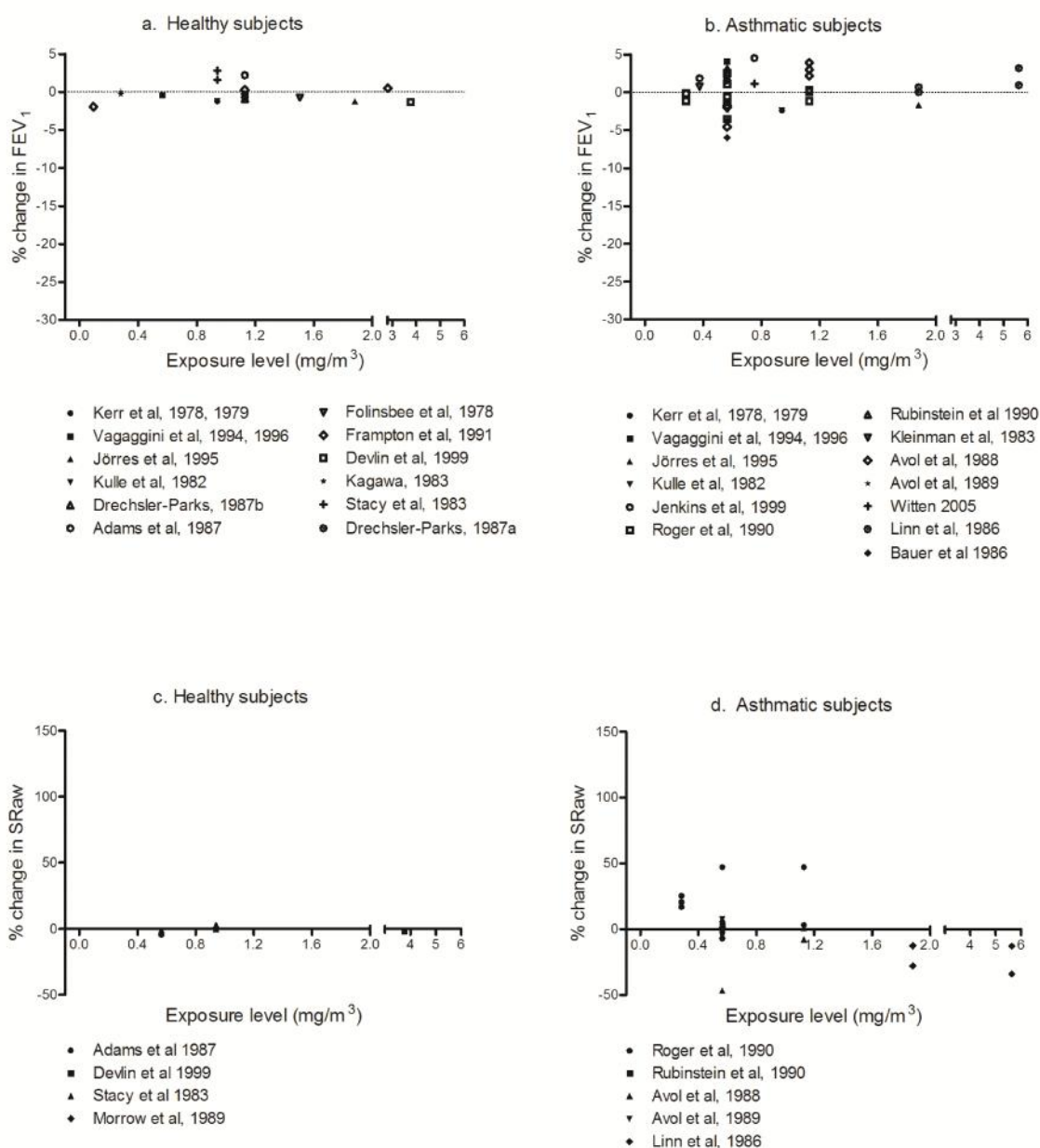


Figure 1. Percentage change in forced expiratory volume in 1 second (FEV₁) and in specific airway resistance (SRaw) in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to nitrogen dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

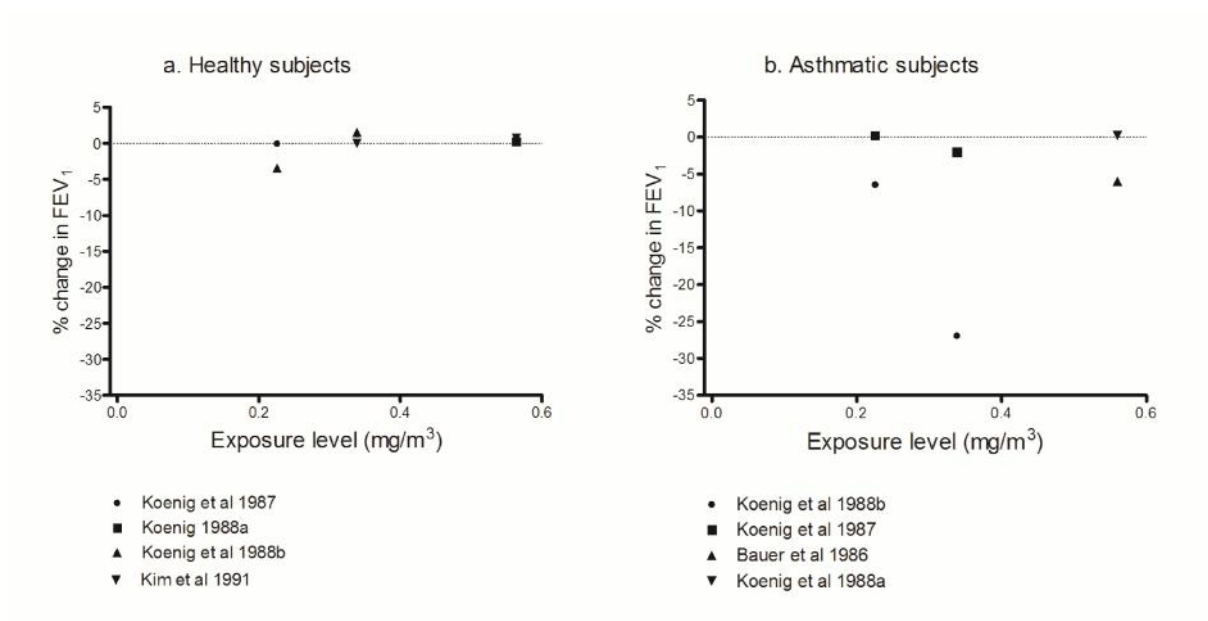


Figure 2. Percentage change in forced expiratory volume in 1 second (FEV₁) in healthy and asthmatic subjects following inhalation exposure (mouth-only breathing) to nitrogen dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

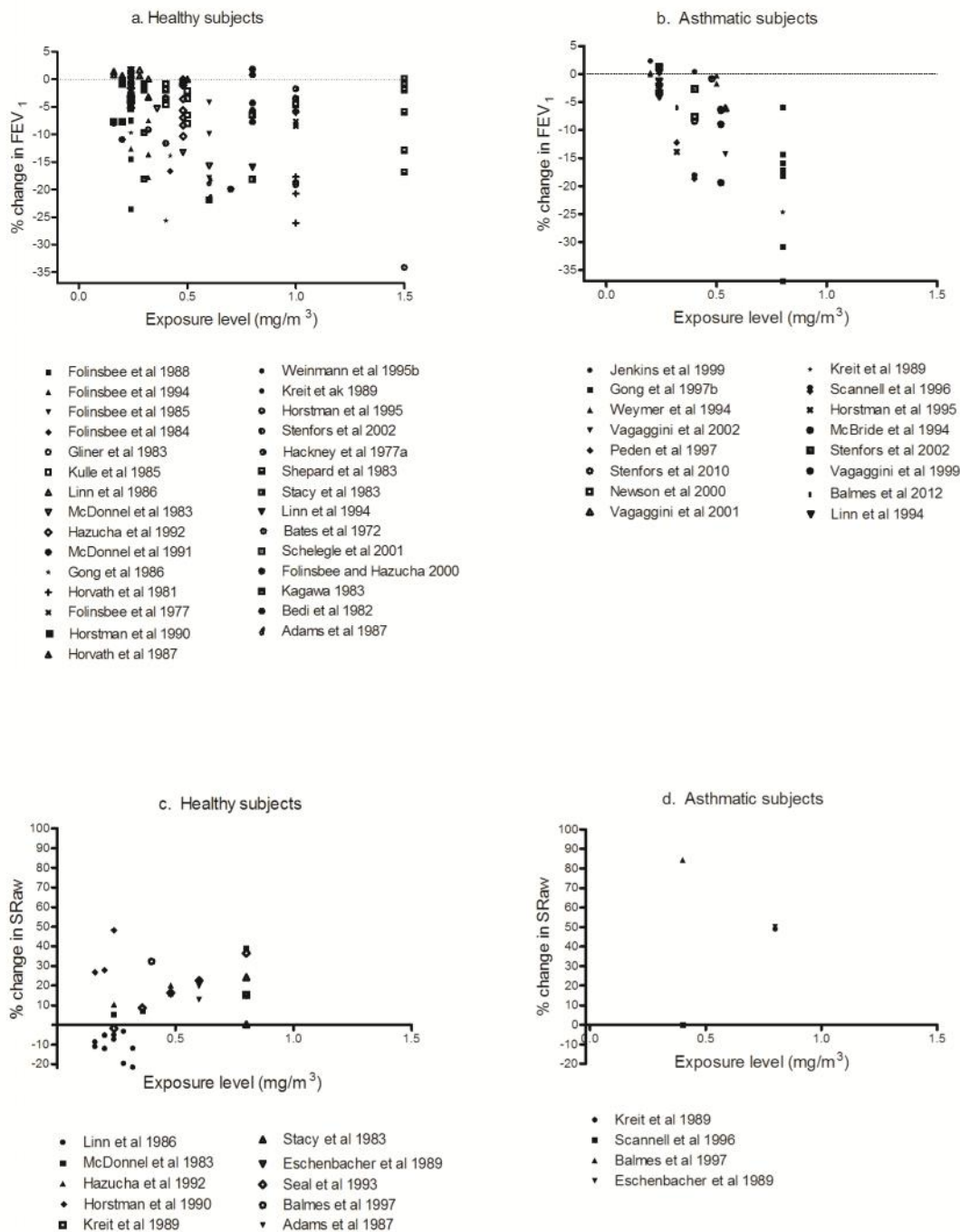


Figure 3. Percentage change in forced expiratory volume in 1 second (FEV_1) and in specific airway resistance ($SRaw$) in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to ozone during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

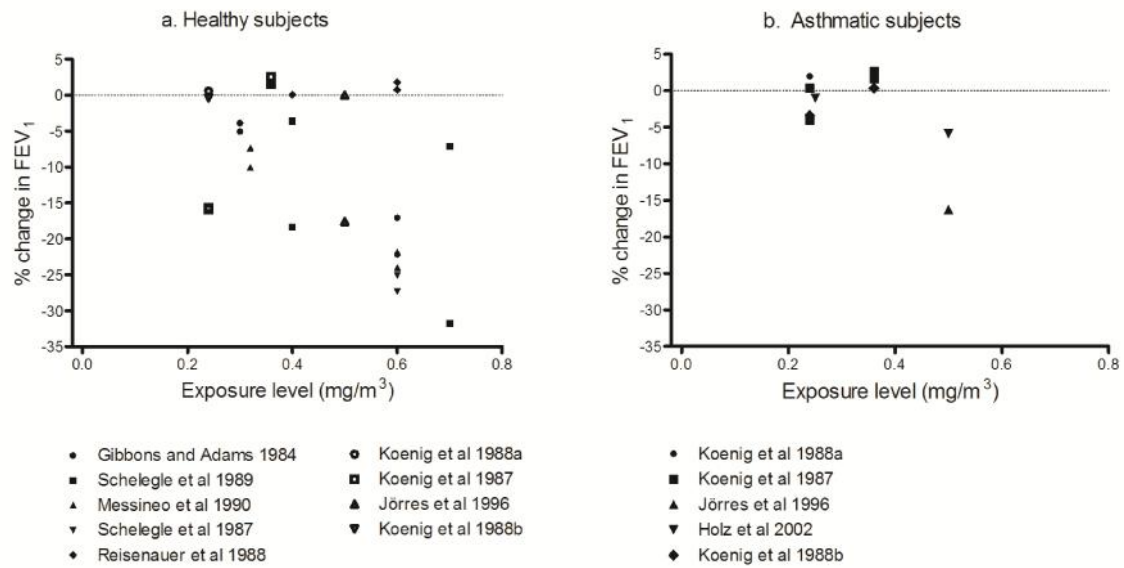


Figure 4. Percentage change in forced expiratory volume in 1 second (FEV₁) in healthy and asthmatic subjects following inhalation exposure (mouth-only breathing) to ozone during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

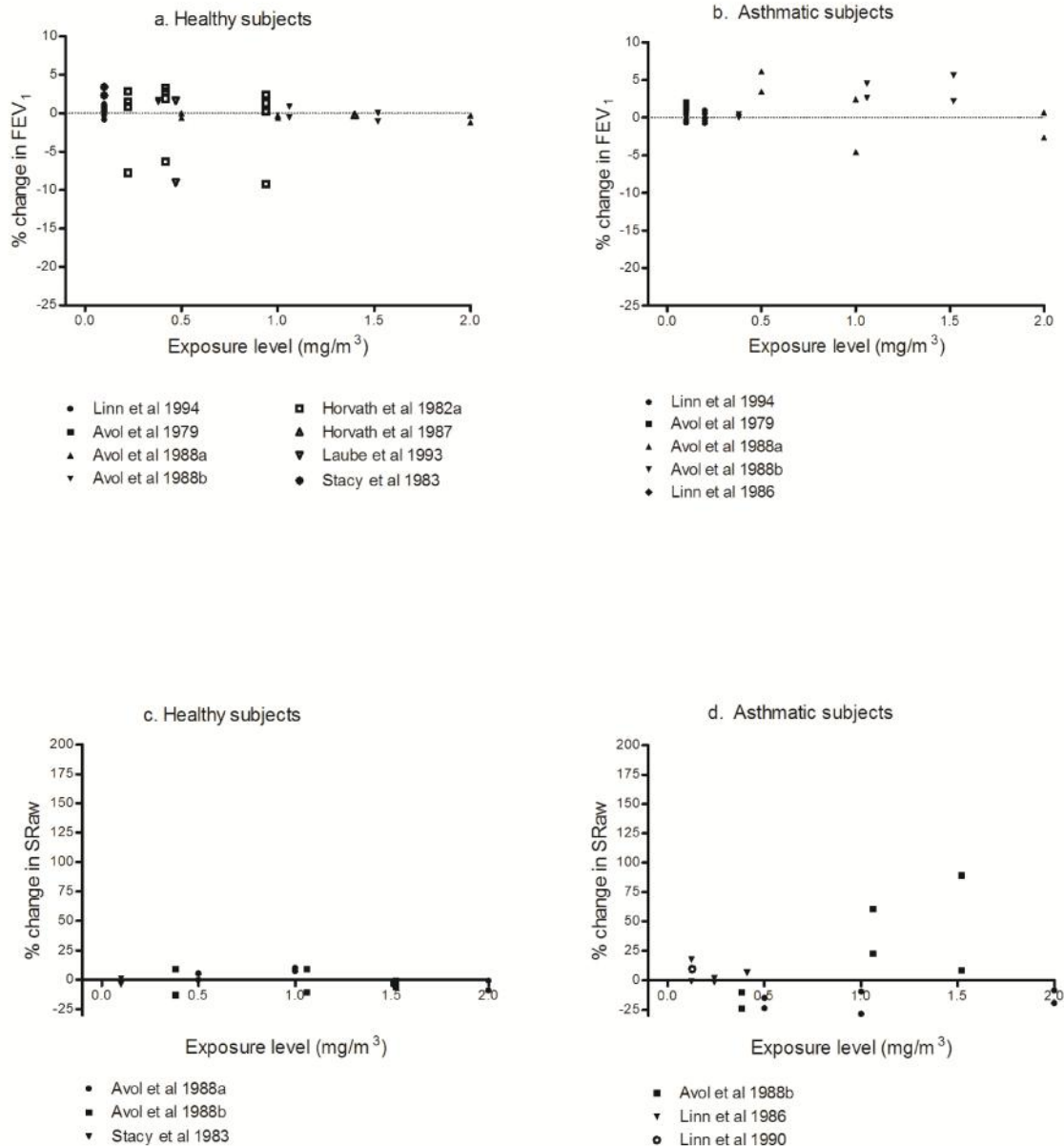


Figure 5. Percentage change in forced expiratory volume in 1 second (FEV₁) and in specific airway resistance (SRaw) in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to sulfuric acid during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

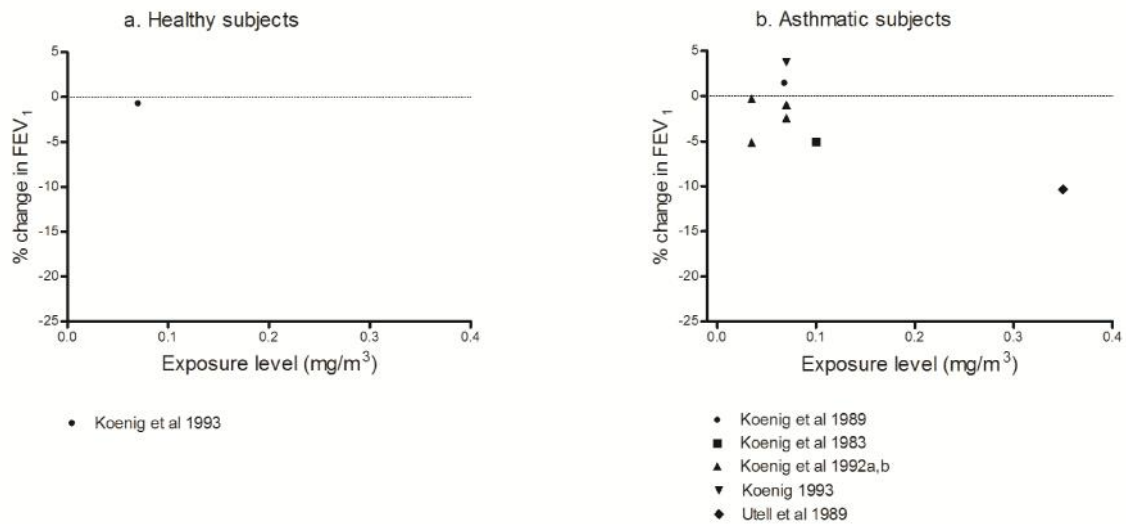


Figure 6. Percentage change in forced expiratory volume in 1 second (FEV₁) in healthy and asthmatic subjects following inhalation exposure (mouth-only breathing) to sulfuric acid during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

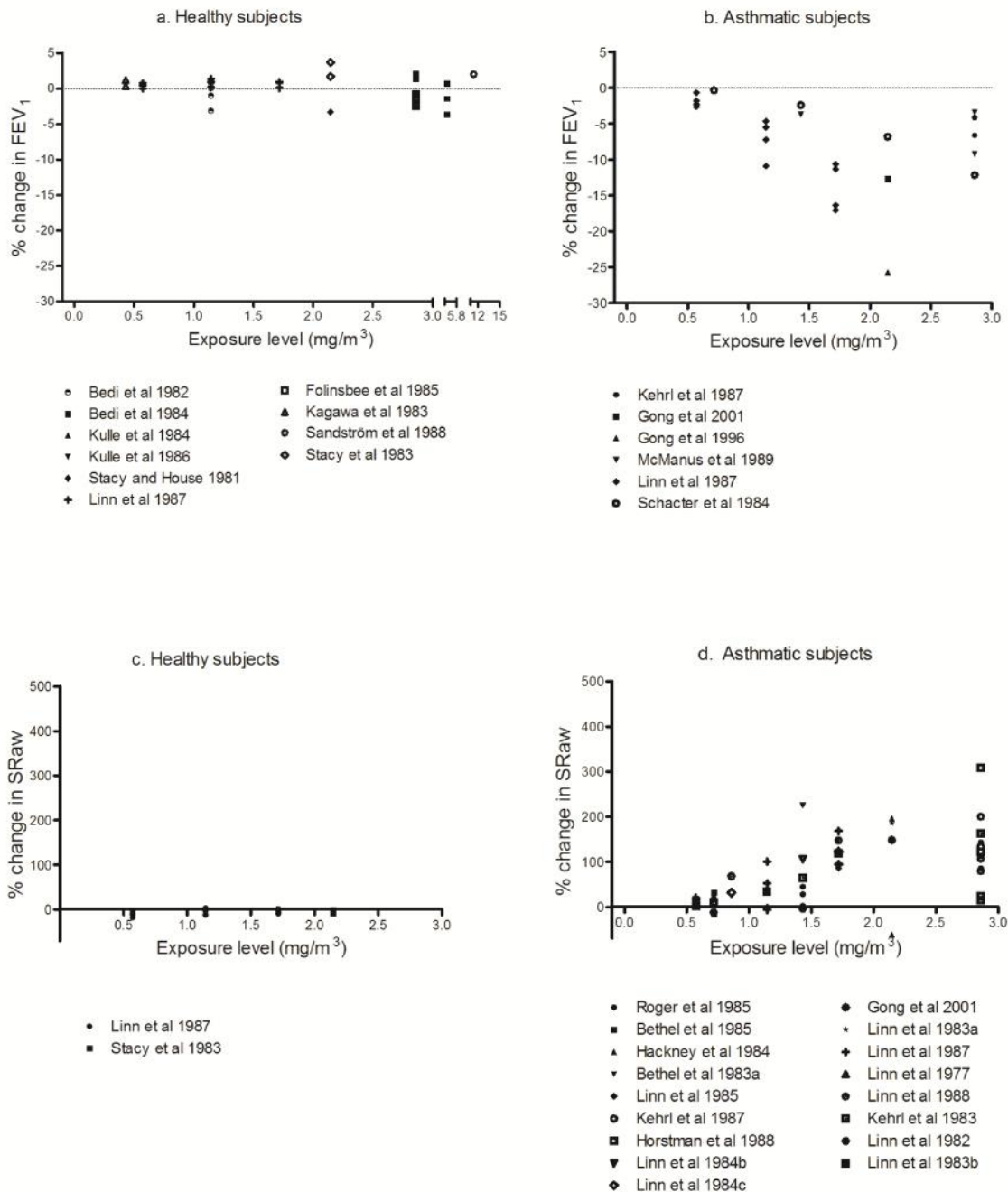


Figure 7. Percentage change in forced expiratory volume in 1 second (FEV₁) and in specific airway resistance (SRaw) in healthy and asthmatic subjects following exposure by inhalation (oronasal breathing) to sulfur dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.

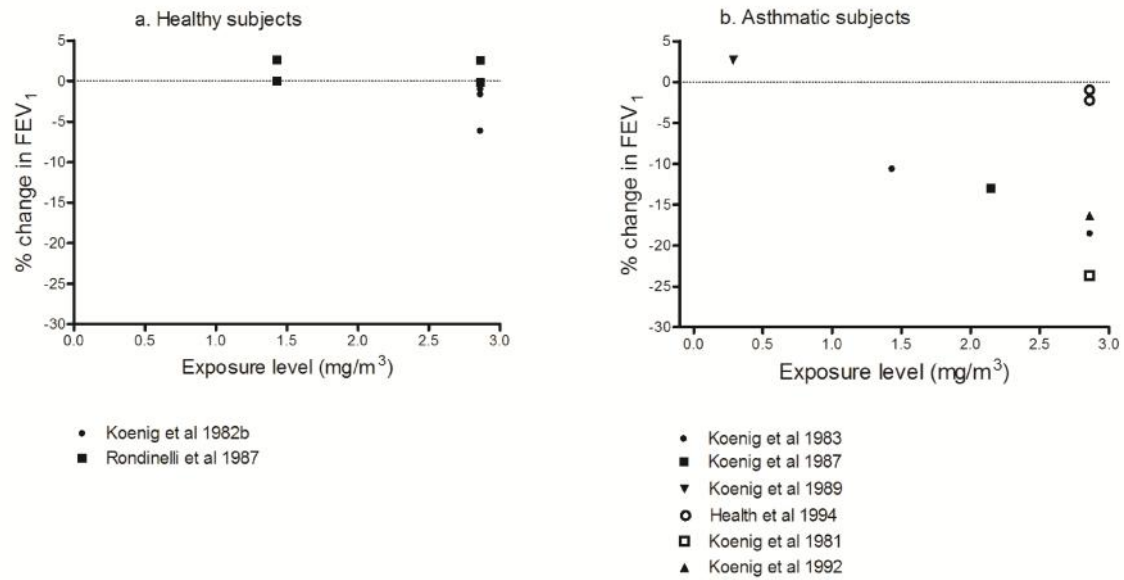


Figure 8. Percentage change in forced expiratory volume in 1 second (FEV₁) in healthy and asthmatic subjects following inhalation exposure (mouth-only breathing) to sulfur dioxide during exercise. Each dot represents the mean response of all subjects in a particular experiment or level of exposure.