HEALTH EFFECTS OF
PROJECT SHAD
CHEMICAL AGENT:

SULFUR DIOXIDE

[CAS 7446-09-5]

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SPECIAL NOTE ON PSYCHOGENIC SEQUELAE OF PERCEIVED EXPOSURE TO BIOCHEMICAL WARFARE AGENTS

This report deals primarily with the biological health challenges engendered by the agent that is the subject of the report. Nevertheless, this report also incorporates, by reference and attachment, a supplement entitled "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents".

The supplement addresses and describes a growing body of health effects research and interest centered upon the psychogenic sequelae of the stress experienced personally from actual or perceived exposure to chemical and biological weaponry. Because awareness of exposure to agents in Project SHAD logically includes the exposed person also possessing a perception of exposure to biochemical warfare agents, the psychogenic health consequences of perceived exposure may be regarded as additional health effects arising from the exposure to Project SHAD agents. This reasoning may also apply to simulants and tracers. Therefore, a general supplement has been created and submitted under this contract to address possible psychogenic effects of perceived exposure to biological and chemical weaponry.

Because such health effects are part of a recent and growing public concern, it is expected that the supplement may be revised and expanded over the course of this contract to reflect the actively evolving literature and interest in the issue.
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I. EXECUTIVE SUMMARY

Sulfur dioxide (SO\textsubscript{2}) has the Chemical Abstracts Service Registry Number (CAS#) 7446-09-5. Under normal conditions, it is a colorless gas with a pungent odor. Sulfur dioxide is a significant component of air pollution and also has a variety of industrial applications, from refining raw materials to preserving food. In Project SHAD, SO\textsubscript{2} was tested to determine if it could be used as a simulant for the nerve gas sarin.

As sulfur dioxide is normally a gas, most exposure is likely to be through the respiratory tract, where the chemical's ready solubility causes it produce sulfurous acid (H\textsubscript{2}SO\textsubscript{3}), a severe irritant. Additionally, sulfur dioxide produces H+, bisulfate (HSO\textsubscript{3}-) and sulfite (SO\textsubscript{3}=), which affect the smooth muscles and nerves involved in bronchoconstriction. These reactive ions have been shown to affect sodium currents and potassium currents in neurons.

The lungs are particularly susceptible to both the chronic and acute effects of SO\textsubscript{2}. Acute reactions to the compound, which typically occur at levels higher than the odor threshold and standard permissible levels, include irritation, bronchoconstriction, asthma-like symptoms and respiratory distress. Asthmatics can be particularly susceptible to the pulmonary effects of SO\textsubscript{2}. Permanent impairment of lung function, particularly in the form of reactive airways dysfunction syndrome (RADS), chronic pulmonary disease or chronic obstructive pulmonary disease (COPD), can result from exposures to high enough levels; asthmatics may suffer enhanced sensitivity.

SO\textsubscript{2} may also cause damage to developing fetuses and to the reproductive system. The testes in particular appear to be especially vulnerable to permanent toxic effects, indicated from both animal and human data. Chronic exposures to elevated SO\textsubscript{2} levels are associated with increases in cerebrovascular and heart disease, pulmonary disorders, increased morbidity and mortality and low birthweights.

At the cellular/molecular level, SO\textsubscript{2} decreases levels of antioxidant enzymes, increases membrane permeability, causes chromosome breakage and is mutagenic or comutagenic.

There exists evidence of a possible correlation between elevated SO\textsubscript{2} levels and increases in cancer. While evidence suggests sulfur dioxide to be a co-carcinogen, there is insufficient evidence to show that it causes cancer directly. (The International Agency for Research on Cancer (IARC) finds SO\textsubscript{2} to be not classifiable as to its carcinogenicity to humans (IARC Group 3), citing inadequate or limited evidence of carcinogenicity from either human or animal studies.)

Psychogenic health effects of perceived exposure to sulfur dioxide have been speculated to have occurred during pollution scares. Respiratory and cardiovascular diseases were proportionately increased in one incident although it could not be ruled out that the increase was from other causes. Information on the general psychogenic issues and effects of perceived exposure to biological or chemical warfare agents is contained in the
supplement report under this contract “Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents.”

Recommended treatments for sulfur dioxide exposure include 2% sodium bicarbonate sprayed into the air as well as inhaled into the lungs to neutralize its effects. Other treatments for SO₂ exposure include s-carboxymethylcysteine for asthmatics; theophylline, zafirlukast (a leukotriene receptor antagonist) and albuterol for patients with a specific allergy.
II. BACKGROUND DATA

Identification & Physical Chemistry

Project SHAD Chemical Agent Name: Sulfur dioxide

Chemical Formula: SO\textsubscript{2}

Chemical Structure: O=S=O

CAS#: 7446-09-5

Alternate Names: Sulphur dioxide, sulfur oxide, sulfurous acid anhydride, sulfurous anhydride, and sulfurous oxide, bisulfite (Air Liquide)

Molecular Weight: 64.06

Vapor Pressure: 2,538 mm Hg at 70.0EF (21.1°C)

Vapor density: 1.43 g/mL (water = 1.00)

Boiling Point: (760 mm Hg): 14.0°F (-10.0°C)

Freezing point: -99.4°F (-72.7°C)

Water solubility: Soluble in water (11.3 g/100 mL at 68°F [20°C])

Flammability: Nonflammable

Equivalency: 1 ppm = 2.62 mg/m\textsuperscript{3}


At room temperature under normal conditions, sulfur dioxide (SO\textsubscript{2}) is a colorless gas. When pressurized or cooled, it is a colorless liquid. A pungent odor is detected by most people at levels of 1-3 ppm and may be adequate to warn of acute exposure.

Sources & Use

The combustion of fossil fuels (75% to 85% of the industrial sources of sulfur dioxide), the smelting of sulfide ores, volcanic emissions, and several other natural sources are primary sources for the release of sulfur dioxide gas. Toxic amounts of sulfur dioxide can be released from the preservative chemical metabisulfite in the presence of water and acid (ATSDR 2004).
Sulfur dioxide has several agricultural and industrial uses (ATSDR 2004). Sulfur dioxide can serve as a warning marker and fire retardant for liquid grain fumigants. 300,000 or so tons are employed every year for the manufacture of sulfur-containing chemicals, particularly hydrosulfites. The bleaching of wood pulp and paper is another common use along with processing, disinfecting, and bleaching food products. There are also uses in metal, ore, and oil refining as well as in waste and water treatment. Sulfur dioxide is used in small amounts as a food and wine preservative (ATSDR 2004; Toxicology Update 1995).

In Project SHAD, SO$_2$ was disseminated to test its usefulness as a simulant for the nerve agent sarin (Fact Sheet 2003).

**Kinetics/Action**

Absorption of SO$_2$ in its common gaseous form usually occurs in the upper part of the lungs (Anonymous 1996). It immediately passes through the mucous membranes into the blood (Petruzzi, et al.1994) whereupon it becomes associated with the alpha-globulin fraction of plasma (Toxicology Update, 1995). At low concentrations, for reasons still obscure, only a small percentage of the dose is absorbed (as little as 5%) while at much higher exposure concentrations (e.g. 100 ppm) much more of the dose is absorbed (Toxicology Update 1995).

SO$_2$ is very soluble in, and reactive with, water. In the moist pulmonary environment, SO$_2$ produces sulfurous acid (H$_2$SO$_3$), a severe irritant, in addition to H+, bisulfate (HSO$_3^-$), sulfite (SO$_3^{=}$), which in turn affect the smooth muscles and nerves involved in bronchoconstriction (Gunnison & Jacobsen 1987; Anonymous 1996, ATSDR 2004). These reactive ions have been shown to affect sodium and potassium currents in neurons (Du & Meng 2004a; Du & Meng, 2004b).

SO$_2$ increases lipid peroxidation of cell membranes and interferes with antioxidative processes by decreasing the levels of superoxide dismutase, catalase and glutathione peroxidase. (The damage from this can affect many systems.) (Meng et al, 2003)

The liver metabolizes SO$_2$ via a molybdenum-dependent sulfide oxidase pathway. The subsequent metabolites, sulfate esters and sulfate, are eliminated through the urine (Anonymous 1996)

Dermal absorption rates have not been quantified (Toxicology Update, 1995).
III. HEALTH EFFECTS/TOXICITY PROFILES

Overview

Sulfur dioxide is considered a primary irritant and can have severe health effects, both short-term and long-term. At sufficiently high doses (over 400 ppm) acute exposure can be fatal. Except in cases of special sensitivity, for significant health effects to occur the acute concentration must be relatively high, normally well above the substance’s odor threshold and well above the standard exposure levels for regularly exposed workers. (ATSDR 2004; Toxicology Update 1995).

Because sulfur dioxide is gaseous under ordinary conditions, the main target system for exposure and toxic action is the respiratory system. Nevertheless, the eye and skin can also be subject to severe irritation effects arising from direct contact. Asthmatics appear to have a special sensitivity to sulfur dioxide. In fact, SO\textsubscript{2} is used for the intentional induction of asthmatic attacks for experimental or therapeutic purposes (ATSDR 2004; Lazarus et al 1997; Koenig et al 1987).

Multiple systems can be affected as a result of sulfur dioxide exposure. In mice, exposure to inhaled SO\textsubscript{2} at 6 hours per day for 7 days caused oxidative damage to the following organs: brain, lung, heart, liver, stomach, intestine, spleen, kidney, and testis (Meng et al 2003; Meng 2003) Chronic exposure, usually associated with high air pollution levels, has been associated with increased morbidity and mortality.

Noted possible long-term or permanent effects of exposure include reactive airways dysfunction syndrome, testicular damage, tumorigenesis, and possible cocarcinogenesis, i.e. serving as a carcinogen only when acting in conjunction with other substances or pollutants like diesel exhaust particles, or perhaps benzo[a]pyrene (Ohyama et al 1999; Reed & Jones 1996; Gunnison et al 1988; Toxicology Update 1995). Increased asthma sensitivity is a noted response to exposure; repeated exposure of guinea pigs to low levels of sulfur has been shown to be associated with the enhanced development of ovalbumin-induced asthma reactions (Park 2001).

Key registries and regulatory bodies recognize sulfur dioxide toxicity. The U.S. Environmental Protection Agency (EPA) characterizes sulfur dioxide as a priority air pollutant (ATSDR 2004). The Registry of the Toxic Effects of Chemical Substances (RTECS) considers SO\textsubscript{2} to be tumorigenic, mutagenic, a primary irritant, and a reproductive effector (RTECS 2004).

Some key regulatory levels are currently determined to be as follows (ATSDR 2004):

ACGIH TLV (Threshold Limit Value) = 2 ppm; 5.2 mg/m3 TWA (time-weighted average)

OSHA PEL (Permissible Exposure Limit) = 5 ppm (averaged over an 8-hour work shift)
NIOSH IDLH (Immediately Dangerous to Life or Health) = 100 ppm

AIHA ERPG-2 = 3 ppm  (This describes the maximum airborne concentration up to which it is believed that nearly all persons could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects, or developing symptoms that could impair their abilities to take protective action)

Acute Exposure/Effects

Sulfur dioxide is considered a primary irritant (RTECS 2004). Sulfur dioxide at toxic levels in the air can greatly irritate the nose and throat (Witek et al 1985a; Witek et al 1985b). The lungs respond strongly as well, usually with bronchoconstriction and increased upper airway resistance (Gunnison & Jacobsen 1987; Witek et al 1985a; Witek et al 1985b).

Toxic sulfur dioxide exposure is a cause of reactive airways dysfunction syndrome (RADS), whose bronchoconstriction symptoms are similar to asthma. Unlike asthma, which is triggered by an allergen, RADS is a response to an acute exposure to an irritating agent (Palczynski, et al. 1994).

Adverse effect on pulmonary function by an exposure at low concentrations (0.75 ppm) is reversible (Petruzzi, et al. 1994). At higher concentrations, airways can become severely obstructed (Rabinovitch et al 1989) and the effects can involve the lower airways (Witek et al 1985a; Witek et al 1985b).

Moderate to high inhalation doses of sulfur dioxide may cause nausea and vomiting (ATSDR 2004).

Effects tend to be dose dependent. Typical levels of human susceptibility run as follows:

At 5 ppm, dryness of the nose and throat can be observed and resistance to bronchial airflow significantly increases. At 6-8 ppm tidal respiratory volume may noticeably decrease. At 10 ppm, sneezing, coughing, and wheezing may be observed, possibly accompanied by eye, nose and throat irritations. Nosebleeds may also be seen. At this level, asthmatics are likely to experience asthmatic paroxysm, lasting possibly for several days. At 20 ppm, bronchospasms tend to begin and eye irritation is very likely. At 50 ppm discomfort becomes extreme, but permanent injury is unlikely if exposure is less than 30 minutes duration. Above 50 ppm, reflex closure of the glottis can take place and last for a period of minutes. Exposure to sulfur dioxide at a concentration of 400 ppm will likely constitute an immediate danger to life. Concentrations above 1000 ppm are usually fatal within 10 minutes; the proximate cause of death is assumed to be respiratory depression. For asthmatics, exposures as low as 0.1 ppm for as short a duration as 10 minutes during strenuous physical activity, can result in significant respiratory changes and asthmatic attacks. (Toxicology Update, 1995)
High doses of inhaled SO2 have also been associated with certain acute neurotoxic effects. These effects include peripheral neuritis, convulsions, agitation, tremor, vertigo, and fever. (Toxicology Update, 1995)

There may also be an altered sense of smell or taste (ATSDR 2004; Toxicology Update 1995).

In rabbits, ocular irritation occurs at 6 ppm after 4 hours, but permanent damage only occurs at extremely high, near-fatal levels. Liquid SO2, which is found in high pressure or low temperature conditions, may induce severe corneal damage. The corneal epithelium turns grey and over a period of hours, the eyelids swell. The conjuntiva may become white and opaque. Thrombosis of ocular blood vessels can also occur (Toxicology Update, 1995).

SO2 exposure to skin can directly cause dermatologic reactions, such as urticaria (Pirila 1954). At sufficiently high doses, sulfur dioxide severely irritates the skin, inducing pain, redness, and blisters (ATSDR 2004).

A case of human parenteral exposure has happened. Sulfur dioxide, in addition to other sulfur volatiles, was discovered in the reverse-osmosis water used at a hemodialysis center. Patients became acutely ill, mostly with chills and nausea, and two died (Selenic et al 2004).

The following table presents some key acute inhalation toxicity values (RTECS 2004):

<table>
<thead>
<tr>
<th>Species</th>
<th>Lowest Published Lethal Concentrations</th>
<th>Lethal Concentration 50% (LC50)</th>
<th>Lowest Published Toxic Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>1000 ppm/10 minutes; 3000 ppm/5 min</td>
<td></td>
<td>12 ppm/1h; 3 ppm/5 days; 2.2 mg/m³/30 min</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>1039 ppm/24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>3000 ppm/30min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>2168 mg/m³</td>
<td>30 mg/m³</td>
<td></td>
</tr>
<tr>
<td>Frog</td>
<td>1 pph/15 min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Long-Term Sequelae of Acute Exposure**

A short exposure to sulfur dioxide may result in long-term consequences. Particularly observed is the potential long-term durability of reactive airways dysfunction syndrome (RADS) (ATSDR 2004).
Upon exposure to sulfur dioxide, and shortly after, acute respiratory distress (Ramakers et al 1995) and severe airways obstruction (Rabinovitch et al 1989) may commence and progress. Over the few weeks following this initial event, measured pulmonary function can decrease and inflammatory responses increase (Harkonen et al 1983; Rabinovitch et al 1989). After a few months (between 3 and 12 months), there may be either some improvement or a halt to the decline in function (Harkonen et al 1983; Rabinovitch et al 1989). The original pulmonary function may not be regained, although in some cases there can be a partial reversibility. Several cases of this type were observed for two years (Rabinovitch et al 1989), four years (Harkonen et al 1983) ten years(Ramakers et al 1995) and thirteen years (Piirila et al 1996). In these cases, the long-term effects were obstruction, either from inflammation or bronchial constriction, and bronchial hyperreactivity.

Increased sensitivity among asthmatics is a possible permanent consequence and animal study gives some confirmation to the existence of that effect. (Park 2001).

SO\(_2\) can be toxic to the reproductive system of mammals after intense but brief exposure. Oxidative damage to testicles occurred in mice exposed to SO\(_2\) at 6 hours per day for 7 days, resulting in decreased levels of superoxide dismutase and glutathione peroxidase (Meng & Bai 2004).

**Chronic Exposure/Effects**

In general, chronic exposure to SO\(_2\) is associated an overall increase in morbidity and mortality (Anonymous 1996; Zhang et al 2000).

Effects of chronic exposure include: wheezing, mild dyspnoea, persistent cough and phlegm (Osterman et al 1989; Chapman et al 1985; Wichmann and Heinrich 1995); bronchial hyperresponsiveness (Jammes 1998); chronic respiratory disease (Abbey et al 1993) and chronic obstructive pulmonary disease (COPD) symptoms (Euler et al 1987).

Increases in mortality have been associated with increased proportions of ambient SO\(_2\) levels. The elevated death rate is due to respiratory and pulmonary diseases, along with cardiovascular and cerebrovascular diseases, including coronary and ischaemic heart diseases and atherosclerotic diseases (Chang et al 2003; Ronneberg 1995). In addition to pulmonary and circulatory mortality increases, elevated levels of SO\(_2\) are associated with an increase in neonatal mortality (Shinkura et al 1999; Petruzzi, et al. 1994)  An increase in sperm abnormality and a decrease in fecundity in humans was found associated with an increase in SO\(_2\) levels in an area in Bohemia (Dejmek et al 2000).

A very recent study of low birth weight neonates in Taiwan found a 20% greater risk of the birth defect in mothers who had been exposed to greater than12.4 ppb of SO\(_2\) in the last trimester (Lin et al 2004). Rodent and rabbit studies indicate low birth weight, musculoskeletal and behavioral defects, and fetotoxicity as consequences of inhalation exposures. Maternal exposures prior to copulation have led to impairment of fertility and to menstrual cycle disorders (RTECS 2004).
Cytotoxicity

Sulfur dioxide is toxic to cells. In the trachea, high concentrations cause epithelial desquamation (Anonymous 1996). The growth of cultured cells is inhibited by SO$_2$ (Petruzzi, et al. 1994) Cellular functioning of alveolar macrophages is impaired by SO$_2$: one cytotoxicity assay found a decrease in the production of the tumor necrosis factor-alpha and interleukin-1 beta cytokines after exposure to SO$_2$ (Knorst et al. 1996). It also damages cells by affecting membrane permeability, according to a cytotoxicity assay that measures lactose dehydrogenase released into the medium (Hayden et al. 1990).

Genotoxicity

SO$_2$ has been shown to inhibit DNA synthesis and is also clastogenic, i.e. it causes chromosome breakage (Petruzzi, et al. 1994; Yi & Meng 2003). These effects were found in sulfuric acid factory workers, whose lymphocytes had high frequencies of micronuclei. (Micronuclei are fragments of chromosomes that are not incorporated into the nucleus during cell division and are used to assess cytogenetic damage) (Meng and Zhang, 1990). SO$_2$’s effect on the roots of Allium (garlic) and Vicia (broad bean) forms the basis of one genotoxicity assay. Exposure to SO$_2$ was associated with a decline in the mitotic index and an increase in micronuclei frequency (Yi & Meng 2003). Sulfur dioxide has been found to be weakly mutagenic, with unknown cofactors hypothesized as necessary for its action (Meng & Zhang 1999).

Tumorigenicity/Carcinogenicity

The Registry of Toxic Effects of Chemical Substances (RTECS) lists SO$_2$ as tumorigenic and cocarcinogenic by inhalation in rats and mice. Studies conflict regarding the cocarcinogenic effect of SO$_2$. Some claim that it enhances the carcinogenic potential of polyaromatic hydrocarbons (PAHs) and diesel exhaust particles to induce tumors in lungs (Menzel et al. 1986; Ohyama K et al. 1999), while another challenges the suggestion that SO$_2$ may have a potentiative effect on the carcinogen benzo[a]pyrene (Gunnison et al. 1988).

The International Agency for Research on Cancer (IARC) finds SO$_2$ to be not classifiable as to its carcinogenicity to humans (IARC Group 3), citing inadequate and limited evidence in either human or animal studies. Human studies that showed a correlation had uncontrolled confounding factors preventing conclusiveness (IARC 1992). The IARC has also found there to be only limited evidence for the carcinogenicity in experimental animals of sulfur dioxide.
IV. PSYCHOGENIC EFFECTS

Psychogenic effects are suggested as a confounder in an examination of the health effects of a five-day period of excessive smog in Germany. During that episode, SO$_2$ concentrations were significantly elevated and public reports of the excess contamination were made. Morbidity and mortality for both respiratory and cardiovascular diseases were proportionately increased. (Wichmann et al 1989)

Information on the general psychogenic issues and effects of perceived exposure to biological or chemical warfare agents is contained in the supplement report under this contract “Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents.”
V. TREATMENT & PREVENTION

Barach (1971) recommends a spray of 2% sodium bicarbonate to neutralize SO$_2$, both in the air as well as inhaled into the lungs. Other recommended treatments for SO$_2$ exposure include s-carboxymethylcysteine (Sugiura et al 1997). For exposed asthmatics, theophylline (Koenig et al 1992) and zafirlukast (a leukotriene receptor antagonist) (Lazarus et al 1997) have been suggested as well as albuterol for patients with allergic responses (Koenig et al 1987).
VI. SECONDARY SOURCE COMMENT

The discussion of sulfur dioxide effects in the "Project SHAD Glossary" stated in is consistent only with symptoms of acute exposure. There is no mention in the statement of long term effects, cytotoxic or genotoxic effects, or mention of SO$_2$ as a possible cocarcinogen. The Agency for Toxic Substances and Disease Registry's Medical Management Guidelines (MMGs) for Sulfur Dioxide reports no genotoxicity or reproductive effects for SO$_2$ (ATSDR 2004). Our reading of the entry on sulfur dioxide for RTECS finds that it attributes damage to animal testes incorrectly to sulfur dioxide when it appears that the animal who were not exposed to SO$_2$ suffered the damage to spermatogenesis.
VII. BIBLIOGRAPHY WITH ABSTRACTS

{The following bibliography includes supplemental material not cited in the text, in addition to the text citations. Unless otherwise noted, the abstracts for the following references are rendered verbatim as provided by the original publication or as made available in a standard print or electronic catalogue, or database. Errors, omissions, or other defects of language, form, style, or substance are strictly those of the original source or its transmission.}

Seventh-day Adventist (SDA) non-smokers who had resided since 1966 within five miles of their 1977 residence (n = 3914) completed a standardized respiratory symptoms questionnaire in 1977 and again in 1987. For each participant, cumulative ambient concentrations from 1977 to 1987 of suspended sulfates (SO4) in excess of several cutoffs as well as mean concentrations were estimated by interpolating monthly ambient concentration statistics from state air monitoring stations to the individual's residential and workplace zip codes. There were significant associations between ambient concentrations of suspended sulfates and development of new cases of asthma, but not new cases of overall airway obstructive disease (AOD) or chronic bronchitis. Comparison of previous analyses, in this population, of respiratory disease symptoms and total suspended particulates (TSP), ozone, and sulfur dioxide (SO2), and multipollutant analyses of these pollutants with SO4, indicated these results were not due to a surrogate relationship with other air pollutants. Development of definite symptoms of AOD and chronic bronchitis was most strongly related to TSP.

OBJECTIVE: To review the literature on ambient air pollution and respiratory disease, and to consider the criteria for defining causation. DATA SOURCES: Medical and scientific journals indexed by Medline, conferences, proceedings and monographs.
STUDY SELECTION: Two kinds of study were selected--(i) controlled clinical trials which have exposed normal or asthmatic subjects and/or patients with chronic obstructive airways disease to sulphur dioxide, nitrogen dioxide or ozone; and (ii) epidemiological studies which have investigated the chronic toxicity of these pollutants, acid aerosols and polycyclic aromatic hydrocarbons. DATA EXTRACTION AND SYNTHESIS: Experimental studies were tabulated under the headings "Design", "Subjects", "Pollutant concentration", "Duration of exposure", "Outcome measures" and "Conclusions". Epidemiological studies were summarised and compared in an attempt to reconcile conflicting results. (The experimental and epidemiological evidence has been used by regulatory bodies to develop ambient air quality guidelines.) CONCLUSIONS: At the present state of knowledge, it is not possible to conclude that air pollution can cause
respiratory disease de novo, but levels marginally above current guidelines certainly have adverse effects on individuals with pre-existing chronic lung disease.


Data from exposure of experimental animals and human subjects to sulfuric acid presents a consistent picture of its toxicology. Effects on airway resistance in asthmatic subjects were well predicted by data obtained on guinea pigs. Sulfuric acid increases the irritant response to ozone in both rats and man. In donkeys, rabbits, and human subjects, sulfuric acid alters clearance of particles from the lung in a similar manner. These changes resemble those produced by cigarette smoke and could well lead to chronic bronchitis.

Data obtained on guinea pigs indicate that very small amounts of sulfuric acid on the surface of ultrafine metal oxide aerosols produce functional, morphological, and biochemical pulmonary effects. Such particles are typical of those emitted from coal combustion and smelting operations. Sulfate is an unsatisfactory surrogate in existing epidemiology studies. Sulfuric acid measurement is a critical need in such studies.


**Amdur. 1969.** Toxicologic Appraisal of Particulate Matter, Oxides of Sulfur, and Sulfuric Acid. *Journal of the Air Pollution Control Association, Vol.19, No 9, pages 638-643, 56 references.* Toxicological review is presented of sulfur-dioxide (7446095) and sulfuric-acid (7664939) as air pollutants. Sulfuric-acid is shown to be a more potent respiratory irritant than pure sulfur-dioxide, with the irritant potential affected by particle size and relative humidity. Sulfur-dioxide as an air pollutant is converted to sulfuric-acid, thus increasing its hazard as a respiratory irritant. Control measures should be aimed at sulfur-dioxide and particulate material and not against either alone.

**Anon. 1985.** Reexamination of the GRAS Status of Sulfiting Agents. *Govt Reports Announcements & Index (GRA&I), Issue 11. TD3.* This report of an ad hoc Review Panel reexamines the GRAS status of sulfiting agents as food ingredients. The Panel estimates that the mean per capita daily consumption of sulfur dioxide equivalents (SDE) is about 10 mg/day (0.17 mg/kg/day). The 99th percentile consumption, reflecting that of the most frequent consumers of the more highly sulfited foods and beverages, is estimated to be approximately 180 mg/day (3 mg/kg/day). Metabolism, acute and chronic toxicity, teratogenicity, mutagenicity, and carcinogenicity of sulfiting agents are reviewed and evaluated. The Panel addresses the use of sulfiting agents on fresh precut potatoes and fresh fruits and vegetables and also considers the acute bronchial reactions experienced by some asthmatic patients following consumption of meals including some foods containing sulfites. Conclusions of the Panel regarding the GRAS status of sulfiting agents are presented. This report contains a bibliography with 166 cited references and 133 other reviewed citations.

Although sources of airborne lead have been reduced over the last decade, particularly with the use of lead-free gasoline, there are still relatively high levels of lead contamination in soils and the residential housing stock built before the 1970s, which pose a risk for continued direct exposure through ingestion or airborne exposure if resuspended. Neurobehavioral effects, particularly as a result of early childhood exposures, have been documented, and, because of the way lead is stored in the body, late effects can become manifest during periods of high bone turnover (e.g., pregnancy, lactation, or hyperthyroidism). Late consequences not only relate to lead excretion affecting the fetus or newborn but also appear to be associated with hypertension in adults. Control of exposure in early life is an important component of appropriate preventive action.


OBJECTIVE: To investigate effects of short-term sulfur dioxide inhalation to the liver. METHODS: Haematoxylin and eosin staining (HE) and transmission electron microscopy (TEM) were used to study the pathologic changes in mice liver after sulfur dioxide (SO(2)) inhalation. RESULTS: Exposure to 56 mg/m(3), 112 mg/m(3) 168 mg/m(3) SO(2) caused increasingly severe liver injuries, as detected by HE staining and TEM. The morphologic changes included spotty necrosis with lymphocyte, monocyte, and neutrophil infiltration, fatty degeneration of hepatocytes with dilatation of rough endoplasmic reticulum and dissociation of ribosomes, as well as degeneration of mitochondria and karyorrhexis. CONCLUSION: SO(2) inhalation can cause marked liver injury in experimental settings.


Air pollution, in particular that generated by road traffic, is a matter of rising public concern and has been implicated in the worsening of asthma. In this article, the evidence that air pollutants (particularly sulphur dioxide, ozone and nitrogen dioxide) can affect the airways of asthmatic patients is reviewed, and the possible molecular mechanisms
that may link air pollution to increased inflammation in the airways are discussed. Airway epithelial cells may respond to oxidant pollutants by the activation of transcription factors, such as nuclear factor kappa B, resulting in increased transcription of genes for certain cytokines, such as interleukin 8 and inflammatory enzymes, such as inducible nitric oxide synthase and cyclo-oxygenase.

**Bates. 1995.** Observations on asthma. *Environ.Health Perspect.* 103 Suppl 6: 243-247. A review of the present understanding of asthma leads to the following conclusions: an elevated IgE is the principal risk factor in the development of childhood asthma; secondary exposure to a wide range of environmental agents (including indoor bioallergens) accounts for the variations in prevalence; prevalence (defined by a positive answer to the question "Have you ever had doctor-diagnosed asthma?") ranges between 4 and 8% in children. Black children have a slightly higher prevalence than white children in the United States, and in both races boys have a higher prevalence than girls. A high prevalence is found in Puerto Rican children in the United States. Patterns of utilization of health care resources (hospital emergency departments, individual physicians, etc.) are dependent on economic circumstances. Low-income children have higher annual morbidity (days in hospital, days off school, etc.) than higher income children and are more dependent on hospital emergency departments for primary care. Relatively little is known about nonatopic asthma in adults, although virus infections and occupational exposures play some part in its induction. There are some striking examples of asthma attack periodicity, and much may be learned from these. Hospital admissions for asthma have increased in many regions over the past 15 years; it is unlikely that this represents the increased admission of milder cases and hence would indicate that asthma has become more severe. This is likely to be a more sensitive indicator of change than mortality. Associations between indices of health effects and air pollutants indicate that these are probably playing a role in the worsening of asthma. Adverse effects related to SO\(_2\) and NO\(_2\) exposures have been documented, and fine particulate pollution (PM10) is also associated with worsening of asthma. Ozone is an intense respiratory irritant, and, together with acid aerosols, may well be playing a role in the worsening of asthma. It is not known whether any of these agents are affecting prevalence.


In 1820 the first malignancies ascribed as due to occupational arsenic exposure were reported as scrotal cancers among smelters. A century later the causal relationship between chronic occupational, environmental or medical arsenical exposure and skin carcinogenesis was firmly established. From 1948 to 1975, nine out of eleven epidemiological studies have shown, initially or upon review, significant excess mortality from respiratory cancer among diverse occupations exposed to various inorganic arsenicals. Two of the nine studies have shown concomitant, significant excess mortality from lymphatic cancer, and another, from skin cancer. Additionally, two such studies have revealed a dose-response relationship between arsenical exposure and lung carcinogenesis. In the first, reported in 1969, the relationship was semi-quantitative, with
a possible interactive role by sulfur dioxide or other contaminants. The other demonstrated a dose-response which was quantitative for arsenic per se. Upon our reinterpretation, this dose-response also demonstrated an increased lung cancer mortality risk apparently at arsenic concentrations above 1 mg/M3, calculated as the 8-hour TWA daily exposure over a 40-year working life. However, these and related data do not reveal a definite no-effect exposure level. Thus, in the absence of data documenting a cancerigenically safe level of occupational exposure and because of the environmental ubiquity of arsenic, the conclusion is drawn that the arsenic body burden of workers should not be occupationally increased above that produced by the ambient level.

The availability of long-acting, locally effective anticholinergic agents that can be delivered by aerosol and that have little systemic toxicity offers an alternative or additional form of therapy for relief of airflow obstruction. Most studies of combination therapy have examined the interaction of anticholinergic drugs with beta-adrenergic agents. For patients with asthma, combination treatment appears not to increase significantly the maximal bronchodilatation achievable with beta-agonists alone but does appear to prolong bronchodilatation and to permit reductions in the dose of beta-agonists without loss of efficacy. For patients with chronic obstructive bronchitis and emphysema, combination therapy may also increase the bronchodilatation achievable with beta-adrenergic agents alone. Anticholinergic agents have been shown also to increase the inhibitory effect of sodium cromoglycate on the bronchospastic response to exercise, eucapnic hyperpnoea and sulphur dioxide.

Since the development of the World Health Organization (WHO) Air Quality Guidelines for Europe, a large number of epidemiologic studies have been published documenting effects of major air pollutants on health at concentrations below existing guidelines and standards. In this review, recent studies are discussed that permit some evaluation of short-term health effects observed at exposure levels lower than the current WHO Guidelines or U.S. Environmental Protection Agency (U.S. EPA) standards. Some studies have been conducted at concentration levels that never exceeded existing guidelines or standards. Other studies have been conducted at exposure levels sometimes exceeding current guidelines or standards. The published analyses of several of these studies permit evaluation of low-level health effects either because analyses were restricted to levels not exceeding the guidelines or graphic analyses were reported suggesting effects at these low levels. For ambient ozone, effects on lung function of subjects exercising outdoors have now been documented at 1-hr maximum levels not exceeding 120 micrograms/m3, i.e., half the current U.S. EPA standard. One study even suggests that such effects occur at levels below 100 micrograms/m3. Several studies are now available documenting effects of particulate air pollution on health in the virtual absence of SO2. Effects on mortality and hospital admissions for asthma have been documented at levels not exceeding 100 micrograms/m3, expressed as 24-hr average inhalable particles PM10 concentration. Effects on lung function, acute respiratory...
symptoms, and medication use have been found at 24-hr average PM10 levels not exceeding 115 micrograms/m3. When the WHO Air Quality Guidelines and the U.S. EPA standard for PM10 were developed, there were no studies available on health effects of PM10. In this review, we include nine studies documenting health effects of measured PM10 at low levels of exposure, indicating that there is now an entirely new epidemiologic database that can be evaluated in the process of revising current guidelines and standards. The low levels of exposure at which effects on health were seen underscore the urgent need for such reevaluations.


To quantitively evaluate the associations between ambient air pollutant and daily mortality of Beijing and to supply the scientific bases for formulating control measures. Air pollutants including CO, SO2, NOx, TSP, PM10. time series analysis Poisson regression was used to evaluate the relationship between cause-specific deaths and air pollutant, considering the potential confounding factors such as seasonal and long-term patterns, meteorological factors (air temperature, air humidity), as well as adjusting the influence of flu epidemics in winter of 1998. The results showed that in single-factor Poisson regression analysis, there is a significant positive correlation between the four pollutants and daily mortality except for the relationship between TSP and coronary heart disease deaths. In multi-factor Poisson regression analysis, when SO2 increase in 100 micrograms/m3, respiratory deaths, cardiovascular and cerebro-vascular deaths, coronary heart disease deaths and chronic obstructive pulmonary deaths increased by 4.21%, 3.97%, 10.68%, 19.22% respectively. Meanwhile, each 100 micrograms/m3 increase in TSP associated with 3.19% increase in the respiratory deaths and 0.62% increase in the cardiovascular and cerebrovascular deaths. It is suggested that air pollution is a risk factor for health and an increase of air pollution level might lead to a raise in daily mortality.

In early 1976, a survey of persistent cough and phlegm (PCP) prevalence was conducted in 5,623 young adults in 4 Utah communities. Over the previous 5 years, community-specific mean sulfur dioxide levels had been 11, 18, 36, and 115 micrograms/m3. Corresponding mean suspended sulfate levels had been 5, 7, 8, and 14 micrograms/m3. No intercommunity exposure gradient of total suspended particulates or suspended nitrates was observed. In nonsmoking mothers, PCP prevalence was 4.2% in the high-exposure community and approximately 2.0% in all other communities. In smoking mothers, PCP prevalence was 21.8% in the high-exposure community and approximately 15.0% elsewhere. In nonsmoking fathers, PCP prevalence was 8.0% in the high-exposure community and averaged 3.0% elsewhere. In smoking fathers, PCP prevalence was less strongly associated with ambient sulfur oxide exposure. Intercommunity prevalence differences in smoking and nonsmoking mothers, and in nonsmoking fathers, were significant at alpha = 0.05. A categorical logistic regression model, testing
ultaneously for effects of community and several covariates on PCP prevalence, yielded similar results. The results of this survey were similar to those of a similar survey conducted in Utah in 1970 and to those of other surveys. These results disclose an association of PCP prevalence with ambient sulfur oxide exposure, stronger in mothers than in fathers, stronger in nonsmokers and ex-smokers than in smokers, and stronger in 1970 than 1976.


The occurrence of sulfites in foods, drug products, and the environment; the characteristics of sulfite-sensitivity reactions; and the management of sulfite-sensitive individuals are reviewed. Sulfites are used in foods, beverages, and pharmaceuticals for their antioxidant properties; they are frequently used in restaurant foods to keep vegetables and fruits looking fresh. Beer, wine, and dried, canned, or frozen fruits often contain sulfites, and seafood and fried potatoes are often prepared with these agents. Sulfites are also present as pollutants in the atmosphere. The incidence of sulfite sensitivity is unknown, but the condition is being recognized with increasing frequency. Bronchospasm is sometimes induced by sulfites in sensitive individuals, and anaphylaxis and death have been reported. Immediate or delayed reactions may occur. The mechanism of toxicity is unknown but is thought to be sulfite-induced stimulation of the afferent limb of the cholinergic reflex. Clinical management is based on avoiding strenuous exercise on days when atmospheric pollution is high and on avoiding foods and drug products containing sulfites. Treatment of sulfite-sensitivity reactions is usually supportive; subcutaneous epinephrine has been effective in some patients. Several drugs have been used investigationally to prevent sulfite-sensitivity reactions. However, few data are available to evaluate their efficacy. Sulfites may induce bronchospasm and anaphylaxis in sensitive individuals. These people should avoid foods and drug products containing sulfites.


The use of chemical preservatives serves to ensure the nutritional adequacy, palatability and safety of processed foods and beverages. The toxicity of some of the more ubiquitous antimicrobial agents (sorbic acid, p-hydroxybenzoates, sulphur dioxide) and antioxidants (propyl gallate, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT)] is reviewed together with the role of metabolic data in assessing the 'safety-in-use' of these and other food-additives.


Recently it has been observed that birth rates in Teplice, a highly polluted district in Northern Bohemia, have been reduced during periods when sulfur dioxide levels were high. This study, which is based on data from 2,585 parental pairs in the same region,
describes an analysis of the impact of SO(2) on fecundability in the first unprotected menstrual cycle (FUMC). We obtained detailed personal data, including time-to-pregnancy information, via maternal questionnaires at delivery. We estimated individual exposures to SO(2) in each of the 4 months before conception on the basis of continual central monitoring. Three concentration intervals were introduced: < 40 microg/m(3) (reference level); 40-80 microg/m(3); and [greater than or equal to] 80 microg/m(3). We estimated adjusted odds ratios (AORs) of conception in the FUMC using logistic regression models. Many variables were screened for confounding. AORs for conception in the FUMC were consistently reduced only for couples exposed in the second month before conception to SO(2) levels as follows: 40-80 microg/m(3), AOR 0.57 [95% confidence interval (CI), 0.37-0.88; p < 0.011]; [greater than or equal to] 80 microg/m(3), AOR 0.49 (CI, 0.29-0.81; p < 0.006). The association was weaker in the second 2 years of the study, probably due to the gradual decrease of SO(2) levels in the region. The relationship between SO(2) and fecundability was greater in couples living close to the central monitoring station (within 3.5 km). The timing of these effects is consistent with the period of sperm maturation. This is in agreement with recent findings; sperm abnormalities originating during spermatid maturation were found in young men from Teplice region who were exposed to the increased levels of ambient SO(2). Alternative explanations of our results are also possible.


The effect of SO2 derivatives, a common air pollutant and exists in vivo as an equilibrium between bisulfate and sulfite, on transient outward currents (TOCS) in hippocampal neurons were studied using the whole cell configuration of patch-clamp technique. TOCS that preliminary included a fast inactivating (A-current or IA) and a slow inactivating (D-current or ID) current, were isolated based on the kinetics and pharmacological properties in the presence of 50 mM TEA. The results showed that SO2 derivatives reversibly increased the amplitudes of TOCS in a concentration dependent and voltage dependent. Half-increase dose on TOCS was 25 microM. In vivo, SO2 derivatives shifted the steady-state inactivation curve of TOCS in the depolarizing direction but had little effect on the activation curve. Half-maximal inactivation voltage of TOCS was -69.6 +/- 1.0 mV before and -56.8 +/- 0.4 mV after application of 10 microM SO2 derivatives. SO2 derivatives increased the maximal conductance and delayed the inactivation process of TOCS. These results suggest that SO2 derivatives would increase the excitability of hippocampal neurons.

The effect of sulfur dioxide (SO2) derivatives, a common air pollutant and exists in vivo as an equilibrium between bisulfate and sulfite, on tetrodotoxin-sensitive (TTX-S) and tetrodotoxin-resistant (TTX-R) sodium channels in cultured post-natal dorsal root ganglion (DRG) neurons were studied using the whole cell configuration of patch-clamp technique.
technique. SO2 derivatives on two types of sodium currents were either inhibitory or stimulatory depending on the kinetic parameters tested. At a holding potential of -80 mV, SO2 derivatives suppressed TTX-S sodium currents when depolarizing potential was negative to -30 mV and TTX-R sodium currents when negative to -10 mV but they increased them when the depolarizing potential was positive to -30 or -10 mV. SO2 derivatives shifted the conductance-voltage curve for TTX-R sodium currents in the depolarizing direction but had little effect on that for TTX-S sodium currents. The steady-state inactivation curve for TTX-R sodium channel was shifted by SO2 derivatives in the depolarizing direction as that for TTX-S sodium channel. SO2 derivatives changed the reversal potential and increased the maximum conductance of two types of sodium channels. SO2 derivatives postponed the activating time and delayed the inactivation of sodium currents. The results suggest that SO2 derivatives would increase the excitability of neurons and alter the ion selectivity for two types of sodium currents.


Epidemiological and animals toxicological studies have indicated that reactions between SO2(g) and metal containing aerosols result in the formation of respiratory irritants. It had initially been suggested by EPA that sulfate per se was responsible for the observed health effects. That now appears unlikely. These studies point out the importance of understanding in detail the chemical species formed by such interactions. In the present paper procedures which have been used to study the formation of aerosol inorganic S(IV) species are described, together with the results obtained from studies in the flue line, workroom, and plume of smelters. Both atmospheric and laboratory studies indicate that very stable complexes of S(IV) with Fe(III) or Cu(?) can form in aerosols. The data suggest that the concentration of these (S(IV) complexes in primary particulate emissions from smelters will be about 10% of the sulfate concentration. In plumes the concentration of inorganic S(IV) varied from 10 to 80% of the sulfate concentration. The most important variable controlling the formation of these S(IV) complexes in a plume aerosol droplet is the aerosol acidity. The formation of aerosol inorganic S(IV) complexes in the plume is not related to the formation of sulfate. There have been no studies previously reported that would allow an unequivocal evaluation of the toxicological implications of the chemistry reviewed in this paper. If these various S(IV) species are responsible at the low concentrations reported here for the "synergistic" effects previously reported between SO2(g) and aerosols, then additional toxicological work would appear warranted.


Risk of chronic obstructive pulmonary disease symptoms due to long-term exposure to ambient levels of total suspended particulates (TSP) and sulfur dioxide (SO2) symptoms was ascertained using the National Heart, Lung, and Blood Institute (NHLBI) respiratory symptoms questionnaire on 7,445 Seventh-Day Adventists. They were non-smokers, at least 25 yr of age, and had lived 11 yr or more in areas ranging from high to low photochemical air pollution in California. Participant cumulative exposures to each
pollutant in excess of four thresholds were estimated using monthly residence zip code histories and interpolated dosages from state air monitoring stations. These pollutant thresholds were entered individually and in combination in multiple logistic regression analyses with eight covariables including passive smoking. Statistically significant associations with chronic symptoms were seen for: SO2 exposure above 4 pphm (104 mcg/m3), (p = .03), relative risk 1.18 for 500 hr/yr of exposure; and for total suspended particulates (TSP) above 200 mcg/m3, (p less than .00001), relative risk of 1.22 for 750 hr/yr.


The toxicity of sulfur oxides is discussed briefly. The effects of sulfur dioxide (SO2) are largely confined to the upper airways except during exercise or if the gas is taken up by a carrier aerosol. SO2 may be adsorbed as a monomolecular layer on dry particles, such as elemental carbon, or dissolved in aqueous droplets. Hydrated SO2 forms bisulfite and sulfite ions, which are rapidly oxidized (detoxified) by sulfite oxidase, an enzyme, to form sulfate. SO2 in carrier aerosols (dry or aqueous solutions) may be oxidized to sulfuric acid. The mixture of SO2 (1 ppm) and a droplet of sodium chloride (1 mg/m3) has been shown to be synergistic in guinea pigs. In healthy adults, the same gas-aerosol mixture caused no functional lung changes at rest (two separate studies), but did cause significant changes following moderate exercise. Shortness of breath and wheezing were experiences by about half of the subjects.


The database for the acute health effects of common outdoor air pollutants is rapidly increasing but important gaps still exist. Greater technical efforts and innovative studies are required to adequately characterize health effects and understand the underlying mechanisms of toxicity. Controlled human exposures provide relevant data about short-term effects and complement animal and epidemiologic investigations. Except for possibly nitrogen dioxide, the clinical data for ozone, sulfur dioxide, and particulates (H2SO4) at contemporary levels indicate potentially untoward or adverse physiologic or clinical responses in healthy individuals and sensitive groups such as children, adolescents, and asthmatic patients. Exercise, duration, and other exposure factors may potentiate pollutant effects on symptoms, lung function, nonspecific bronchial reactivity, mucociliary clearance, and BAL markers of inflammation. Continued animal, clinical,

This report summarizes the potential impact of the acid precipitation phenomenon on human health. There are two major components to this phenomenon: the predepositional phase, during which there is direct human exposure to acidic substances from ambient air, and the post-depositional phase, in which the deposition of acid materials on water and soil results in the mobilization, transport, and even chemical transformation of toxic metals. Acidification increases bioconversion of mercury to methylmercury, which accumulates in fish, increasing the risk to toxicity in people who eat fish. Increase in water and soil content of lead and cadmium increases human exposure to these metals which become additive to other sources presently under regulatory control. The potential adverse health effects of increased human exposure to aluminum is not known at the present time.


In recent years, developing insight into the pathophysiology of asthma and advances in asthma management have been substantial. Despite these advancements, asthma remains a significant health problem in the paediatric population. In the USA, the prevalence of asthma in children under 18 years of age is estimated at 7\% [US Environmental Health Protection Agency. Publication # EPA-100-r-018. Washington, DC, 2000]. Prevalence rates in various subpopulations, particularly African and Hispanic Americans, are much higher. Certain inner-city census tracts have estimated prevalence rates of 20 to 25\% [Crain EF Weiss KP, Stein REK. Pediatric 1994; 94: 356-362]. Many of these subpopulations experience alarmingly disparate and apparently increasing morbidity and mortality associated with asthma. Similar trends in prevalence and morbidity have been observed in urban populations outside the USA as well [Sears MR. Lancet 1997; 350: 1015-1020]. There is considerable controversy as to the scientific basis for these observed trends. While the identification of a single factor or even a closely related group of factors appears unlikely, there is considerable speculation about the role of environmental factors, particularly outdoor air quality. In the USA, the National Ambient Air Quality Standards (NAAQs) offer specific standards for air quality. These standards are applied to certain criteria pollutants, including ozone, particulate matter (both PM(10) and PM(2.5)), sulfur dioxide, nitrogen dioxide, lead and carbon monoxide [Committee on Environmental Health, AAP. In: Handbook of Pediatric Environmental Health. Elk Grove Village, IL, 1999; 181-191]. The NAAQs were recently revised for both ozone and particulate matter based on data that suggested health risks existed at levels below those set forth in the previous standards. Monitoring data reveals that urban populations are more likely to be exposed to elevated levels of these pollutants [Dickey JH. Disease Monitor 2000; 46(9): 566-589]. Children are uniquely predisposed to the potential harmful effects of these pollutants. This predisposition is related to unique physiologic, anatomic and behavioural characteristics of the infant, child and adolescent. There is compelling evidence that an interplay of genetic predisposition and environmental
exposure to a number of chemical and infectious agents may be operative in both the inception and persistence of the clinical asthma phenotype. The relative role of the criteria air pollutants in this interplay is the subject of considerable study. The potential value of intervention by regulatory agencies or by behavioural modification among individuals or communities should be explored. At the very least, the current data offers implications for situational strategies of asthma management based on local monitoring data.


Sulfiting agents (sulfur dioxide and the sodium and potassium salts of bisulfite, sulfite, and metabisulfite) are widely used as preservatives in foods, beverages, and pharmaceuticals. Within the past 5 years, there have been numerous reports of adverse reactions to sulfiting agents. This review presents a comprehensive compilation and discussion of reports describing reactions to ingested, inhaled, and parenterally administered sulfite. Sulfite hypersensitivity is usually, but not exclusively, found within the chronic asthmatic population. Although there is some disagreement on its prevalence, a number of studies have indicated that 5 to 10% of all chronic asthmatics are sulfite hypersensitive. This review also describes respiratory sulfur dioxide sensitivity which essentially all asthmatics experience. Possible mechanisms of sulfite hypersensitivity and sulfur dioxide sensitivity are discussed in detail. Sulfite metabolism and the role of sulfite oxidase in the detoxification of exogenous sulfite are reviewed in relationship to the etiology of sulfite hypersensitivity.


We report on the distribution, metabolism, and toxicity of sulfite in the respiratory tract and other tissues of rats exposed to endogenously generated sulfite or to inhaled sulfur dioxide (SO2). Graded sulfite oxidase deficiency was induced in several groups of rats by manipulating their tungsten to molybdenum intake ratio. Endogenously generated sulfite and S-sulfonate compounds (a class of sulfite metabolite) accumulated in the respiratory tract tissues and in the plasma of these rats in inverse proportion to hepatic sulfite oxidase activity. In contrast to this systemic mode of exposure, sulfite exposure of normal, sulfite oxidase-competent rats via inhaled SO2 (10 and 30 ppm) was restricted to the airways. Minor pathological changes consisting of epithelial hyperplasia, mucoid degeneration, and desquamation of epithelium were observed only in the tracheas and bronchi of the rats inhaling SO2, even though the concentration of sulfite plus S-sulfonates in the tracheas and bronchi of these rats was considerably lower than that in the endogenously exposed rats. We attribute this histological damage to hydrogen ions stemming from inhaled SO2, not to the sulfite/bisulfite ions that are also a product of inhaled SO2. In addition to the lungs and trachea, all other tissues examined, except the testes, appeared to be refractory to high concentrations of endogenously generated sulfite. The testes of grossly sulfite oxidase-deficient rats were severely atrophied and devoid of spermatogenic cells.
Gunnison, et al. 1988. The effect of inhaled sulfur dioxide and systemic sulfite on the induction of lung carcinoma in rats by benzo[a]pyrene. Environ. Res. Vol. 46(1): 59-73. In a previous study at this Institute, inhaled sulfur dioxide (SO2) was shown to enhance the induction by inhaled benzo[a]pyrene (BaP) of squamous cell carcinoma (SQCA) of the respiratory tract of rats (S. Laskin, M. Kuschner, A. Sellakumar, and G. V. Katz, 1976, In "Air Pollution and the Lung," pp. 190-213). We attempted to confirm and extend this finding by using an experimental protocol intended to illuminate the role of SO2. Rats were treated with BaP by 15 consecutive weekly intratracheal instillations. Some of these rats were simultaneously exposed either to SO2 by inhalation or to sulfite/bisulfite anions that accumulated systemically from endogenous generation in rats with induced sulfite oxidase deficiency. The total treatment period spanned 21 weeks, after which the rats were observed for the development of tumors. BaP-treated rats began to die with SQCA of the respiratory tract at approximately 200 days after the first BaP treatment and at 2 years after the first treatment nearly all rats in the BaP-treated groups had died, most with SQCA. Survival in the control groups was excellent and the health of all groups (aside from pulmonary SQCA in BaP-treated groups) was also excellent. The probability of dying with a pulmonary SQCA in the experimental groups treated with BaP, BaP plus inhaled SO2, and BaP plus systemic sulfite/bisulfite was calculated by the logrank analysis. The data sets of SQCA probability from these groups were not statistically different (i.e., P greater than 0.05) by the chi 2 test indicating that, in this experiment, neither inhalation exposure to SO2 nor systemic exposure to sulfite/bisulfite anions affected the induction of SQCA of the lung by intratracheally instilled BaP. We conclude that the results of this study do not support an etiological role for either SO2 or sulfite/bisulfite anions in the induction of SQCA of the respiratory tract by BaP.

Harkema, et al. 1993. Ozone- and endotoxin-induced mucous cell metaplasia in rat airway epithelium: novel animal models to study toxicant-induced epithelial transformation in airways. Toxicol.Lett. 68(1-2): 251-263. Mucous (goblet) cell proliferation and hypersecretion of airway mucus are important characteristics of human respiratory disorders, especially chronic bronchitis and cystic fibrosis. These changes in secretory patterns also occur in animals experimentally exposed to chemical irritants such as ozone (O3), sulfur dioxide (SO2), and cigarette smoke. The cellular and molecular mechanisms involved in irritant-induced mucous cell metaplasia (MCM; transformation of airway epithelium, normally devoid of mucous cells, to a secretory epithelium containing numerous mucous cells) are still unclear. We used two experimental models of toxicant-induced MCM in rat airways to study the cellular and molecular changes that occur during the development of this respiratory tract lesion. MCM can be induced in the nasal transitional epithelium of rats by repeated exposure to ambient levels of ozone. In addition, MCM can be induced in the tracheobronchial airways of rats repeatedly exposed to endotoxin, a lipopolysaccharide-protein molecule found in the outer walls of Gram-negative bacteria. The pathogenesis of ozone- or endotoxin-induced MCM has been partially characterized using a variety of morphometric and histochemical techniques. Toxicant-induced changes in the numbers and types of airway epithelial cells have been estimated using morphometric methods.
designed for estimating the abundance of cell populations. Nasal pulmonary airway tissues are also processed for light microscopy and stained with Alcian Blue (pH 2.5)/Periodic Acid Schiff (AB/PAS) for detection of acidic and neutral mucosubstances (the specific glycoprotein product of mucous cells), respectively, within the tissue. Computerized image analysis is used to quantitate the amount of the stained mucous product within the airway epithelium. To better characterize the molecular and cellular events in the pathogenesis of ozone- or endotoxin-induced MCM in the rat airway epithelium, we are conducting studies to determine when, and in which epithelial cells, the mucin gene is expressed after exposure to the toxicant. In these studies, rats undergo single or repeated exposures to ozone or endotoxin and are then sacrificed immediately or a few days after the end of the exposures. Airway tissues are microdissected from specific regions of the exposed respiratory tract, and changes in mucin core polypeptide mRNA are evaluated by Northern analysis using human and rat mucin cDNA. In future studies using in situ hybridization, we will establish when, and in which epithelial cells, the expression of high molecular weight airway mucin is initiated in response to ozone or endotoxin….

The lung function of 7 men accidentally exposed to sulfur dioxide (SO2) in a pyrite dust explosion was followed for 4 yr. The greatest decrease in forced vital capacity, forced expiratory volume in one second, and maximal midexpiratory flow was observed 1 wk after the accident. After about 3 months no further decrement occurred. The pattern of spirometric findings was obstructive in 6 and restrictive in 1 of the patients. Four years after the accident a reversible obstruction of the bronchi was still observable in 3. Four patients reacted positively to the histamine challenge test. Two patients either did not respond to bronchodilator or did not react to histamine. The results suggest that bronchial hyperreactivity is a frequent sequela after exposure to high concentrations of SO2. The hyperreactivity may persist for several years.


Air pollution has become a major public and political concern since the beginning of industrialization, particularly motor exhaust over the past three decades. Epidemiological studies, together with clinical trials and experiments in exposition chambers (including biochemical model reactions), have contributed to our knowledge of potential dangers and increased our understanding of the corresponding mechanisms and dose-response effects. Comparison of the threatening reports that appear almost daily in the press with the digest of over 800 scientific publications allows the statement that the impact of ozone and nitric oxide on the health and performance of plants and animals is widely overestimated and appears to be used as a political instrument. In contrast, the combination of SO₂ with soot and asbestos particles may represent an underestimated toxic potential. In this communication, we shall concentrate on basic redox mechanisms.
involving $\text{SO}_2$ and important target molecules, as well as looking at the cooperative effects of sulphite and soot particles.


The authors studied the association between long-term exposure (i.e., > 10 y) to outdoor air pollution and the severity of obstructive pulmonary disease and prevalence of bronchial hyperreactivity to beta2 agonists in two groups of adult patients who were of similar ages and who had similar smoking habits. The subjects lived in downtown districts or in the outer suburbs of Marseilles, the neighborhood that contained air samplers. The regions were similar with respect to sulfur dioxide levels, but levels of nitric oxides and particulate matter (10 millimeters or less) were higher in the downtown area than the suburbs. The authors assessed airway obstruction, as determined by a decrease in forced expiratory volume in 1 s, mean forced expiratory flow measured between 25% and 75% of vital capacity, and an elevated value of central airway resistance. The authors tested the changes in these variables induced by inhalation of a beta2 agonist. Baseline lung function was altered more significantly in both male and female patients who lived in downtown Marseilles than in those who resided in the suburbs, and the differences persisted regardless of the season during which the study occurred. Prevalence of bronchial hyperreactivity and symptoms of asthma (but not of rhinitis) were higher in the downtown than suburban male subjects. The results of this study suggest that an association exists between actual environmental exposure to outdoor air pollution (i.e., nitrogen oxides and/or particulate matter of 10 millimeters or less) and respiratory effects in sensitive adults represented by patients with chronic obstructive pulmonary disease or asthma.


This review deals with the toxicology of sulfur in ruminants including toxicity, neurotoxic effects, and mechanism of toxic action of hydrogen sulfide, clinical signs, and treatment. It will report effects of excessive intake of sulfur by ruminants on feed intake, animal performance, ruminal digestion and motility, rumination, and other physiological functions. Poisoning of animals with sulfur from industrial emissions (sulfur dioxide) also is discussed. Excessive quantities of dietary sulfur (above .3 to .4%) as sulfate or elemental sulfur may cause toxic effects and in extreme cases can be fatal. The means is discussed whereby consumption of excessive amounts of sulfur leads to toxic effects.


The adverse health effects of air pollution became widely acknowledged after severe pollution episodes occurred in Europe and North America before the 1960s. In these areas, pollutant levels have decreased. During the last 15 years, however, consistent results, mainly from epidemiological studies, have provided evidence that current air
pollutant levels have been associated with adverse long- and short-term health effects, including an increase in mortality. These effects have been better studied for ambient particle concentrations but there is also substantial evidence concerning gaseous pollutants such as ozone, NO(2) and CO. Attempts to estimate the impact of air pollution effects on health in terms of the attributable number of events indicate that the ubiquitous nature of the exposure results in a considerable public health burden from relatively weak relative risks.


An experimental study was undertaken to investigate the in vitro effect of sulfur dioxide on the chemotactic activity of alveolar macrophages (AM) and blood monocytes (BM). The cells were placed on a polycarbonate membrane and exposed to SO2 0.5, 1.5 and 2.5 ppm for 15 min. Control experiments were performed with exposure of the cells to synthetic air with 5% CO2. After gas exposure the cells were incubated with the chemotactic active agent C5a in 5% carbon dioxide (CO2) at 37 degrees C for 60 min. The numbers of AM and BM passing actively through the membrane were quantified using light microscopy. Our results show a dose-dependent reduction in the migration rate of cells under SO2 exposure. SO2 0.5 ppm induced a 29% and SO2 2.5 ppm a 53% decrease in migration of AM compared with the control exposure to synthetic air (P <; 0.01). Identical experiments with BM resulted in a decrease in migration of up to 57% (P <; 0.01). At SO2 concentrations of up to 2.5 ppm no significant cytotoxic effects were observed for AM or BM. The data demonstrate that exposure to SO2 may reduce the chemotactic activity of AM and BM. Our results further suggest that the decrease in cell migration induced by SO2 is due to changes in chemotactic mechanisms and not to cell death.


Tumor necrosis factor-alpha, interleukin-1beta, interleukin-6, and transforming growth factor-beta are cytokines synthesized by alveolar macrophages. We investigated the effect of sulfur dioxide, a major air pollutant, on the production of these cytokines by alveolar macrophages. The cells were layered on a polycarbonate membrane and exposed for 30 min to 0.0, 1.0, 2.5, and 5.0 ppm sulfur dioxide at 37 degrees C and 100% air humidity. The cells were incubated for 24 h after exposure, thus allowing cytokine release. Cytotoxic effects of sulfur dioxide were evaluated by trypan blue exclusion. Cytokines were measured with enzyme-linked immunosorbent assays (i.e., tumor necrosis factor-alpha, interleukin-1beta, and interleukin-6) or by use of a specific bioassay (i.e., transforming growth factor-beta). The toxicity of sulfur dioxide for alveolar macrophages ranged from 3.1 % to 9.5 %. A 30-min exposure to sulfur dioxide induced a significant decrease in spontaneous and lipopolysaccharide-stimulated tumor necrosis factor-alpha (p <; .001) and lipopolysaccharide-stimulated interleukin-1beta
release (p < .05). The release of interleukin-6 and transforming growth factor-beta was not affected significantly by sulfur dioxide exposure. Our results demonstrated a functional impairment of alveolar macrophages after sulfur dioxide exposure (i.e., release of tumor necrosis factor-alpha and interleukin-1beta). Neither spontaneous nor stimulated release of interleukin-6 and transforming growth factors were influenced by exposure to sulfur dioxide.


Sulfur dioxide (SO2) and Asbest are frequently found at workplaces. They can induce airway and lung parenchymal injury. Alveolar macrophages (AM) play an important and decisive role in the damage of respiratory tissue. We evaluated the reactive oxygen intermediates (ROI) production of AM and peripheral blood mononuclear cells after exposure with SO2 and Chrysotile B. The cells were exposed in a special gas exposure chamber at 37 degrees C and 100% air humidity for 30 minutes to 1.5 or 2.5 ppm SO2. Afterwards they were incubated for one hour with 100 micrograms or 200 micrograms Chrysotile B. Control experiments were performed with cell exposure to synthetic air without SO2 and Chrysotile B. Spontaneous and phorbol myristate acetate (PMA) stimulated ROI-release were measured by chemiluminescence and the cell toxicity was evaluated with the trypan blue exclusion test. Our results show a dose-dependent increase of the spontaneous ROI-production of AM after SO2 and Chrysotile B exposure. Exposure to 100 micrograms Chrysotile B caused an 1.5 fold, exposure to 1.5 or 2.5 ppm SO2 plus 100 micrograms Chrysotile B resulted in an 2.4 respectively 3.3 fold increase in ROI-release compared to control experiments. Exposure of AM to 200 micrograms Chrysotile B yielded an 1.9 fold, exposure to 2.5 ppm SO2 plus 200 micrograms Chrysotile B a 3.9 fold elevation in the spontaneous ROI-production compared to control experiment with standard air. A similar reaction pattern was observed in PMA-stimulated AM and in peripheral blood mononuclear cells….


We studied the effect of sulfur dioxide (SO2) and nitrogen dioxide (NO2) on mucociliary activity (MCA) and ciliary beat frequency (CBF) in 63 guinea pig tracheas. The tracheas were placed in a gas cylinder and exposed for 30 minutes to SO2 concentrations ranging from 2.5 to 12.5 ppm or to NO2 concentrations ranging from 3.0 to 15.0 ppm. Control experiments were performed with exposure of the tracheas to synthetic air. MCA was measured by recording the light reflected from ciliated mucous membranes using an infrared barcode reader and CBF using video-interference microscopy. The exposure to 2.5 ppm SO2 caused a reduction in mean MCA of 63% and no significant changes in CBF. Higher SO2 concentrations caused a further impairment of MCA as well as a dose-dependent decrease in CBF. 10.0 or 12.5 ppm SO2 induced a decrease from baseline values to approximately 20% in MCA and to roughly 30% in mean CBF. The exposure to NO2 at concentrations ranging from 3.0 to 15.0 ppm did not induce any changes in MCA or CBF of the guinea pig tracheas. Our results show that exposure to SO2 for 30 minutes
is able to depress the mucociliary clearance of guinea pig tracheas, whereas the exposure to equivalent NO2 concentrations for the same time do not alter the mucociliary transport.


Asthma is a disease syndrome that has captured a great deal of attention for several years. One of the perplexing aspects to asthma is that the prevalence is increasing in most industrialized countries. The reasons for this widespread increase are largely unknown. Another aspect of industrialization is the persistence of air pollution in urban areas. Because much air pollution is due to vehicles, no solution appears in sight. The topic of this article is the association between air pollution and various signs and symptoms of asthma. Air pollution is convincingly associated with many signs of asthma aggravation. These include pulmonary function decrements, increased bronchial hyperresponsiveness, visits to emergency departments, hospital admissions, increased medication use and symptom reporting, inflammatory changes, interactions between air pollution and allergen challenges, and immune system changes. With the exception of exposure to environmental tobacco smoke, common air pollutants have not been shown to cause asthma. It seems prudent for clinicians to counsel their patients about the potential risks of asthma aggravation from common outdoor air pollutants.


The objective of the study was to investigate the ability of a sustained-release (SR) theophylline tablet (Uniphyl; Purdue Frederick Co., Norwalk, Conn.) to block or mitigate sulfur dioxide (SO2)-induced bronchoconstriction in adult subjects with asthma. Eight subjects participated in a double-blind, crossover study with a 400 mg theophylline tablet or placebo once a day for a week before a 10-minute SO2 challenge. FEV1 and total respiratory resistance (RT) were measured before and after the SO2 challenge and on a different day before and after an air exposure. After exposure to SO2, average values of FEV1 dropped 16% after placebo treatment and 7% after theophylline treatment. The corresponding percentages for RT were a 37% increase after placebo and a 7% increase after theophylline treatment. Analysis of variance demonstrated a significant difference between the SO2-induced decrease in FEV1 and increase in RT after SR theophylline treatment compared with that of placebo treatment. Thus, we conclude that SR theophylline tablets, taken at this concentration for 1 week, mitigate SO2-induced bronchoconstriction.


Ten allergic subjects with exercise-induced bronchospasm were studied to determine whether albuterol could prevent sulfur dioxide (SO2)-induced bronchoconstriction. Albuterol or placebo (180 micrograms) were administered by metered-dose inhaler 20 minutes before a 10-minute exposure to SO2 or clean air during moderate exercise on a treadmill at an exercise level that by itself did not produce exercise-induced bronchospasm. Pulmonary functions (FEV1 and total respiratory resistance [RT]) were
measured before the drug, after the drug, and after exposure to SO2 or clean air. Albuterol treatment produced significant bronchodilation and also prevented SO2-induced bronchoconstriction. Following SO2 inhalation after placebo, FEV1 decreased 15% (p less than 0.02) and RT increased 50% (p less than 0.03). Following SO2 inhalation after albuterol treatment, neither FEV1 or RT changed significantly. We conclude that albuterol, a beta 2-agonist, inhibits SO2-induced bronchoconstriction. This result suggests that the adrenergic nervous system or mast cell degranulation are involved in SO2-induced bronchoconstriction.


Although there is no known dietary requirement for inorganic sulfur, it is an essential element for all animal species in as much as they all require the sulfur-containing amino acid methionine. There are three predominate forms of organic sulfur in animals and humans: 1) the thiomethyl of methionine residues in protein; 2) the sulfhydryl disulfides of protein; and 3) the compounds containing ester or amide bound sulfates of glycosaminoglycans, steroids, and many xenobiotic metabolites. Thus, sulfur becomes an important constituent of amino acids, proteins, enzymes, vitamins and other biomolecules. Unlike mammalian species, plants can use inorganic sulfur and synthesize methionine from which are synthesized all the other important sulfur compounds. Hence, sulfur deficiency occurs mainly when plants are grown in sulfur-depleted soils and when humans and animals consume low-protein diets. In recent times, however, the increasing prevalence of refining petroleum and smelting sulfur compounds of metallic minerals into free metals are having a large impact on the balance of sulfur in the environment. Sulfur toxicity is associated mainly with high levels of the element and its toxic volatile substances in the environment. Sulfur dioxide (SO2), a major air pollutant, may adversely affect animal and human health by causing bronchitis, bronchoconstriction, and increased pulmonary resistance.


The evidence that asthma is increasing in prevalence is becoming increasingly compelling. This trend has been demonstrated not only in the United States, but also in the United Kingdom, New Zealand, Australia, and several other Western countries. In the United States, the increase is largest in the group under 18 years of age. There is mounting evidence that certain environmental air pollutants are involved in exacerbating asthma. This is based primarily on epidemiologic studies and more recent clinical studies. The U.S. Clean Air Act of 1970 provides special consideration to the class of outdoor air pollutants referred to as criteria pollutants, including O3, sulfur dioxide (SO2), particulate matter (PM), NOx, CO, and Pb. Standards for these pollutants are set by the U.S. Environmental Protection Agency with particular concern for populations at risk. Current evidence suggests that asthmatics are more sensitive to the effects of O3, SO2, PM, and NO2, and are therefore at risk. High SO2 and particulate concentrations have been associated with short-term increases in morbidity and mortality in the general population during dramatic air pollution episodes in the past. Controlled exposure studies have clearly shown that asthmatics are sensitive to low levels of SO2. Exercising asthmatics
exposed to SO\(_2\) develop bronchoconstriction within minutes, even at levels of 0.25 ppm. Responses are modified by air temperature, humidity, and exercise level. Recent epidemiologic studies have suggested that exposure to PM is strongly associated with morbidity and mortality in the general population and that hospital admissions for bronchitis and asthma were associated with PM10 levels. In controlled clinical studies, asthmatics appear to be no more reactive to aerosols than healthy subjects. Consequently, it is difficult to attribute the increased mortality observed in epidemiologic studies to specific effects demonstrated in controlled human studies. Epidemiologic studies of hospital admissions for asthma have implicated O\(_3\) as contributing to the exacerbation of asthma; however, most study designs could not separate the O\(_3\) effects from the concomitant effects of acid aerosols and SO\(_2\). Controlled human clinical studies have suggested that asthmatics have similar changes in spirometry and airway reactivity in response to O\(_3\) exposure compared to healthy adults. However, a possible role of O\(_3\) in worsening atopic asthma has recently been suggested in studies combining allergen challenge following exposure to O\(_3\). Attempts at identification of factors that predispose asthmatics to responsiveness to NO\(_2\) has produced inconsistent results and requires further investigation. In summary, asthmatics have been shown to be a sensitive subpopulation relative to several of the criteria pollutants. Further research linking epidemiologic, clinical, and toxicologic approaches is required to better understand and characterize the risk of exposing asthmatics to these pollutants.


OBJECTIVE: Though many contaminants are released into the atmosphere, in the US only six air pollutants—ozone, particulate matter, sulfur dioxide, carbon monoxide, nitrogen dioxide, and lead—are closely monitored and carefully assessed for health significance. Other pollutants, even if highly toxic, are neither widely monitored nor routinely assessed at the national level. The goal of this study was to analyze the availability of information needed to characterize the health significance of hazardous air pollutants, focusing on urban areas in California. METHODS: The authors compared different approaches to identifying which contaminants should be considered hazardous air pollutants of potential health concern; reviewed the availability of toxicity values for these pollutants; and analyzed the usefulness of air monitoring data from California agencies for determining populations risks, by comparing method detection limits with health benchmarks. RESULTS: Approaches to identifying air contaminants of possible health concern differ. Toxicity values are not available for many hazardous air pollutants, including those identified in the Clean Air Act. In California, monitoring data are available for many, though not all, pollutants of concern. Monitoring methods for several pollutants do not have adequate sensitivity to detect all relevant concentrations.

CONCLUSION: The information necessary to fully assess the health significance of hazardous air pollutants is not currently available.


Inhalation of sulfur dioxide (SO\(_2\)) causes bronchoconstriction in most people with
To examine the role of leukotrienes in this response, the antagonism of SO2-induced bronchoconstriction by a single oral dose of the leukotriene receptor antagonist zafirlukast was assessed in a double-blind, placebo-controlled, two-period crossover trial in 12 subjects with mild-to-moderate asthma. Subjects had bronchial hyperresponsiveness, an FEV1 <; or = 70% of predicted, and a positive response to inhaled SO2 (an 8-unit increase in specific airway resistance on inhaling an SO2 concentration of <; or = 4 ppm (PC8SRaw). Subjects were treated with zafirlukast (20 mg) or placebo on two treatment days 5 to 14 d apart. Two and 10 hours after treatment, subjects inhaled SO2 (0.25, 0.5, 1.0, 2.0, 4.0, and 8.0 ppm) during eucapnic hyperventilation at 20 L/min. PC8SRaw was determined after each challenge. Blood samples were collected to assess zafirlukast plasma concentrations versus effect. PC8SRaw was significantly higher 2 h after zafirlukast compared with placebo (3.1 versus 1.5 ppm; p = 0.02) and remained higher 10 h after treatment with zafirlukast (2.7 versus 1.9 ppm; p = 0.09). An association was found between zafirlukast plasma concentrations and increases in PC8SRaw 10 h after treatment (p = 0.001). The safety profile of zafirlukast was not clinically different from placebo. A single 20-mg dose of zafirlukast attenuated SO2-induced bronchoconstriction. We conclude that SO2-induced bronchoconstriction involves release of leukotrienes and that treatment with zafirlukast attenuates the bronchoconstrictor response.


The main primary pollutants released into the atmosphere are sulfur dioxide (SO2), nitrogen monoxide and dioxide (NOx), particulate dust and in a less important part carbon monoxide (CO), hydrocarbons and heavy metals (Pb, Cd). Sulfur and nitrogen oxides are released from combustion of coals and fuels. Sulfates, nitrates and ozone are secondary pollutants resulting from chemical reactions within the atmosphere. While governmental directives limiting emissions have decreased SO2 and particulate matter levels, air quality in urban regions has improved in the last two decades. The role of air pollution as a risk factor for respiratory infections is difficult to address. Animal experiments demonstrate that air pollutants decrease the efficacy of lung defense mechanisms and increase the sensibility to respiratory infections. Nevertheless, because of difference in sensitivity between animal species and between exposure conditions, these effects are difficult to extrapolate to humans. Moreover, it is obvious that direct exposure studies of the sensibility of humans to respiratory infections are rare for ethical reasons. Epidemiological data addressing the role of air pollutants at usual levels can only suggest that some pollutants (SO2, suspended particulates) constitute a risk factor for respiratory infections. Since most of these studies do not include bacteriologic and virologic confirmation, it is unclear whether this respiratory morbidity is due to respiratory irritation or infection. In conclusion, we think that high concentrations of air pollutants are very likely to increase sensibility to respiratory infections in humans. There are however no sufficient data to clearly establish whether air pollution constitutes a risk factor for respiratory infections at usual ambient concentrations.
Lin, et al. 2004. Association between maternal exposure to elevated ambient sulfur dioxide during pregnancy and term low birth weight. *Environ.Res.* Vol. 96(1): 41-50. This retrospective cohort study investigated whether the risk of delivering full term (37-44 completed weeks of gestation) low birth weight (LBW) infants is associated with differences in exposure to air pollutants in different trimesters. Full-term infants (37 completed weeks of gestation) with a birth weight below 2500 g were classified as term LBW infants. The study infants comprised 92,288 full-term live singletons identified from the Taiwan birth registry and born in the city of Taipei or Kaoshiung in Taiwan between 1995 and 1997. Maternal exposures to various air pollutants including CO, SO2, O3, NO2, and PM10 in each trimester of pregnancy was estimated as the arithmetic means of all daily measurements taken by the air quality monitoring station nearest to the district of residence of the mother at birth. The multivariable logistic regression model with adjustment for potential confounders was used to assess the independent effect of specific air pollutants on the risk of term LBW. This study suggested a 26% increase in term LBW risk given maternal ambient exposure to SO2 concentration exceeding 11.4 ppb during pregnancy compared to low exposure (<7.1 ppb) (OR=1.26, 95% CI=1.04-1.53). Since the relative risk of term LBW was reassessed according to exposure level in each trimester, mothers exposed to >12.4 ppb of SO2 in the last trimester showed 20% higher risk (OR=1.20, 95% CI=1.01-1.41) of term LBW delivery than mothers with lower exposure (<6.8 ppb). No significant elevation ORs was observed for other air pollutants.


STUDY OBJECTIVE: Assess associations between short-term exposure to gaseous pollutants and asthma hospitalisation among boys and girls 6 to 12 years of age. DESIGN: A bi-directional case-crossover analysis was used. Conditional logistic regression models were fitted to the data for boys and girls separately. Exposures averaged over periods ranging from one to seven days were used to assess the effects of gaseous pollutants on asthma hospitalisation. Estimated relative risks for asthma hospitalisation were calculated for an incremental exposure corresponding to the interquartile range in pollutant levels, adjusted for daily weather conditions and concomitant exposure to particulate matter. SETTING: Toronto, Ontario, Canada. PARTICIPANTS: A total of 7319 asthma hospitalisations for children 6 to 12 years of age (4629 for boys and 2690 for girls) in Toronto between 1981 and 1993. MAIN RESULTS: A significant acute effect of carbon monoxide on asthma hospitalisation was found in boys, and sulphur dioxide showed significant effects of prolonged exposure in girls. Nitrogen dioxide was positively associated with asthma admissions in both sexes. The lag time for certain gaseous pollutant effects seemed to be shorter in boys (around two to three days for carbon monoxide and nitrogen dioxide), as compared with girls (about six to seven days for sulphur dioxide and nitrogen dioxide). The effects of gaseous pollutants on asthma hospitalisation remained after adjustment of particulate matter. The data showed no association between ozone and asthma hospitalisation in children. CONCLUSIONS: The study showed positive relations between gaseous pollutants (carbon monoxide, sulphur dioxide, and nitrogen dioxide) at comparatively low levels and asthma hospitalisation in...
children, using bi-directional case-crossover analyses. Though, the effects of certain specific gaseous pollutants were found to vary in boys and girls.


In this study, we used both case-crossover and time-series analyses to assess the associations between size-fractionated particulate matter and asthma hospitalization among children 6-12 years old living in Toronto between 1981 and 1993. Specifically, we used exposures averaged over periods varying from 1 to 7 days to assess the effects of particulate matter on asthma hospitalization. We calculated estimates of the relative risk of asthma hospitalization adjusted for daily weather conditions (maximum and minimum temperatures, and average relative humidity) for an incremental exposure corresponding to the interquartile range in particulate matter. Both bidirectional case-crossover and time-series analyses revealed that coarse particulate matter (PM10-2.5) averaged over 5-6 days was significantly associated with asthma hospitalization in both males and females. The magnitude of this effect appeared to increase with increasing number of days of exposure averaging for most models, with the relative risk estimates stabilizing at about 6 days. Using a bidirectional case-crossover analysis, the estimated relative risks were 1.14 (95% confidence interval (CI), 1.02, 1.28) for males and 1.18 (95% CI, 1.02, 1.36) for females, for an increment of 8.4 microg/m(3) in 6-day averages of PM10-2.5. The corresponding relative risk estimates were 1.10 and 1.18, respectively, when we used time-series analysis. The effect of PM10-2.5 remained positive after adjustment for the effects of the gaseous pollutants carbon monoxide (CO), nitrogen dioxide (NO2), sulfur dioxide (SO2), and ozone (O3). We did not find significant effects of fine particulate matter (PM2.5) or of thoracic particulate matter (PM10) on asthma hospitalizations using either of these two analytic approaches. For the most part, relative risk estimates from the unidirectional case-crossover analysis were more pronounced compared with both bidirectional case-crossover and time-series analyses.


Associations of gaseous air pollutants (including carbon monoxide, sulfur dioxide, nitrogen dioxide, and ozone) with asthma hospitalization, stratified by sex and socioeconomic status, were examined among children 6-12 years of age in Vancouver, British Columbia, Canada, between 1987 and 1998. Relative risks for an exposure increment corresponding to the interquartile range for each gaseous air pollutant were estimated for asthma hospitalization after adjustment for weather conditions, including daily maximum and minimum temperatures as well as average relative humidity. Similar results were obtained by using locally weighted smoothing functions (LOESS) with default convergence criteria and by using natural cubic splines with a more stringent setting. Exposures to nitrogen dioxide were found to be significantly and positively associated with asthma hospitalization for males in the low socioeconomic group but not in the high socioeconomic group. For females, this same pattern of association was observed for exposures to sulfur dioxide. No significantly positive associations were
found between carbon monoxide and ozone and asthma hospitalization in either low or high socioeconomic groups.

The validity of a risk assessment can be no better than that of the exposure assessment upon which it is based. The general paucity of relevant exposure data, combined with the limited appreciation by most risk assessors of the critical dimensions and metrics of exposure, often leads to an overreliance on exposure models of questionable validity. The problems of identifying and interpreting relevant metrics of exposure for epidemiologic studies and risk assessments are illustrated through the presentation of three case studies. The first examines the effects of ozone on respiratory mechanical function and demonstrates that the appropriate averaging time is greater than or equal to 6 hr, rather than 1 hr, as is implied by the current ambient air quality standard. The second case study examines the effects of sulfur oxides and particulate matter in ambient air on morbidity and mortality. It indicates that the effects are most closely associated with the acidity of the aerosol, providing a basis for an index of exposure more relevant than those currently used, i.e., sulfur dioxide and nonspecific gravimetric mass concentration of particulate matter. The third case study examines the effects of lead on blood pressure. It shows that blood lead in concentrations below 35 micrograms/dL correlates with blood pressure in both humans and animals independently of other known causal factors for blood pressure elevation. It also examines the variable relations between levels of lead in blood and in environmental media to illustrate the potential problems which can arise from the use of biological markers, such as lead in blood, as indices of exposure.


**McLaughlin. 1985.** EFFECTS OF AIR POLLUTION ON FORESTS: A CRITICAL REVIEW. *Journal of Air.Pollution Control.Association* 35(5):512-530;. HMTC A review of the effects of air pollution on forests attributes many of the changes seen in the forest to sulfur dioxide. Forest declines in several European countries and the U.S. may also be related to ozone and foliar leaching of magnesium and calcium. Declines can also be traced to the release of toxic metals that inhibit the growth of roots and shoots. The review includes conceptual and historical perspectives and regional-scale changes in forests in Europe, the U.S., and the Pacific. Concentrations and patterns of atmospheric pollution are examined in reference to sulfur and nitrogen emissions, precipitation chemistry, gaseous pollutants, and heavy metals. The impact of pollution, especially gaseous pollutants, is illustrated. Forest responses may take the form of altered plant-water relations, resistance to secondary stresses, changes in forest nutrition, or growth and reproduction problems associated with acid rain and heavy metal toxicity. (203 ref.)


Cu,Zn-superoxide dismutase (SOD), Se-dependent glutathione peroxidase (GSH-Px),
catalase (CAT), and glutathione (GSH) play an important role in attenuating free radical-induced oxidative damage. The purpose of this research was to determine (1) whether sulfur dioxide (SO(2)) increases levels of lipid peroxidation and alters intracellular redox status in multiple organs of mice, and (2) whether SO(2) is a systemic toxic agent. The effect of SO(2) on levels of thiobarbituric acid-reactive substances (TBARS) and GSH and activities of SOD, GSH-Px, and CAT were investigated in nine organs (brain, lung, heart, liver, stomach, intestine, spleen, kidney, and testis) of Kunming albino mice of both sexes. SO(2) at 20 ppm (56 mg/m(3)) was administrated to the animals of SO(2) groups in an exposure chamber for 6 h/day for 7 days while control groups were exposed to filtered air in the same condition. Results show that SO(2) inhalation decreased significantly activities of SOD and GSH-Px in all organs tested in all SO(2) groups, with respect to their corresponding control groups; CAT activities in all organs tested of both sexual mice were significantly unaltered, except CAT activities in livers were significantly lowered by SO(2); SO(2) exposure decreased significantly GSH contents and significantly increased TBARS levels of all organs tested, in comparison with their respective control groups. These results lead to two conclusions: (1) SO(2) is a systemic oxidative damage agent. It results in a significant increase in the lipid peroxidation process in all organs tested of mice of both sexes, which is accompanied by changes of antioxidant status in these organs. (2) SO(2) may cause toxicological damage to multiple organs of animals, and it is suggested that the oxidative damage produced by SO(2) inhalation may influence or promote the progression or occurrence of some disease states of various organs, not only to respiratory system. Further work is required to understand the toxicological role of SO(2) on multiple or even all organs in mammals.

Meng & Zhang 1999. Polymerase chain reaction-based deletion screening of bisulfite (sulfur dioxide)-enhanced gpt-mutants in CHO-AS52 cells. Mutat Res. 425(1):81-5. In this study, we have examined the mutagenicity of bisulfite (sulfur dioxide) at the xanthine-guanine phosphoribosyl transferase locus (gpt) in the pSV2 gpt-transformed CHO cell line, AS52. Our results provide evidence for bisulfite as a weak gene mutagen because the chemical at high doses and at high cytotoxicity causes a 4-fold increase in mutant frequency (MF) and less than a doubling of the gpt gene deletion frequency compared to control. We suggest that the increase of MF in bisulfite-treated cells results from bisulfite activity, as a comutagen, enhancing the induction effect of unknown endogenous or exogenous factors on spontaneous mutagenesis of AS52 cells. For the spontaneous, 5 mM bisulfite- and 10 mM bisulfite-enhanced spontaneous mutants in AS52 cells, the percentage of total deletion mutations of the gpt gene is 36%, 44% and 65%, respectively Copyright 1999 Elsevier Science B.V.

Meng & Zhang 1990. Chromosomal aberrations and sister-chromatid exchanges in lymphocytes of workers exposed to sulphur dioxide. Mutat Res. Vol. 241(1): 15-20. The frequencies of chromosomal aberrations and sister-chromatid exchanges (SCE) in peripheral blood lymphocytes of 40 workers chronically exposed to sulphur dioxide (SO2) at a sulphuric acid factory in Taiyuan City (North China), were studied. It was shown that the mean frequency of chromosomal aberrations and the mean frequency of lymphocytes with chromosomal aberrations of the SO2-exposed workers were both
higher than the controls. The mean per 1000 metaphase frequencies of severe chromosomal aberration types (chromosome rings, translocations, and dicentrics) of the workers and the controls were 9.63 and 2.27, respectively. The difference between them was statistically significant (p less than 0.01). It was also shown that the mean SCEs/cell of SO2-exposed workers and non-exposed controls were 6.72 +/- 0.22/cell and 2.71 +/- 0.13/cell (p less than 0.01) respectively. SCEs/cell in 39 workers were all higher than 5, only 1 worker was 4.73. However, 41 controls were all lower than 4, only 1 control was 4.92. The difference between the worker and the control group was statistically significant. These results show that SO2 is a clastogenic and genotoxic agent. No positive correlation between the frequencies of chromosomal aberrations or SCE and length of service in the workers has been observed. No significant difference between smokers and non-smokers was found in these assays.

The effects of sulfur dioxide (SO2) on levels of thiobarbituric acid reactive substances (TBARS), levels of reduced glutathione (GSH), and the activities of Cu,Zn-superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) were investigated in testicles of Kunming albino male mice. SO2 at different concentrations (22, 56, and 112 mg/m3) was administered to animals of SO2 groups in different exposure chambers for 6 h/day for 7 days, while control groups were exposed to filtered air under the same conditions. Our results show that SO2 caused lipid peroxidation and changes in antioxidative status in testicles of mice. Exposure to SO2 at all concentrations tested significantly increased TBARS levels in testicles of mice. SO2 at all concentrations tested tended to decrease activities of SOD and GPx enzymes and levels of GSH relative to control animals, but only the decreases in SOD and GPx activities caused by SO2 exposures of higher concentrations were statistically significant. SO2 at all concentrations tested tended to increase activities of CAT relative to control animals, but the increases of CAT activities caused by SO2 exposures of low concentrations (22 and 56 mg/m3) were statistically significant. These results lead to the conclusion that SO2 exposure can cause oxidative damage to testicles of male mice, and SO2 is a toxin to the reproductive system of mammals, not only to the respiratory system. Further work is required to understand the toxicological role of SO2 in reproduction organs or even sperm from humans and animals.

This study was designed to investigate effects of sulfur dioxide (SO(2)) and its derivatives (bisulfite and sulfite) on the rat blood pressure. The blood pressures of male Wistar rats exposed to SO(2) and its derivatives at various doses were measured. Findings were that: (1) with acute-one time exposure to SO(2) for 6 h, the rat blood pressures were lowered in contrast to their controls and their background levels in a dose-dependent manner. (2) There were both a dose-response relationship and a time-response relationship between subchronic SO(2) exposure and the rat blood pressure. For SO(2) exposure at 10 ppm, first the blood pressures decreased significantly with exposure days in contrast to their controls and their background levels, and then these decreases became not significant, suggesting an adaption mechanism might be induced. However, SO(2)
exposures at 40 ppm caused significant decreases of the blood pressures during the whole experiment, and no adaptation process was found. (3) SO(2) derivatives (bisulfite and sulfite) also caused the decreases of rat blood pressures in a dose-dependent manner. There are two conclusions: (1) Short-time, even acute one-time, exposure to SO(2) or its derivatives may cause a decrease of blood pressure of the animals in both dose-dependent and time-dependent manners. (2) SO(2) is a systemic toxic agent, not only to the respiratory system. SO(2) can cause at least functional damage to the cardiovascular system.

Effects of sulfur dioxide (SO2) on concentrations of thiobarbituric acid-reactive substances (TBARS) and reduced glutathione (GSH), activities of Cu,Zn-superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) were investigated in lungs and hearts of Kunming albino mice of both sexes. The mice of SO2 groups were exposed to various concentrations (22, 56, and 112 mg/m3) of SO2 in separate exposure chambers for 6 h/day for 7 days, whereas control groups were exposed to filtered air under otherwise the same conditions. Our results show that SO2 caused lipid peroxidation and changes of antioxidative status in both lungs and hearts of mice. Exposure to SO2 at all concentrations tested caused a significant increase of TBARS and a significant decrease in GSH content in lungs and hearts of mice, with the exception of GSH content in the hearts of female mice. For lungs, SO2 at low concentrations significantly increased SOD and GPx activities, whereas at high concentrations it significantly decreased these same activities in mice of both sexes. For hearts, SO2 at all tested concentrations significantly decreased activities of SOD from mice of both sexes, as well as that of GPx from male mice, but the decrease of GPx activities in hearts from female mice was statistically insignificant. SO2 inhalation tended to decrease activities of CAT in lungs and hearts from mice of both sexes, whereas only the decrease of CAT activities caused by SO2 in lungs from male mice was statistically significant, at 112 mg/m3. The results also show a gender difference in oxidative stress and antioxidation status caused by SO2 exposure. These results lead us to conclude that SO2 exposure can cause oxidative damage to lungs and hearts of mice, and SO2 is toxic not only to the respiratory system, but to the heart as well. Additional work is required to understand the toxicological role of SO2 on many or even all mammalian organs.

OBJECTIVE: To investigate the inhalation of sulfur dioxide (SO(2)) on the DNA damage of brain cells in mammalian animals. METHOD: Single cell microgel electrophoresis technique (comet test) was used to test the DNA damage of brain cells. RESULTS: (1) After the exposure to SO(2) at 0, 7, 14, 28 mg/m(3), the tail lengths of nuclear DNA in brain cells from male mice were 8.02, 23.14, 46.43 and 53.49 micro m respectively; and that from female mice were 7.23, 12.43, 20.39 and 54.83 micro m respectively. The results showed that: (1) SO(2) inhalation caused damage on DNA of brain cells in a dose-dependent manner; (2) Even under lower concentration of SO(2) as 7 mg SO(2)/m(3), the damage on DNA of brain cells was also reached to 98.8%. It implied that the brain cells of mammalian animals were very sensitive to SO(2) inhalation; (3)
The DNA damage of brain cells from male mice is more serious than that from female mice. The reasons remain to be further studied. CONCLUSIONS: SO(2) pollution even at lower concentrations also had a potential risk to the genetic material DNA of brain cells from mammalian animals. The results of our study might explain the recently published epidemiological studies that the workers exposed to SO(2) or SO(2) derivatives had suffered an increase of mortality from brain cancer.


In the chronic inhalation experiment of sulfur dioxide(SO2), micronuclei(MN) frequencies in the polychromatophilic erythroblasts(PCE) of mouse bone marrow and the frequencies of cells with MN were significantly increased in dose-dependent manner. There was a significant difference between the male and the female animals. The results also showed that SO2 inhibited urethane-induced MN formation. These results furtherly confirm that SO2 inhalation was a clastogenic and genotoxic agent to mammalian cells, and the combined effects of SO2 and other mutagens are complex.


OBJECTIVE: To investigate the induction effects of sulfur dioxide (SO(2)) inhalation on chromosomal aberrations (CA) in mouse bone marrow cells. METHODS: The mice were treated with SO(2) for 4 h/day x 7 days at various concentrations of SO(2), then mitotic indices and CA in the bone marrow cells were analyzed. RESULTS: SO(2) increase the frequencies of CA and aberrant cells in mouse bone marrow cells in dose-dependent manner. The frequencies (%) of the aberrant cells in mouse bone marrow cells induced by SO(2) at concentrations of 0, 14, 28, 56 and 84 mg/m(3) were 1.81, 3.00, 3.58, 4.26 and 4.86, respectively. SO(2) at low concentrations induced only chromatid-type CA, but at high concentrations it induced both chromatid-type and chromosome-type CA. SO(2) inhalation decreased the mitotic indices of the bone marrow cells. CONCLUSIONS: SO(2) inhalation may inhibit mitoses and increase CA frequencies of the bone marrow cells; therefore, it is a clastogenic and genotoxic agent. It implies that long time exposure of SO(2) pollutant at low concentration in air may be a potential risk to induce damage of cytogenetic material in humans.


To investigate the induction of chromosome aberrations (CA) in mouse bone marrow cells by sulfur dioxide (SO(2)) inhalation, mice were treated by SO(2) exposure for 4 h/day for 7 days at various concentrations of SO(2), then mitotic indices and CA in mouse bone marrow cells were analyzed. The present results show that SO(2) might increase the frequencies of CA and aberrant cells in mouse bone marrow in a dose-dependent manner. The frequencies (%) of aberrant cells in mouse bone marrow induced
by SO(2) at concentrations of 0, 7, 14, 28 and 56 mg/m(3) were 1.81, 3.00, 3.58, 4.26, 4.86, respectively. At low concentrations SO(2) induced only chromatid-type CA, while at high concentrations SO(2) induced both chromatid-type and chromosome-type CA. SO(2) inhalation decreased the mitotic indices of bone marrow cells. The results imply that SO(2) inhalation may inhibit mitoses and increase CA frequencies of bone marrow cells and that it is a clastogenic and genotoxic agent. Long exposure to SO(2) pollution at low concentrations in the environment may be a potential risk for induction of cytogenetic damage in vivo in humans.

**Meng, et al. 1999.** Polymerase chain reaction-based deletion screening of bisulfite (sulfur dioxide)-enhanced gpt-mutants in CHO-AS52 cells. *Mutat.Res.* Vol. 425(1): 81-85. In this study, we have examined the mutagenicity of bisulfite (sulfur dioxide) at the xanthine-guanine phosphoribosyl transferase locus (gpt) in the pSV2 gpt-transformed CHO cell line, AS52. Our results provide evidence for bisulfite as a weak gene mutagen because the chemical at high doses and at high cytotoxicity causes a 4-fold increase in mutant frequency (MF) and less than a doubling of the gpt gene deletion frequency compared to control. We suggest that the increase of MF in bisulfite-treated cells results from bisulfite activity, as a comutagen, enhancing the induction effect of unknown endogenous or exogenous factors on spontaneous mutagenesis of AS52 cells. For the spontaneous, 5 mM bisulfite- and 10 mM bisulfite-enhanced spontaneous mutants in AS52 cells, the percentage of total deletion mutations of the gpt gene is 36%, 44% and 65%, respectively Copyright 1999 Elsevier Science B.V.

**Meng, et al. 1994.** Chromosomal aberrations, sister chromatid exchanges and micronuclei induced in human lymphocytes by sodium bisulfite (sulfur dioxide). *Yi Chuan Xue Bao.* Vol. 21(1): 1-6. The frequencies of chromosomal aberrations (CA), sister chromatid exchanges (SCE) and micronuclei (MN) in human blood lymphocytes exposed to sodium bisulfite (sulfur dioxide) at varies concentrations ranging from 5 x 10(-5) to 2 x 10(-3) mol/L in vitro were studied. It was shown that sodium bisulfite (NaHSO3 and Na2SO3, 1:3 mol/L) caused an increase in SCE and MN of human blood lymphocytes in a dose-dependent manner, and also induced mitotic delays and decreased mitotic index of the lymphocytes. For CA, our results indicated that sodium bisulfite induced an increase of chromatid-type aberrations of the lymphocytes from three of four donors in a dose-dependent manner. The chemical at low concentrations induced chromatid-type aberrations but not chromosome-type aberrations; at high concentrations induced both chromatid and chromosome-type aberrations of lymphocytes. No cytogenetic effects of sodium bisulfite on the human blood lymphocytes were observed in these assays. The results have confirmed that sulfur dioxide is a clastogenic and genotoxic agent.

**Menzel, et al. 1986.** Covalent reactions in the toxicity of SO2 and sulfite. *Adv.Exp.Med.Biol.* Vol. 197 477-492. Toxic effects of SO2 and sulfite such as bronchitis and bronchoconstriction have been well documented. SO2 has also been suggested to potentiate carcinogenic effects of PAH. However, the molecular basis of these toxic effects is unclear. We have examined the
covalent reaction of SO2 and sulfite with cellular proteinacious and nonproteinaceous sulphydryl compounds using rat liver, and lung and human lung derived A549 cells. Reactions of sulfite and protein in rat and human lung cells reveals at least three proteins with sulfite-reactive disulfide bonds. Besides fibronectin and serum albumin, which had been reported to contain sulfonated products following exposure to sulfite, we have found one other protein with sulfite-binding capabilities. Since the integrity of disulfide bonds is crucial to the tertiary structure and thus protein function, the disruption of protein structure by sulfitolysis may result in altered cellular activities leading to biochemical lesions. Using carefully controlled conditions, reproducible GSH contents can be found in cultured cells and used as an experimental basis for studying alterations in the GSH and GSSG content of cells. Sulfitolysis of GSSG results in the formation of GSSO3H in A549 cells, and possibly in the lung. GSSO3H can be reduced enzymatically by GSSG reductase. However, the Km of GSSO3H is high compared to that of GSSG, suggesting the existence of a transient concentration of GSSO3H once it is formed. Cysteine S-sulfonate is, however, not reduced by cytosolic extracts in the presence of NADPH and would have to be eliminated from the cell by other means. GSSO3H is a strong competitive inhibitor of GST in rat liver and lung and A549 cells, using 1-chloro-2,4-dinitrobenzene as a substrate. It also inhibits the formation of GSH conjugates of BP 4,5-oxide, anti and syn BPDE, but to a lesser extent. These results suggest that SO2 may affect the detoxification of xenobiotic compounds by inhibiting, via formation of GSSO3H, the enzymatic conjugation of GSH and reactive electrophiles. Since GSH conjugation represents the major pathway of elimination of BP epoxides in the lung, our results offer a possible explanation for the cocarcinogenicity of SO2 with PAHs. These data suggest that the sulfitolysis reaction of sulfite is the common reaction mechanism mediating the underlying biochemical reactions leading to both the toxic and cocarcinogenic properties of SO2. Quantitation of sulfitolysis products and their interaction with cellular processes should provide a coherent scheme relating SO2 and sulfite toxicity among animal species and humans.


Sodium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Potassium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite are inorganic salts that function as reducing agents in cosmetic formulations. All except Sodium Metabisulfite also function as hair-waving/straightening agents. In addition, Sodium Sulfite, Potassium Sulfite, Sodium Bisulfite, and Sodium Metabisulfite function as antioxidants. Although Ammonium Sulfite is not in current use, the others are widely used in hair care products. Sulfites that enter mammals via ingestion, inhalation, or injection are metabolized by sulfite oxidase to sulfate. In oral-dose animal toxicity studies, hyperplastic changes in the gastric mucosa were the most common findings at high doses. Ammonium Sulfite aerosol had an acute LC(50) of >400 mg/m(3) in guinea pigs. A single exposure to low concentrations of a Sodium Sulfite fine aerosol produced dose-related changes in the lung capacity parameters of guinea pigs. A 3-day exposure of rats to a Sodium Sulfite fine aerosol produced mild pulmonary edema and irritation of the tracheal epithelium. Severe epithelial changes were observed in dogs exposed for 290 days to 1 mg/m(3) of a Sodium
Metabisulfite fine aerosol. These fine aerosols contained fine respirable particle sizes that are not found in cosmetic aerosols or pump sprays. None of the cosmetic product types, however, in which these ingredients are used are aerosolized. Sodium Bisulfite (tested at 38%) and Sodium Metabisulfite (undiluted) were not irritants to rabbits following occlusive exposures. Sodium Metabisulfite (tested at 50%) was irritating to guinea pigs following repeated exposure. In rats, Sodium Sulfite heptahydrate at large doses (up to 3.3 g/kg) produced fetal toxicity but not teratogenicity. Sodium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite were not teratogenic for mice, rats, hamsters, or rabbits at doses up to 160 mg/kg. Generally, Sodium Sulfite, Sodium Metabisulfite, and Potassium Metabisulfite were negative in mutagenicity studies. Sodium Bisulfite produced both positive and negative results. Clinical oral and ocular-exposure studies reported no adverse effects. Sodium Sulfite was not irritating or sensitizing in clinical tests. These ingredients, however, may produce positive reactions in dermatologic patients under patch test. In evaluating the positive genotoxicity data found with Sodium Bisulfite, the equilibrium chemistry of sulfurous acid, sulfur dioxide, bisulfite, sulfite, and metabisulfite was considered. This information, however, suggests that some bisulfite may have been present in genotoxicity tests involving the other ingredients and vice versa. On that basis, the genotoxicity data did not give a clear, consistent picture. In cosmetics, however, the bisulfite form is used at very low concentrations (0.03% to 0.7%) in most products except wave sets. In wave sets, the pH ranges from 8 to 9 where the sulfite form would predominate. Skin penetration would be low due to the highly charged nature of these particles and any sulfite that did penetrate would be converted to sulfate by the enzyme sulfate oxidase. As used in cosmetics, therefore, these ingredients would not present a genotoxicity risk. The Cosmetic Ingredient Review Expert Panel concluded that Sodium Sulfite, Potassium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite are safe as used in cosmetic formulations.


The human body releases endogenous nitric oxide (NO) from three main sources: neurons, inflammatory processes (induced NO) and endothelium. The chemical industry produces NO by reacting sulfur dioxide and nitric acid, or sodium nitrite and sulfuric acid, or by oxidation of ammonia. Inhaled NO acts on smooth muscle cells of the pulmonary endothelium, causing relaxation by stimulation of guanylate-cyclase. The short half life of NO and its immediate breakdown into hemodynamically inactive but toxic metabolites make this drug a selective pulmonary vasodilator that can decrease pulmonary arterial pressure, improving right ventricular ejection fraction while decreasing intrapulmonary shunt and improving oxygenation. NO has demonstrated its usefulness in treating right ventricular failure secondary to pulmonary hypertension after heart surgery, especially in the transplanted patient. Doses have usually ranged from 5 to 20 parts per million. However, great individual variability in response to NO has been reported. Between 30 and 40% of patients do not respond to treatment. NO is also used to assess the reversibility of chronic pulmonary hypertension in patients who are candidates for heart transplants. Other uses have been suggested, such as reversion of pulmonary
vasoconstriction induced by protamine. Applications are limited by the toxicity of metabolites and by route of administration.


On a temporal basis, air has immense capacity for moving a large mass of pollutants. Mammals and birds are exposed to pollutants in air by the inhalation (nose and mouth), cutaneous or ocular routes. Most laboratory studies on air pollutants have been limited to single air pollutants and very little research has been done on the complex mixture of compounds that exist in ambient air. Complex mixtures are further complicated by dynamic chemical reactions that occur after the emissions leave point sources. Exposure parameters are also important in the toxicity of air pollutants. Intermittent exposure of monkeys to ozone increased the adverse pulmonary effects. Superimposing spikes of 0.8 ppm nitrogen dioxide on a baseline of 0.2 ppm, as occurs on a calm winter day, increased the susceptibility of mice to bacteria-induced pneumonia. Sulfur dioxide at concentrations of 5 ppm increased pulmonary resistance by 39%. Sulfuric acid is the predominate acid particle in the atmosphere. Exposure for 1 h to > 200 micrograms sulfuric acid/m3 depressed bronchomucociliary clearance. Concentrations of 100 micrograms/m3 of photochemical products caused headaches and 510 micrograms/m3 produced cough and chest pain. For chemical interactions in dose response, nitrogen dioxide is synergistic with ozone and ammonium sulfate. When all 3 chemicals are used in mixture, the response was 340%. Atmospheric conditions, such as fog, can alter the toxicity of air pollutants. The dose response to a single chemical can be altered by chemical mixtures and pre-existing disease conditions. Understanding these relationships is important for establishing no observable adverse effect levels. Mechanisms for multiple chemical interactions are multifaceted. One chemical may interfere with the metabolism or detoxification of another. Others may interact at cell receptors. To understand the effects of multiple chemical interactions of air pollutants, there is a need for a blend of epidemiological, laboratory and field studies. Studies are expensive. In the rural agricultural settings, the economic and environmental health risks are high. Should field observations and chemical problems be used as "red flags" for action?


This experiment was carried out to clarify the roles of diesel exhaust particle (DEP) extracts and the promotive effects of nitrogen dioxide (NO2) and/or sulfur dioxide (SO2) exposure on rat lung tumorigenesis. F344 male rats were intratracheally administered DEP extract-coated carbon black particles (DEcCBP) and exposed to 6 ppm NO2 and/or 4 ppm SO2 for 10 months. At 18 months after starting the experiment, lung lesions were histopathologically investigated and DNA in rat lungs was analyzed for the presence of adducts using the 32P-postlabeling assay. Infiltration of alveolar macrophages, which was significant in the lungs of rats administered carbon black particles, was not prominent in those administered DEcCBP. DEcCBP occasionally formed small hyaline masses in the alveolar ducts and alveolar bronchiolization developed in the epithelium of alveolar ducts near the masses. Lung tumorigenesis and DNA aduct formation were
observed in the animals administered DEcCBP with exposure to NO2 and/or SO2, but not in those administered DEcCBP alone. The results of the present study suggested that DEP extracts eluting from the small masses cause DNA damage in alveolar epithelial cells and alveolar epithelial cell proliferation, and that NO2 and/or SO2 exposure promote lung tumor induction by DEP extracts.


Relations between pulmonary symptoms and exposure to respirable dust and sulphur dioxide (SO2) were evaluated for 145 silicon carbide (SiC) production workers with an average of 13.9 (range 3-41) years of experience in this industry. Eight hour time weighted average exposures to SO2 were 1.5 ppm or less with momentary peaks up to 4 ppm. Cumulative SO2 exposure averaged 1.94 (range 0.02-19.5) ppm-years. Low level respirable dust exposures also occurred (0.63 +/- 0.26 mg/m3). After adjusting for age and current smoking status in multiple logistic regression models, highly significant, positive, dose dependent relations were found between cumulative and average exposure to SO2, and symptoms of usual and chronic phlegm, usual and chronic wheeze, and mild exertional dyspnoea. Mild and moderate dyspnoea were also associated with most recent exposure to SO2. Cough was not associated with SO2. No pulmonary symptoms were associated with exposure to respirable dust nor were any symptoms attributable to an interaction between dust and SO2. Cigarette smoking was strongly associated with cough, phlegm, and wheezing, but not dyspnoea. A greater than additive (synergistic) effect between smoking and exposure to SO2 was present for most symptoms. These findings suggest that long term, variable exposure to SO2 at 1.5 ppm or less was associated with significantly raised rates of phlegm, wheezing, and mild dyspnoea in SiC production workers, and that current threshold limits for SO2 may not adequately protect workers in this industry.


BACKGROUND: Sulfur dioxide (SO2) is one of the major air pollutants. It is known to aggravate asthma symptoms in human beings, but few studies have focused on the effects of SO2 upon the development of bronchial asthma in animal models. OBJECTIVE: This study was undertaken to evaluate the role of SO2 upon the development of ovalbumin (OA)-induced asthmatic reactions in guinea pigs. METHODS: Guinea pigs were divided into four groups: (1) OA- and SO2-exposed group (n = 12), (2) SO2-exposed group (n = 12), (3) OA-exposed group (n = 11), and (4) saline-exposed group (n = 7). Guinea pigs of the first and second groups were exposed to 0.1 ppm SO2 for 5 hours a day on 5 consecutive days. Guinea pigs in the first and third groups inhaled 0.1% OA aerosols for 45 minutes a day on days 3, 4, and 5. One week after the sensitization procedure, all the guinea pigs underwent bronchial challenge with 1.0% OA aerosols, using unrestricted whole-body plethysmography. Bronchoalveolar lavage and histopathologic examination were performed 24 hours after the bronchial challenge. RESULTS: Increases in enhanced pause (Penh), as an index of airway obstruction, after the bronchial challenge was significantly higher in OA- and SO2-exposed group (group 1) than the other groups (P <
.05, respectively). Eosinophil counts in bronchoalveolar lavage fluids were also significantly higher in group 1 than in the other groups (P < .05, respectively). Histopathologic findings of bronchial and lung tissue in the group 1 showed an infiltration of inflammatory cells, bronchiolar epithelial damage, and mucus and cell plug in the lumen, but no significant abnormalities were observed in the other groups.

CONCLUSIONS: These results indicate that repeated exposure to low levels of sulfur dioxide may enhance the development of ovalbumin-induced asthmatic reactions in guinea pigs.


Sulphur dioxide (SO₂) is a common air pollutant found both in indoor and outdoor environments. Studies of controlled human exposure as well as epidemiological and animal investigations have documented several short- and long-term effects of SO₂ exposure on the respiratory and other systems. Exercise, duration and other exposure factors may potentiate the pollutant's effects, especially in sensitive individuals such as children and asthmatics. Early postnatal somatic and behavioural alterations have been shown after maternal SO₂ exposure, during pregnancy and neonatal exposure. Such exposure should be considered as a complex toxic hazard which may interfere with the developmental processes in the offspring.


OBJECTIVES: In 1977, nine men were accidentally exposed to sulfur dioxide in an explosion in a pyrite mine. The lung function of seven men was followed after the accident. A four-year follow-up has been published previously. The greatest decrease in forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1.0), and maximal midexpiratory flow (MMEF) was observed one week after the accident, after which all these parameters improved without reaching the preaccident level. Reversible bronchial obstruction was still present in three patients, and a positive reaction in the histamine challenge test was found for four. In the present paper, the lung function follow-up 13 years after the accident is reported for six men. METHODS: The patients' clinical condition, chest X-ray, spirometry, and histamine challenge test were studied 13 years after the incident. RESULTS: Spirometry was normal in one worker, two displayed obstruction, and three had a combined obstructive and restrictive, mainly obstructive, ventilatory impairment. In the histamine challenge test, four patients showed bronchial hyperreactivity, one with a nearly significant reaction. Because of bronchial obstruction one patient could not perform the challenge test. CONCLUSIONS: This 13-year follow-up showed that acute inflammatory obstruction caused by exposure to sulfur dioxide left, as sequelae, obstructive impairment of ventilatory function and permanent bronchial hyperreactivity. The clinical picture displayed by these patients was named the "reactive airways dysfunction syndrome" (RADS) in 1985. Four of the patients also showed symptoms of chronic bronchitis.


We present clinical and laboratory results (including nuclear imaging) obtained over a period of two years in two nonsmoking miners who were exposed to high concentrations of sulfur dioxide (SO2) after a mine explosion. Within 3 wk of the accident, both miners had evidence of severe airways obstruction, hypoxemia, markedly reduced exercise tolerance, ventilation-perfusion mismatch, and evidence of active inflammation as documented by positive gallium lung scan. Serial ventilation-perfusion scans over the first 12 months showed progressive improvement without returning to normal. After the initial recovery, there has been no significant change over the subsequent two years postinjury. Pulmonary function and exercise tests also displayed a similar pattern of initial improvement. We conclude that (1) acute exposure to high concentrations of SO2 results in severe airways obstruction, (2) pulmonary function abnormalities are partially reversible, and (3) most of the improvement occurs within 12 months after the initial injury.


We report on an acute accidental inhalation of sulfurous anhydride, by a man aged thirty in the course of his work. This intoxication, followed by acute respiratory distress, first showed an improvement, then re-aggravation 26 days after the accident. This episode has not been explained. The patient then developed a chronic obstructive bronchopathy. Ten years of regular observation allows us to maintain that the severe obstructive syndrome


Sulfur dioxide, a ubiquitous air pollutant, is a co-carcinogen for benzo[a]pyrene (BP). We have demonstrated previously that the interaction between sulfite, the physiological form of sulfur dioxide, and (+/-) -7r,8t-dihydroxy-9t,10t-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (anti-BPDE), the ultimate carcinogenic form of BP, results in an enhanced mutagenic effect in Salmonella typhimurium strains TA98 and TA100. We report here that this same co-mutagenic effect of sulfite occurs in a mammalian cell line. Treatment of Chinese hamster V79 cells with 50 nM anti-BPDE, a concentration on the linear portion of the dose-response, resulted in a four-fold increase in mutations at the hprt locus relative to the spontaneous rate. When V79 cells were exposed to 1 or 10 mM sulfite immediately prior to the addition of anti-BPDE, the mutation rate increased by 73% and 210%, respectively, over that elicited by anti-BPDE alone. Sulfite itself was moderately cytotoxic, but caused no increase in mutation over the spontaneous rate. Characterization of the dose- and time-dependance of this enhancement of diol epoxide mutagenicity by sulfite closely resembled the effects seen previously in the bacterial system. In particular, enhancement by sulfite was evident when sulfite was added to the
cells between 60 min and 1 min prior to the addition of the diol epoxide. Concurrent addition of sulfite and the diol epoxide attenuated the enhancement, and the effect was lost altogether when sulfite was added 10 min after the diol epoxide. The specificity of this effect of sulfite was shown by comparison with sulfate, which at concentrations of either 1 or 10 mM exhibited modest cytotoxicity, but neither was directly mutagenic nor able to enhance the mutagenic effect of anti-BPDE. Binding studies with labeled anti-BPDE showed that the addition of 10 mM sulfite increased binding of anti-BPDE to DNA by over 43%, corresponding to the observed increase in mutant frequency. Interestingly, this difference in level of DNA modification was not apparent after 30 min to 2 h exposures, but only emerged at the 4 h time point. The 4 h point was routinely used for all mutagenicity studies. Binding of anti-BPDE-derived materials to cellular RNA was not altered by 10 mM sulfite. The emergence of increased DNA modification at the latest time point suggests either a more prolonged period of active DNA binding than would occur with diol epoxide, or a difference in the ability to recognize and clear specific DNA adducts. Both possibilities are discussed in regard to the observed formation of 7r,8t,9t-trihydroxy-7,8,9,10-tetrahydrobenzo[a] pyrene-10c-sulfonate (BPT-10-sulfonate) in those incubations. BPT-10-sulfonate is a relatively stable BP derivative which retains the ability to covalently modify DNA. The role of this derivative in the enhancement of diol epoxide mutagenicity by sulfite is strongly suggested by these data.


The effects of environmental exposures to toxic agents, are related to different levels of exposure, genetic and biological susceptibility, risk perception and socioeconomic status (SES). In the present study we suggest that environmental influences on human reproduction should include investigations on SES, that can play an important role in embryo-foetal development. Low birth weight (LBW) is a risk factor for developing in adulthood coronary hearth disease, hypertension and type 2 diabetes. Maternal nutritional status and other hypothesis could explain LBW, however, environmental exposures are recognised as essential risk factors. Different studies evidenced an increased risk of LBW in relation to increased environmental air levels of particulate matter, carbon monoxide, and sulphur dioxide. Considering different risk possibilities and different risk perceptions, there is a need of a different scientific approach in which the scientific knowledge is connected with ethical and socioeconomic factors, for risk management, in order to overcome the environmental health inequities based on social contest.


The airways of asthmatics are hyperreactive, not only to allergens but to a wide range of non-specific physical and chemical stimuli. Four mechanisms which have been proposed to be causes of hyperreactivity are (i) a decrease in baseline airway calibre (ii) an increase in the responsiveness of the bronchial smooth muscle (iii) an imbalance in the autonomic neurophysiological regulation of airway calibre and (iv) epithelial changes which lead to an increase in the accessibility of allergens and non-specific stimuli to the mast cells, sensory nerve endings or bronchial smooth muscle beneath the airway mucosa. We have studied the effects of some of the proposed mediators of asthma on lung mechanics and
irritant receptor activity in dogs with a respiratory tract infection and in dogs following exposure to SO₂ gas at a concentration (400 ppl) sufficient to damage the airway epithelium (Jackson and Richards, 1980). In dogs naturally infected with Bordetella bronchiseptica there was an increased airway reactivity to histamine which was almost completely abolished by vagotomy. The hyperreactivity to histamine was shown to be due to an increased responsiveness of lung irritant receptors. In dogs exposed to SO₂ gas changes in RL induced by 5-hydroxytryptamine or electrical stimulation of the vagus nerves were significantly increased when compared to the responses in normal dogs. Altounyan (1970) has shown that continuous exposure to allergens in patients with seasonal allergic asthma also leads to an increase in non-specific bronchial reactivity. Pharmacological modulation of airway reactivity can be divided into the acute and long term effects of drugs. Acute effects of drugs have been studied by several groups of workers using the airway responses to inhalation of various non-specific stimuli (e.g. distilled water, cold air, SO₂ gas). Beta-stimulants and sodium cromoglycate are usually effective inhibitors and anticholinergic drugs are effective when a reflex component contributes to the bronchoconstriction. Few controlled studies of the effect of long-term treatment with drugs on bronchial hyperreactivity have been carried out although as early as 1970 Altounyan showed that long-term treatment with sodium cromoglycate could inhibit the development of non-specific hyperreactivity during the pollen season in pollen-sensitive asthmatics. A number of further studies have confirmed these early observations.


OBJECTIVE--To investigate associations between exposure to pot emissions (fluorides, sulphur dioxide) and mortality from chronic obstructive lung disease, coal tar pitch volatiles and mortality from diseases related to atherosclerosis, and carbon monoxide and mortality from ischaemic heart disease. METHODS--Mortality between 1962 to 1991 was investigated in a cohort of 1085 men hired by a Norwegian aluminium smelter between 1922 and 1975. Associations between cumulative exposure and mortality were investigated through SMR analysis based on national mortality rates; temporal relations were explored by considering exposures only within specific time windows. Circulatory mortality was also investigated by Poisson regression analysis. RESULTS--There were 501 deaths v 471.3 expected in the cohort. The excess was confined to short term workers and did not seem to be associated with exposures in the smelter. Analysis of mortality among the 661 men with at least three years employment showed associations between cumulative exposure to tar 40 years before observation and atherosclerotic mortality (P = 0.03), and between exposure to pot emissions 20-39 years before observation and mortality from chronic obstructive lung disease (P = 0.06). No association was found between exposure to carbon monoxide and mortality from ischaemic heart disease, but cerebrovascular mortality was associated with exposure to pot emissions (P = 0.02). Results for atherosclerotic and cerebrovascular diseases were confirmed through Poisson regression analysis. CONCLUSIONS--The data support previous findings of increased mortality from ischaemic heart disease in workers exposed to tar, and some support is also provided for earlier reports of increased respiratory mortality in potroom workers.

Sanders. 1986. Coal and Oil. *Toxicological Aspects of Energy Production; Columbus, Ohio, Battelle Press, pages 181-209, 64 references.* The major topics considered in this review included: coal workers pneumoconiosis (CWP), carbon-dioxide (124389) production, acid precipitation, coal fly ash, carcinogens from fossil fuel sources, aliphatic hydrocarbons, crude oil, oil fly ash, gasoline, diesel fuel, and toxic effects of fossil fuel combustion. Studies have indicated that once coal dust has been deposited in the pulmonary region, it has a long retention time and can result in mild to severe pulmonary disease manifested by nonreversible fibrotic lesions causing progressive loss of pulmonary function as the dust burden increases. Over 70 percent of underground coal miners were affected by CWP; the incidence of emphysema ranged up to 80 percent. The increased combustion of fossil fuels has caused an increase in the amount of carbon-dioxide in the atmosphere where it absorbs infrared radiation and reduces the amount of radiant energy reaching the surface of the earth. Several studies have demonstrated the effects of carbon-dioxide in the atmosphere on the weather patterns experienced on earth. Coal combustion also releases sulfur-dioxide (7446095) and nitrogen oxides which are returned to the surface of the earth with precipitation resulting in acid rain or snow. Fly ash particles are emitted to the air during the combustion of coal. Alveolar macrophages rapidly phagocytize inhaled ash particles, greatly increasing the elemental concentration of toxic metals in individual cells and impairing the bactericidal capacity of macrophages. Of interest from a carcinogenicity standpoint are the polycyclic aromatic and heterocyclic hydrocarbons present in fossil fuels and their combustion products. While there has been no evidence that prolonged, chronic exposure to gasoline vapors causes toxicity, exposure can produce narcosis, with central nervous system depression, and death resulting from fatal cardiac arrhythmia due to the release of epinephrine acting on the myocardium, and respiratory failure.


OBJECTIVE: To determine the cause of acute illness on August 30, 2000, among patients at an outpatient dialysis center (center A). DESIGN: We performed a cohort study of all patients receiving dialysis on August 30, 2000; reviewed dialysis procedures; and analyzed dialysis water samples using microbiologic and chemical assays. SETTING: Dialysis center (center A). PATIENTS: A case-patient was defined as a patient who developed chills within 5 hours after starting hemodialysis at center A on August 30, 2000. RESULTS: Sixteen (36%) of 44 patients at center A met the case definition. All case-patients were hospitalized; 2 died. Besides chills, 15 (94%) of the case-patients experienced nausea; 12 (75%), vomiting; and 4 (25%), fever. Illness was
more frequent on the second than the first dialysis shift (16 of 20 vs 0 of 24, \(P < .001\)); no other risk factors were identified. The center's water treatment system had received inadequate maintenance and disinfection and a sulfurous odor was noted during sampling of the water from the reverse osmosis (RO) unit. The water had elevated bacterial counts. Volatile sulfur-containing compounds (ie, methanethiol, carbon disulfide, dimethyldisulfide, and sulfur dioxide) were detected by gas chromatography and mass spectrometry in 8 of 12 water samples from the RO unit and in 0 of 28 samples from other areas (\(P < .001\)). Results of tests for heavy metals and chloramines were within normal limits. CONCLUSIONS: Parenteral exposure to volatile sulfur-containing compounds, produced under anaerobic conditions in the RO unit, could have caused the outbreak. This investigation demonstrates the importance of appropriate disinfection and maintenance of water treatment systems in hemodialysis centers.


Shinkura, et al. 1999. Relationship between ambient sulfur dioxide levels and neonatal mortality near the Mt. Sakurajima volcano in Japan. *J.Epidemiol.* Vol. 9(5): 344-349. We examined the association between neonatal mortality and ambient sulfur dioxide (SO2) levels in the neighborhood of Mt. Sakurajima, Yamashita public health district of Kagoshima City, during the period between 1978 and 1988. The analysis using Poisson regression models showed that the monthly average level of SO2 was positively associated with the neonatal mortality (\(P = 0.002\)). When the SO2 levels were categorized into four groups to estimate the relative risk (RR) of neonatal mortality using the lowest exposure category as a reference, the RR increased with elevated exposure levels (\(P\) for trend \(< 0.001\)) and was the highest in the group with the highest level of exposure (RR = 2.2, 95% confidence interval: 1.2-4.1). Other than SO2, we also examined the number of eruptions, the amount of ashfall, and the average level of suspended particulate matter. None of these factors was associated with neonatal mortality. Although the present study suggests that increase in SO2 levels has had an adverse effect on neonatal mortality in the neighborhood of Mt. Sakurajima, it is difficult to determine the source of the SO2. Further studies are necessary to elucidate the mechanisms of the excess neonatal mortality probably associated with the volcanic SO2 levels.

Smith. 1998. A risk-benefit assessment of antileukotrienes in asthma. *Drug Saf.* 19(3): 205-218. The antileukotriene drugs are the first new therapeutic agents approved for the treatment of asthma in more than 20 years. The currently available compounds are orally active and either prevent the cysteinyl leukotrienes from binding to and activating the cysLT-1
receptor in the lung (leukotriene receptor antagonists) or inhibit leukotriene synthesis (leukotriene synthesis inhibitors). Studies performed in individuals without asthma and patients with asthma reveal that antileukotrienes prevent the bronchoconstriction produced by exercise, cold-air, allergen, aspirin (acetylsalicylic acid) and sulphur dioxide. Except for the setting of aspirin sensitivity where the antileukotrienes are nearly uniformly effective, individual responses to them are variable with complete protection in some, no protection in others and a modest degree of protection in the majority. The antileukotrienes bronchodilate the airways of patients with baseline bronchoconstriction, although usually not as well as beta-agonists. When given for weeks to months they rapidly improve pulmonary function and symptoms in patients with mild-to-moderate asthma, and probably in patients with more severe asthma as well, and these improvements persist for the duration of treatment. Here too, their beneficial effects are variable and not predictable based on clinical criteria. Recent studies suggest they can reduce asthma-induced airway inflammation and are equal or more effective than sodium cromoglycate, but equal or less effective than low-to-moderate dosages of inhaled corticosteroids. Initial experience with the antileukotrienes reveals limited toxicity and what appears to be a favourable therapeutic-to-toxic ratio. However, exposure of more patients with differing characteristics for longer periods of time is needed to substantiate this initial impression. The exact role of the antileukotrienes in the treatment of asthma remains to be determined, as does the relative potency of the various agents.

The development of a survival model for post-crash aircraft cabin fires is described in this paper. Its development is based on an extensive review of the literature on the toxicity of combustion gases and on thermal hazards. This model is to be used as a predictive tool to gauge human survivability in full scale aircraft cabin fire tests. The extensive literature search was conducted for carbon monoxide (CO), carbon dioxide (CO2), hydrogen cyanide (HCN), low oxygen, hydrogen fluoride (HF), hydrogen chloride (HCl), hydrogen bromide (HBr), nitrogen dioxide (NO2), sulfur dioxide (SO2), acrolein (CH2CHCHO), and heat exposures. Those studies by various investigators of exposures to single and mixed gases on humans, primates, rats, and mice at different physical activity levels were compared. Regression equations were derived from those studies to give the best fit to the gas exposure concentration and duration data. The equation judged to best model the human escaping from an aircraft cabin was selected for each gas. This survival model uses incapacitation data to obtain a fractional effective dose (FED) for incapacitation (FED(I)) and lethality data, inclusive of post exposure deaths, to obtain a FED for lethality (FED(L)). The exposure time required for either FED(I) or FED(L) to reach unity, using a projected set of gas concentrations, represents the exposure time available to escape from the specified fire environment or to survive post exposure, respectively. The effect of CO2 in increasing the uptake of other gases was factored into the concentration term in the FED equation for all gases with the exception of CO2 and oxygen. Higher respiratory minute volumes due to CO2 exposure were found to be an important factor in predicting the time available to escape. This FED-based model can be applied to the evaluation of the toxicity of smoke in computer modeling of aircraft fire situations.
SPEITEL. 1996. Fractional effective dose model for post-crash aircraft survivability. *Toxicology; 115 (1-3).* BIOSIS COPYRIGHT: BIOL ABS. The development of a survival model for post-crash aircraft cabin fires is described in this paper. Its development is based on an extensive review of the literature on the toxicity of combustion gases and on thermal hazards. This model is to be used as a predictive tool to gauge human survivability in full scale aircraft cabin fire tests. The extensive literature search was conducted for carbon monoxide (CO), carbon dioxide (CO2), hydrogen cyanide (HCN), low oxygen, hydrogen fluoride (HF), hydrogen chloride (HCl), hydrogen bromide (HBr), nitrogen dioxide (NO2), sulfur dioxide (SO2), acrolein (CH2CHCHO), and heat exposures. Those studies by various investigators of exposures to single and mixed gases on humans, primates, rats, and mice at different physical activity levels were compared. Regression equations were derived from those studies to give the best fit to the gas exposure concentration and duration data.

Stokinger. 1972. Toxicity of Airborne Chemicals: Air Quality Standards-A National and International View. *Annual Review of Pharmacology, Vol.12, pages 407-421.* A comparison of air quality standards of the USA and the USSR shows that each country lists about 500 substances for industrial air, but that there is some difference in which pollutants are of concern. Also, limiting values for the same substance tend to differ; in general, USSR standards are lower, both for community air and industrial air. The USA has both primary and secondary standards for some substances; the primary deals with health protection and the secondary (which are more stringent), with protection of the environment. As for industrial air of other nations, non-communist countries have in general adopted the standards of the USA; and communist countries have in general adopted standards intermediate between those of the USSR and the USA. Community standards are much more stringent than those for industry, reflecting, among other factors, the greater margin of safety required for the population at large. Substances for which there are such differences include carbon-monoxide (630080), sulfur-dioxide (7446095), nitrogen-dioxide (10102440), hydrocarbons, ozone (10028156), particulates, and lead (7439921).

Stokinger. 1965. Pollutant Gases. *Respiration II, Chapter 42, Handbook of Physiology, pages 1067-1086, 98 references.* Review of physical and chemical properties, and toxic characteristics of pollutant gases and aerosols, particularly ozone, nitrogen-dioxide (10102440), and sulfur-dioxide, and sodium-chloride (NaCl) aerosol, and with some attention to nitrogen oxides, generally. Topics include acute and chronic toxicity in man and animals; toxic mechanisms; tolerance development and cross tolerance; effects in lower organisms and cell structure; physiological, biochemical, and environmental factors affecting toxicity; effect of intermittent and continuous exposures; and interactions.

Since s-carboxymethylcysteine (S-CMC) can directly enhance the ciliary activity in the maxillary sinus mucosa of patients with chronic sinusitis in the absence of significant organic changes of ciliated cells, the nebulization therapy using this medicine might be more effective in the treatment of chronic sinusitis than oral administration of the medicine. The safety of using 0.5-10% of S-SMC as a medicine for nebulization has been experimentally established. The present study was designed to experimentally examine the effectiveness of nebulization using 0.5-10% of S-CMC solution in the treatment of experimental chronic sinusitis in rabbits recurrently exposed to 20 ppm of sulfur dioxide. Thirty-three healthy rabbits were used; 3 of them were used as controls. The remaining 30 were exposed to 20 ppm of sulfur dioxide for 4 h a day for 4 successive weeks. Twelve animals were not treated with any medication during the post-exposure period, and sacrificed at 24 h or 15 days after completion of the final exposure to sulfur dioxide. The remaining 18 animals were treated with nebulization using 10%, 5% or 0.5% of S-CMC solution for 20 min a day for 14 successive days after the final exposure to sulfur dioxide, and they were sacrificed at 24 h after the final nebulization using S-CMC. At the time of sacrifice, the ciliary activity and the morphology of the sinus mucosa were observed to assess the effectiveness of S-CMC nebulization. In the animals sacrificed 24 h after the final exposure, the mucosa of the sinus demonstrated marked epithelial cell injuries, and the ciliary activity was extremely reduced. Complete recovery of the epithelium and the ciliary activity was not recognized in the animals sacrificed 15 days after completion of the exposure. By contrast, epithelial recovery was more accelerated in the animals treated with S-CMC nebulization during the 14 days after the exposure. In the animals treated with 0.5% of S-CMC, the ciliary activity was inferior to that of the control animals, and the epithelial repair was not complete. In the animals treated with 10% of S-CMC, however, ciliary activity and epithelial morphology were completely recovered. In conclusion, our study suggests that clinical application of 10% of S-CMC nebulization may provide otolaryngologists with a new tool in the treatment of sinus diseases such as chronic sinusitis.


The prime factors influencing survivability from 10 major fire-related public transport aircraft accidents were assessed. Regulatory requirements were assessed against derived criteria and alternate concepts evaluated to identify a preferred strategy for enhanced survival; the provision of passenger protective breathing equipment (PPBE) was part of the twin strategy selected. PPBE tests conducted by the UK Air Accidents Investigation Branch using lung simulators and semi-controlled complex challenge combustion atmospheres generated from defined mixtures of cabin interior materials indicated that Hopcalite filters could provide satisfactory protection against carbon monoxide, hydrogen cyanide, hydrogen fluoride, hydrogen chloride, nitrogen oxides, sulphur dioxide, ammonia, acrolein, and other hydrocarbon compounds, for periods up to 30 min. Filtered levels of carbon dioxide (CO2) could be maintained within a 5% limit (inhaled atmosphere + dead space) against such atmospheres containing up to 4% CO2. Concentrations of oxygen downstream from the filters were up to some 1.0% above that.
present in the challenge atmospheres. Separate lung simulator tests on breathable gas (oxygen) hoods indicated that satisfactory respiratory protection could be provided for periods of up to 31 min. A possible filter modification of the passenger oxygen mask concept is discussed. It is recommended that research should be emphasized on the development of a means (e.g. PPBE) for providing in-flight smoke protection for passengers.


In East Germany ambient air pollution is characterized by high concentrations of sulfur dioxide (SO$_2$) and suspended particulates (SP). Since acidity and sulfate are surprisingly low, oxidation of SO$_2$ seems to be incomplete and neutralization seems to play an important role. Few studies on health effects of air pollution in the former German Democratic Republic have been performed. They showed an increased prevalence in polluted areas of respiratory symptoms, lung function decrement, mild anemia, nonspecific stimulation of the immune system and, retardation of skeletal maturation of children. Since the German unification in 1990, several large-scale studies have been started. Short-term effects of air pollution on daily mortality have been investigated in Erfurt retrospectively for 1980 to 1989. Logarithmic exposure-effect curves have been found for both SO$_2$ and SP. The number of deaths increased by about 10% with SO$_2$ and by more than 20% with SP if the 95th percentile of the pollutant is compared to the 5th percentile. The logarithmic shape shows that the increase of ambient concentrations at the beginning of the heating season in fall is more important than further increases in concentrations later in winter. A second study on short-term effects was conducted using daily peak flow measurements and respiratory symptoms in 270 patients with asthma and other obstructive airway diseases in East Germany and the Czech Republic between 1990 and 1992. From regression analysis it follows that an increase by 500 micrograms/m$^3$ of SO$_2$ leads to a mean decrease of the average patient's peak flow below 2%.


In January 1985 a smog period occurred for 5 days in parts of West Germany, including the Rhur District. Mortality (24,000 death certificates), morbidity in hospitals (13,000 hospital admissions, 5400 outpatients, 1500 ambulance transports) and consultations in doctors' offices (1,250,000 contacts) were studied for a 6-week period including the smog episode and a time interval before and thereafter. The study region was the State of North Rhine-Westfalia (16 million inhabitants), but the analysis is restricted to the comparison of the polluted area and a control area (6 million inhabitants each). During the smog period, mortality and morbidity in hospitals increased in the polluted area, but there was no substantial increase in the control area. The increases were for the total number of deaths 8 vs. 2% (polluted area vs. control area), for hospital admissions 15 vs. 3%, for outpatients 12 vs. 5% and for deliveries by ambulance to hospitals 28% in the polluted area.
area (not investigated in the control area). The effects were more pronounced for cardiovascular diseases than for respiratory diseases. The consultations in doctors' offices show a slight decrease (-2 vs. -4%). Regression analysis shows a moderate influence of temperature, but a strong influence of ambient air pollution. The maxima of the ambient concentrations are more important on the same day, whereas the influence of the daily averages is more pronounced after a delay of 2 days. The results are discussed considering other possible confounders such as indoor pollution and psychogenic influences of the alarm situation. In total, the study suggests moderate health effects due to increased air pollution during the smog episode.

Sulfur dioxide (SO2) is a common air pollutant found in the workplace. Considerable variation exists in the airway responses of asthmatics to the inhalation of SO2. To determine if such variation among asthmatics is related to nonspecific airway reactivity, we compared the threshold doses of methacholine and SO2 required to produce significant changes in flow rates at 60% of the vital capacity below total lung capacity on the partial expiratory flow volume curve in a group of eight mildly asthmatic subjects. A significant correlation between the dose of SO2 and the dose of methacholine required to produce bronchoconstriction (r = .86, p less than .05) was observed, suggesting that there is a relationship between the response to SO2 and the response to methacholine in mildly asthmatic individuals. More generally, nonspecific airway hyperreactivity may help to predict untoward airway responses to inhaled SO2 in the workplace.

Exposures to sulfur dioxide (SO2) have been associated with progressive, dose-dependent bronchoconstriction in sensitive individuals. The clinical significance of such changes remains poorly characterized. We studied subjective responses following exposure to low level concentrations of SO2 (less than 1 ppm) in a group of 10 healthy and 10 asthmatic subjects. The number and severity of complaints associated with SO2 increased with concentrations in both healthy and asthmatic subjects. Asthmatics indicated progressive lower respiratory complaints, such as wheezing, chest tightness, dyspnea and cough with increasing levels of SO2 while healthy subjects complained more frequently of upper airway complaints such as taste and odor with increasing levels of SO2. Exercise increased the frequency of lower airway symptoms in asthmatics but led to no increases in symptoms in healthy subjects.

The hockey stick regression method is a convenient method to estimate safe doses, which is a kind of regression method using segmented lines. The method seems intuitively to be useful, but needs the assumption of the existence of the positive threshold value. The validity of the assumption is considered to be difficult to be shown. The alternative methods which are not based on the assumption, are given under suitable dose-response
curves by introducing a risk level. Here the method using the probit model is compared with the hockey stick regression method. Computational results suggest that the alternative method is preferable. Furthermore, similar problems in the case that response is measured as a continuous value are also extended. Data exemplified are concerned with relations of SO$_2$ to simple chronic bronchitis, relations of photochemical oxidants to eye discomfort and residual antibiotics in the lever of the chicks. These data was analyzed by the original authors under the assumption of the existence of the positive threshold values.

Genotoxicity of sulfur dioxide (SO(2)) and its hydrates (bisulfite and sulfite) in human lymphocytes and other mammalian cells have been found earlier in our laboratory. In the present studies, we used Allium staviyum and Vicia faba cytogenetic tests, which are the highly sensitive and simple plant bioassays. A mixture of sodium bisulfite and sodium sulfite (1:3), at various concentrations from 1 x 10(-4) to 2 x 10(-3)M was used for the treatment. Genotoxicity was expressed in terms of anaphase aberration (AA) frequencies in the Vicia-AA test and in terms of micronuclei (MCN) frequencies in both Vicia-MCN test and Alllium-MCN test. On average, the results showed a 1.7-3.9-fold increase of AA frequencies and a 3.5-4.5-fold increase of MCN frequencies in Vicia root tips as compared with the negative control. Similarly, results of Allium-MCN test also showed a significant increase in MCN frequencies in the treated samples. In addition, pycnotic cells (PNC) appeared in Allium root tips of treated groups. The frequencies of MCN, AA and PNC increased dose-dependently and the cell cycle delayed at the same time in bisulfite treated samples. Results of the present study suggest that the Vicia and Allium cytogenetic bioassays are efficient, simple and reproducible in genotoxicity studies of bisulfite.

On the experimental table of fluidized bed which scale was phi 150 mm x 1000 mm and temperature interval was from 840 degrees C to 960 degrees C, the influence of desulfurizer variety, particle size and molar ratios Ca/S on nitrogen conversion to NO were studied. This paper elaborated on the mechanism of calcium-based desulfurizer lead to the increase of NO conversion rate. Experiment presented that given identical quantities, burnt calcium had maximum NO conversion rate, then limestone, calcite last. Nitrogen conversion to NO increased with increasing molar ratios Ca/S. When the particle size was between 1-2 mm, the NO conversion rate was the maximum, second was 2-3 mm, the last 0.2-1 mm. HCl, HF, SO2 decreased with calcium addition. At the same time H, OH, HO2 radicals increased. The CO oxidation was favored, the reaction of monoxide and NO catalyzed by char, sand, ash will weaken, therefore NO content will increase.

In this study, ecological analysis was used to assess the relationship between ambient air pollution and human mortality. All the data on environmental measures and related factors, population size and number of deaths were collected for the city of Beijing, PR China and its eight districts for the years 1980-1992. In this study the concentration of SO(4)2- was selected as a main indicator of environmental pollution for the following reasons: (i) SO(4)2- data are available to cover all urban and suburban areas in Beijing compared with other air pollutants during the study period; (ii) SO(4)2- levels indicate the concentration of sulfide (include sulfate) and acid fog in the air, and they are significantly lower in cleaner districts than in others; and (iii) analyses showed that SO(4)2- levels are significantly correlated with daily mean concentrations of sulfur dioxide and nitrogen oxide, annual coal combustion, number of households using gas fuel, counts of motor vehicles and population density. Age-standardised mortality rates due to specific diseases were calculated using the Chinese population census data in 1990. Statistically significant correlations were observed between SO(4)2- concentration and total mortality and mortality due to cardiovascular disease, malignant tumour and lung cancer (r > 0.50 in all cases). The correlations were not only found between the current SO(4)2- concentration and these mortalities, but also for SO(4)2- levels measured up to 12 years prior to death, which may suggest long-term effects of air pollution. No significant correlations were observed for mortality from respiratory diseases and cerebrovascular diseases (r = 0.30-0.50). This study indicates that the concentration of SO(4)2- in air is a useful air pollution indicator in the areas where coal is used as the main source of energy. Areas with high levels of SO(4)2- experienced higher mortality due to a variety of chronic diseases.