Draft
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Air Quality Criteria
for Particulate Matter
and Sulfur Oxides

Volume IV
Health Effects

NOTICE

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This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

Preface to Volume IV

Volume IV of this Criteria Document addresses the effects of sulfur oxides and particulate matter on health. To understand these effects, however, one must first appreciate the characteristics of these substances as they occur in the environment. This prerequisite information may be found in Volume II, which covers chemical and physical properties, analytical and measurement techniques, sources and emissions, environmental concentrations and exposures, and atmospheric transmission.

This volume begins its assessment of health effects by examining respiratory deposition and biological fate of inhaled aerosols and sulfur dioxide (Chapter 11). The respiratory system is the principal route of exposure to airborne particles and gaseous sulfur oxides, viz. SO_2. Such exposure is a function of physicochemical properties of the pollutants as well as anatomical and physiological features of the exposed organism. Moreover, exposure consists not only of the inhalation and deposition of substances, but their movement to other organs, biological transformation, or removal from the body.

Chapter 12 assesses _in vitro_ and _in vivo_ studies of toxic effects of sulfur oxides and particulate matter. _In vitro_ studies focus on specific mechanisms whereas _in vivo_ studies examine morphological and physiological responses of whole organisms after chronic or acute exposures.

Although animal toxicological studies provide essential information on the basic mechanisms of the health effects of sulfur oxides and particulate matter, they are, of course, limited to subjects other than humans. Controlled

human studies, discussed in Chapter 13, provide an important perspective on the health effects of these pollutants by exposing humans under controlled laboratory conditions. It has thus been possible to evaluate respiratory and other responses of humans to a number of specific forms of sulfur oxides and particulate matter. Human studies are limited, however, to relatively short-term exposure regimens. For information on long-term exposures, epidemiological studies must be used.

Chapter 14 evaluates evidence relating certain health indices in selected populations exposed to ambient conditions. In contrast to controlled experiments discussed in the two previous chapters, epidemiological studies do not examine variables under the control of the investigator. That is, they must deal with variations in pollution as they occur in the real world. Evaluation of such studies is complicated by differences in study design and conduct, selection of variables, assessment of pollution exposure, assessment of health status, and suitability of statistical techniques. Such studies necessarily include possible confounding variables, but have the advantage of direct relevance to other human exposures.

The progression from in vitro and in vivo animal studies to human laboratory studies to epidemiological studies reflects the trade-offs that must be made in any analysis of the health effects of environmental pollutants. The more specific the conditions of exposure and experimental manipulation, the less general are the results thus obtained; and the more general the conditions of study, the less precise are the findings that result. Taken as a whole, however, these various types of studies provide a basis for formulating conclusions regarding the health effects of sulfur oxides and particulate matter.

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Terms and Symbols Used in Respiratory Physiology

A. General

P	Pressures in general
$\bar{X}$	Dash above any symbol indicates a mean value
$\dot{X}$	Dot above any symbol indicates a time derivative
$\ddot{X}$	Two dots above any symbol indicate the second time derivative
%X	Percent sign preceding a symbol indicates percentage of the predicted normal value
X/Y%	Percent sign after a symbol indicates a ratio function with the ratio function with the ratio expressed as a percentage. Both components of the ratio must be designated; e.g., $FEV_1/FEV\% = 100 \times FEV_1/FVC$
f	Frequency of any event in time, e.g., respiratory frequency: the number of breathing cycles per unit of time
t	Time
anat	Anatomical
max	Maximum

B. Gas Phase Symbols

1. Primary

V	Gas volume in general. Pressure, temperature, and percent saturation with water vapor must be stated
F	Fractional concentration in dry gas phase

2. Qualifying

I	Inspired
E	Expired
A	Alveolar
T	Tidal
D	Dead Space
B	Barometric
STPD	Standard temperature and pressure, dry. These are the conditions of a volume of gas at 0°C, at 760 torr, without water vapor
BTPS	Body temperature (37°C), barometric pressure (at sea level = 760 torr), and saturated with water vapor
ATPD	Ambient temperature, pressure, dry
ATPS	Ambient temperature and pressure, saturated with water vapor
L	Lung

C. Blood Phase Symbols

1. Primary

Q	Volume flow of blood
C	Concentration in blood phase
S	Saturation in blood phase

2. Qualifying

b   Blood in general
a   Arterial. Exact location to be specified in text when term is used
v   Venous. Exact location to be specified in text when term is used
v̄   Mixed venous
c   Capillary. Exact location to be specified in text when term is used
c'   Pulmonary end-capillary

D. Pulmonary Function

1. Lung volumes (expressed as BTPS)

RV   Residual volume: volume of air remaining in the lungs after
                     maximum exhalation
ERV   Expiratory reserve volume: maximum volume of air that can
                     be exhaled from the end-tidal volume
V_T Tidal Volume: volume of gas that is inspired or expired
                     during one ventilatory cycle
IRV   Inspiratory reserve volume: maximum volume that can be inspired
                     from an end-tidal inspiratory level
VL   Volume of the lung, including the conducting airways. Conditions
                     of measurement must be stated
IC   Inspiratory capacity: volume that can be inspired from the end-tidal
                     expiratory volume
IVC   Inspiratory vital capacity: maximum volume measured on inspiration
                     after a full expiration
VC   Vital capacity: volume measured on complete expiration after the
                     deepest inspiration, but without respect to the effort involved
FRC   Functional residual capacity: volume of gas remaining in the lungs
                     and airways at the end of a resting tidal expiration
TLC   Total lung capacity: volume of gas in the lung and airways after
                     as much gas as possible has been inhaled
RV/TLC%   Residual volume to total lung capacity ratio, expressed as a percent
V_C Physiological dead space: calculated volume (BPTS), which accounts
                     for the difference between the presures of CO_2 in expired gas and
                     arterial blood. Physiological dead space reflects the combination
                     of anatomical dead space and alveolar dead space, the volume of the
                     latter increasing with the importance of the nonuniformity of the
                     ventilation/perfusion ratio in the lung
VD_{anat} Volume of the anatomic dead space (BTPS)
VD_A The alveolar dead-space volume (BTPS)

2. Forced respiratory maneuvers (expressed as BTPS)
FVC   Forced vital capacity: The volume of gas expired after full
                     inspiration, and with expiration performed as rapidly and
                     completely as possible
FIVC   Forced inspiratory vital capacity: maximal volume of air inspired
                     after a maximum expiration, and with inspiration performed as rapidly
                     and completely as possible
FEV_t Denotes the volume of gas that is exhaled in a given time interval
                     during the execution of a forced vital capacity
$FEV_t/FVC\%$ Ratio of timed forced expiratory volume to forced vital capacity,
                     expressed as a percentage

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PEF	Peak expiratory flow (liters/min or liters/sec)
$\dot{V}max_{xx\%}$	Maximum expiratory flow (instantaneous) qualified by the volume at which measured, expressed as percent of the FVC that has been exhaled. (Example: $\dot{V}max_{75\%}$ is the maximum expiratory flow after 75% of the FVC has been exhaled and 25% remains to be exhaled)
$\dot{V}max_{xx\%TLC}$	Maximum expiratory flow (instantaneous) qualified by the volume at which measured, expressed as percent of the TLC that remains in the lung. (Example: $\dot{V}max_{40\%TLC}$ is the maximum expiratory flow when 40 percent of the TLC remains in the lung)
FEF_{x-y}	Forced expiratory flow between two designated volume points in the FVC. These points may be designated as absolute volumes starting from the full inspiratory point or by designating the percent of FVC exhaled
$FEF_{.2-1.2L}$	Forced expiratory flow between 200 ml and 1,200 ml of the FVC; formerly called maximum expiratory flow
$FEF_{25\%-75\%}$	Forced expiratory flow during the middle half of the FVC; formerly called maximum midexpiratory flow
MVV	Maximum voluntary ventilation: maximum volume of air that can be breathed per min by a subject breathing quickly and as deeply as possible. The time of measurement of this tiring lung function test is usually between 12 and 30 sec, but the test result is given in liters (BTPS)/min
FET_x	Forced expiratory time required to exhale a specifed FVC, e.g., $FET_{95\%}$ is the time required to deliver the first 95% of the FVC; $FET_{25\%-75\%}$ is the time required to deliver the middle half of the FVC
MIF_x	Maximum inspiratory flow (instantaneous). As in the case of the FET, appropriate modifiers designate the volume at which flow is being measured. Unless otherwise specified, the volume qualifiers indicate the volume inspired from RV at the point of measurement

3. Measurements of ventilation

$\dot{V}E$	Expired volume per min (BTPS)
$\dot{V}I$	Inspired volume per min (BTPS)
$\dot{V}co_2$	Carbon dioxide production per min (STPD)
$\dot{V}o_2$	Oxygen consumption per min (STPD)
R	Respiratory exchange ratio in general. Quotient of the volume of CO_2 produced divided by the volume of O_2 consumed
$\dot{V}A$	Alveolar ventilation: physiological process by which alveolar gas is completely removed and replaced with fresh gas. The volume of alveolar gas actually expelled completely is equal to the tidal volume minus the volume of the dead space
$\dot{V}D$	Ventilation per min of the physiologic dead space, BTPS
$\dot{V}D_{anat}$	Ventilation per min of the anatomic dead space, that portion of the conducting airway in which no significant gas exchange occurs (BTPS)
$\dot{V}D_A$	Ventilation of the alveolar dead space (BTPS), defined by the equation $\dot{V}D_A = \dot{V}D - \dot{V}D_{anat}$

4. Mechanics of breathing (all pressures are expressed relative to ambient pressure unless otherwise specified)

(a) Pressure terms

Paw	Pressure at any point along the airways
Pao	Pressure at the airway opening, i.e., mouth, nose, tracheal cannula

Ppl	Pleural pressure: the pressure between the visceral and parietal pleura relative to atmospheric pressure, in cm H_2O
Palv	Alveolar pressure
PL	Transpulmonary pressure: transpulmonary pressure, PL = Palv - Ppl, measurement conditions to be defined
PstL	Static recoil pressure of the lung; transpulmonary pressure measured under static conditions
Pbs	Pressure at the body surface
Pes	Esophageal pressure used to estimate Ppl
Pw	Transthoracic pressure: pressure difference between parietal pleural surface and body surface. Transthoracic in the sense used means "across the wall." Pw + Ppl - Pbs
Ptm	Transmural pressure pertaining to an airway or blood vessel
Prs	Transrespiratory pressure: pressure across the respiratory system. Prs + Palv - Pbs = PL + Pw

(b) Flow-pressure relationships

R	Flow resistance: the ratio of the flow-resistive components of pressure to simultaneous flow in cm H_2O/liter per sec
Raw	Airway resistance calculated from pressure difference between airway opening (Pao) and alveoli (Palv) divided by the airflow, cm H_2O/liter/sec
RL	Total pulmonary resistance includes the frictional resistance of the lungs and air passages. It equals the sum of airway resistance and lung tissue resistance. It is measured by relating flow-dependent transpulmonary pressure to airflow at the mouth
Rrs	Total respiratory resistance includes the sum of airway resistance, lung tissue resistance, and chest wall resistance. It is measured by relating flow dependent transrespiratory pressure to airflow at the mouth.
Rus	Resistance of the airways on the upstream (alveolar) side of the point in the airways where intraluminal pressure equals Ppl (equal pressure point), measured during maximum expiratory flow
Rds	Resistance of the airways on the downstream (mouth) side of the point in the airways where intraluminal pressure equals Ppl, measured during maximum expiratory flow
Gaw	Airway conductance, reciprocal of Raw
Gaw/VL	Specific conductance expressed per liter of lung volume at which Gaw is measured

(c) Volume-pressure relationships

C	Compliance: the slope of a static volume-pressure curve at a point, or the linear approximation of a nearly straight portion of such a curve expressed in liter/cm H_2O or ml/cm H_2O
Cdyn	Dynamic compliance: the ratio of the tidal volume to the tidal volume to the change in intrapleural pressure between the points of zero flow at the extremes of tidal volume in liter/cm H_2O or ml/cm H_2O
Cst	Static compliance, value for compliance determined on the basis of measurements made during periods of cessation of airflow

C/VL	Specific compliance: compliance divided by the lung volume at which it is determined, usually FRC
E	Elastance: the reciprocal of compliance; expressed in cm H_2O/liter or cm H_2/ml
Pst	Static components of pressure
W	Work of breathing: the energy required for breathing movements

5. Diffusing Capacity

DL	Diffusing capacity of the lung: Amount of gas (O_2, CO, CO_2) commonly expressed as ml gas (STPD) diffusing between alveolar gas and pulmonary capillary blood per torr mean gas pressure difference per min. Total resistance to diffusion for oxygen $\frac{1}{DL_{O_2}}$ and CO $\frac{1}{DL_{CO}}$ includes resistance to diffusion of the the gas across the alveolar-capillary membrane, through plasma in the capillary, and across the red cell membrane (1/DM), and the resistance to diffusion within the red cell arising from the chemical reaction between the gas and hemoglobin, ($1/\theta V_c$), according to the formulation $\frac{1}{DL} = \frac{1}{DM} + \frac{1}{\theta Vc}$
DM	The diffusing capacity of the pulmonary membrane
θ	The rate of gas uptake by 1 ml of normal whole blood per min for a partial pressure of 1 torr
Vc	Average volume of blood in the capillary bed in milliliters
DL/VA	Diffusion per unit of alveolar volume. DL is expressed STPD, and VA is expressed in liters (BTPS)

6. Respiratory Gases

Pa_x	Arterial tension of gas x, torr (mm Hg)
PA_x	Alveolar tension of gas x, torr (mm Hg)
Sa_{O2}	Arterial oxygen saturation (percent)
C	Concentration: for example, Ca_{CO_2} is the concentration of oxygen in a blood sample, including both oxygen combined with hemoglobin and physically dissolved oxygen, ordinarily expressed at ml O_2 (STPD)/100 ml blood, or mmole O_2/liter
PA-Pa	Alveolar-arterial gas pressure difference: the difference in partial pressure of a gas (e.g., O_2 or N_2) in the alveolar gas spaces and that in the systemic arterial blood, measured in torr. For oxygen, as an example, $PA_{O2} - Pa_{O2}$ Also symbolixed AaD_{O2}
Ca-Cv	Arterial-venous concentration difference. For oxygen, as an example, $Ca_{O2} - Cv_{O2}$

7. Pulmonary shunts

Q̇s   Shunt: vascular connection between circulatory pathways so that venous blood is diverted into vessels containing arterialized blood (right-to-left shunt, venous admixture) or vice versa (left-to-right shunt). Right-to-left shunt within the lung, heart, or large vessels due to malformations are more important in respiratory physiology. Flow from left to right through a shunt should be marked with a negative sign.

E. Pulmonary Dysfunction

1. Altered breathing

dysanea   An unpleasant subjective feeling of difficult or labored breathing

hyperventilation   An alveolar ventilation that is excessive relative to the simultaneous metabolic rate. As a result the alveolar P_{CO_2} is significantly reduced below the normal for the altitude

hypoventhetion   An alveolar ventilation that is small relative to the simultaneous metabolic rate so that alveolar P_{CO_2} rises significantly above the normal for the altitude

2. Altered blood gases

hypoxia   Any state in which the oxygen in the lung, blood, and/or tissues is abnormally low compared with that of normal resting person breathing air at sea level

hypoxernia   A state in which the oxygen pressure and/or concentration in arterial blood is lower than its normal value at sea level. Normal oxygen pressures at seal level are 85-100 torr in arterial blood. In adult humans the normal oxygen concentration is 17-23 ml O_2/100 ml arterial blood

hypocapnie   Any state in which the systemic arterial carbon dioxide pressure is significantly below 40 torr, as in hyperventilation

hyparcapnia   Any state in which the systemic arterial carbon dioxide pressure is significantly above 40 torr. May occur when alveolar ventilation is inadequate for a given metabolic rate (hypoventilation) or during CO_2 inhalation

3. Altered acid-base balance

acidemia   Any state of systemic arterial plasma in which the pH is significantly less than the normal value, 7.41 ± 0.02 in adult man at rest

alkelemia   Any state of systemic arterial plasma in which the pH is significantly greater than the normal value, 7.41 ± 0.02 in adult man at rest

base excess (BE)   Base excess: A measure of metabolic alkalosis or metabolic acidosis (negative values of base excess) expressed as the rnEq of strong acid or strong alkali required to titrate a sample of 1 liter of blood to a pH of 7.40. The titration is made with the blood sample kept at 37°C, oxygenated, and equilibrated to P_{CO_2} of 40 torr

acidosis	The result of any process that by itself adds excess CO_2 (respiratory acidosis) or nonvolatile acids (metabolic acidosis) to arterial blood. Acidemia does not necessarily result, because compensating mechanisms (increase of HCO_3 in respiratory acidosis, increase of ventilation and consequently decrease of arterial CO_2 in metabolic acidosis) may intervene to restore plasma pH to normal
alkelosis	The result of any process that, by itself, diminishes acids (respiratory alkalosis) or increases bases (metabolic alkalosis) in arterial blood. Alkalemia does not necessarily result, because compensating mechanisms may intervene to restore plasma pH to normal

4. Other

pulmonary insufficiency	Altered function of the lung, which produces clinical symptoms that usually include dyspnea
acute respiratory failure	Rapidly occurring hypoxemia, hypercabia, or both caused by a disorder of the respiratory system. The duration of the illness and the values of arterial oxygen tension and arterial carbon dioxide tension used as criteria for this term should be given. The term acute ventilatory failure should be used only when the arterial carbon dioxide tension is increased. The term pulmonary failure has been used to indicate respiratory failure specifically caused by disorders of the lung
chronic respiratory failure	Chronic hypoxemia or hypercapnia caused by a disorder of the respiratory system. The duration of the condition and the values of arterial oxygen tension and arterial carbon dioxide tension used as criteria for this term should be given
obstructive ventilatory defect	Slowing of air flow during forced ventilatory maneuvers
restrictive ventilatory defect	Reduction of vital capacity not explainable by airflow obstruction
impairment	A measurable degree of anatomic or functional abnormality that may or may not have clinical significance. Permanent impairment is that which persists for some period of time, e.g., one year after maximum medical rehabilitation has been achieved
disability	A legally or administratively determined state in which a patient's ability to engage in a specific activity under certain circumstances is reduced or absent because of physical or mental impairment. Other factors, such as age, education, and customary way of making a livelihood, are considered in evaluating disability. Permanent disability exists when no substantial improvement of the patient's ability to engage in the specific activity can be expected

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Mr. John Acquavella
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Roy E. Albert
Institute of Environmental Medicine
New York University Medical Center
New York, New York 10016

Dr. Martin Alexander
Department of Agronomy
Cornell University
Ithaca, New York 14850

Dr. A. P. Altshuller
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. David S. Anthony
Department of Botany
University of Florida
Gainesville, Florida 32611

Mr. John D. Bachmann
Strategies and Air Standards Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Allen C. Basala
Strategies and Air Standards Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Neil Berg
Monitoring and Data Analysis Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Michael A. Berry
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Francis M. Black
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Joseph Blair
Environmental Division
U. S. Department of Energy
Washington, D.C.   20545

Dr. Edward Bobalek
Industrial Environmental Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Ms. F. Vandiver P. Bradow
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Ronald L. Bradow
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Robert Bruce
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Angelo Capparella
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Robert Chapman
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Robert J. Charlson
Department of Environmental Medicine
University of Washington
Seattle, Washington 98195

Dr. Peter Coffey
New York State Department of Environmental Conservation
Division of Air Resources
Albany, New York 12233

Mr. Chatten Cowherd
Midwest Research Institute
425 Volker Boulevard
Kansas City, Missouri 64110

Dr. Ellis B. Cowling
School of Forest Resources
North Carolina State University
Raleigh, North Carolina 27650

Mr. William M. Cox
Monitoring and Data Analysis Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. T. Timothy Crocker
Department of Community and Environmental Medicine
Irvine, California 92664

Mr. Stanley T. Cuffe
Emission Standards and Engineering Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Thomas C. Curran
Monitoring and Data Analysis Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Michael Davis
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Gerrold A. Demarrais
National Oceanic and Atmospheric Administration
U. S. Department Of Commerce

Dr. Jerrold L. Dodd
Natural Resources Ecology Laboratory
Colorado State University
Fort Collins, Colorado 80523

Dr. Thomas G. Dzubay
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Thomas G. Ellestad
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. John Evans
School of Public Health
Harvard University
Boston, Massachusetts 02115

Dr. Lance Evans
Department of Energy and Environment
Brookhaven National Laboratory
Upton, New York 11973

Mr. Douglas Fennell
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Benjamin G. Ferris, Jr.
School of Public Health
Harvard University
Boston, Massachusetts 02115

Mr. Patrick Festa
New York Department of Environmental Conservation
Division of Fish and Wildlife
Albany, New York 12233

Mr. Terrence Fitz-Simmons
Environmental Monitoring Systems Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Christopher R. Fortune
Northrop Services, Inc.-Environmental Sciences
P. O. Box 12313
Research Triangle Park, Nortn Carolina 27709

Dr. Robert Frank
Department of Environmental Health
University of Washington
Seattle, Washington 98195

Dr. Warren Galke
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Phil Galvin
New York Department of Environmental Conservation
Division of Air Resources
Albany, New York 12233

Dr. Donald Gardner
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. J.H.B. Garner
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Donald Gillette
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Judy Graham
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Lester D. Grant
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Armin Gropp
Department of Chemistry
University of Miami
Miami, Florida 33124

Dr. Jack Hackney
Rancho Los Amigos Hospital
Downey, California 90242

Mr. Bertil Hagerhall
Ministry of Agriculture
Fack
S-163 20 Stockholm
Sweden

Dr. Douglas Hammer
2910 Wycliff Road
Raleigh, North Carolina 27607

Mr. R. P. Hangebrauck
Industrial Environmental Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Thomas A. Hartlage
Environmental Monitoring Systems Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Victor Hasselblad
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Thomas R. Hauser
Environmental Monitoring Systems Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Carl Hayes
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Fred H. Haynie
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Walter Heck
Department of Botany
North Carolina State University
Raleigh, North Carolina 27650

Dr. Howard Heggestad
USDA-SAE
The Plant Stress Laboratory
Plant Physiology Institute
Beltsville, Maryland 20705

Dr. George R. Hendrey
Department of Energy and Environment
Brookhaven National Laboratory
Upton, New York 11973

Dr. Ian Higgins
Department of Epidemiology
School of Public Health
University of Michigan
Ann Arbor, Michigan 48109

Mrs. Patricia Hodgson
Editorial Associates
Chapel Hill, North Carolina 27514

Mr. George C. Holzworth
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Robert Horton
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Steven M. Horvath
Institute of Environmental Stress
University of California
Santa Barbara, California 93106

Dr. F. Gordon Hueter
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Janja Husar
CAPITA
Washington University
St. Louis, Missouri 63130

Dr. Rudolf Husar
Department of Mechanical Engineering
Washington University
St. Louis, Missouri 63130

Dr. William T. Ingram
Consulting Engineer
7 North Drive
Whitestone, New York 11357

Dr. Patricia M. Irving
Argonne National Laboratory
9700 South Cass Avenue
Argonne, Illinois 60439

Dr. Jay Jacobson
Boyce Thompson Institute
Cornell University
Ithaca, New York 14850

Mr. James Kawecki
Biospherics, Inc.
4928 Wyaconda Road
Rockville, Maryland 20852

Dr. Sagar V. Krupa
Department of Plant Pathology
University of Minnesota
St. Paul, Minnesota 55108

Dr. Edmund J. LaVoie
Section of Metabolic Biochemistry
American Health Foundation
Dana Road
Valhalla, New York 10592

Dr. Michael D. Lebowitz
Arizona Health Sciences Center
1501 North Campbell
Tucson, Arizona 85724

Dr. Robert E. Lee
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Allan H. Legge
Environmental Science Center
University of Calgary
Calgary, Alberta, Canada T2N 1N4

Ms. Peggy Le Sueur
Atmospheric Environment Service
Downsview, Ontario, Canada M3H5T4

Dr. Morton Lippmann
Institute of Environmental Medicine
New York University
New York, New York 10016

Dr. James P. Lodge
385 Broadway
Boulder, Colorado 80903

Dr. Gory J. Love
Institute of Environmental Studies
University of North Carolina
Chapel Hill, North Carolina 27514

Dr. David T. Mage
Environmental Monitoring Systems Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Delbert McCune
Boyce Thompson Institute
Cornell University
Ithaca, New York 14850

Mr. Frank F. McElroy
Environmental Monitoring Systems Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. David J. McKee
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Thomas McMullen
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Daniel B. Menzel
Department of Pharmacology
Duke University Medical Center
Durham, North Carolina 27710

Dr. Edwin L. Meyer
Monitoring and Data Analysis Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr Fred Miller
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. John O. Milliken
Industrial Environmental Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Jarvis Moyers
Department of Chemistry
University of Arizona
Tucson, Arizona 85721

Dr. Thaddeus J. Murawski
New York State Department of Health
Empire State Plaza
Albany New York 12337

Dr. David S. Natusch
Department of Chemistry
Colorado State University
Fort Collins, Colorado 80523

Dr. Stephen A. Nielsen
Environmental Affairs
Joyce Environmental Consultants
414 Live Oak Boulevard
Casselberry, Florida 32707

Dr. Kenneth Noll
Department of Environmental Engineering
Illinois Institute of Technology
Chicago, Illinois 60616

Mr. John R. O'Connor
Strategies and Air Standards Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Thompson G. Pace
Monitoring and Data Analysis Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Jean Parker
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Nancy Pate
Strategies and Air Standards Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Thomas W. Peterson
Department of Chemical Engineering
University of Arizona
Tucson, Arizona 85721

Mr. Martin Pfeiffer
New York State Department of Environmental Conservation
Bureau of Fisheries
Raybrook, New York 12977

Dr. Marlene Phillips
Atmospheric Chemistry Division
Environment Canada
Downsview, Ontario, Canada M3H5T4

Dr. Charles Powers
Environmental Research Laboratory
U.S. Environmental Protection Agency
Corvallis, Oregon 97330

Mr. Larry J. Purdue
Environmental Monitoring Systems Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. John C. Puzak
Environmental Monitoring Systems Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Otto Raabe
Radiobiology Laboratory
University of California
Davis, California 95616

Mr. Danny Rambo
Environmental Research Laboratory
U.S. Environmental Protection Agency
Corvallis, Oregon 97330

Mr. Kenneth A. Rehme
Environmental Monitoring Systems Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Elmer Robinson
Department of Chemical Engineering
Washington State University
Pullman, Washington 99163

Mr. Charles E. Rodes
Environmental Monitoring Systems Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Douglas R. Roeck
GCA Corporation
Technology Division
Burlington Road
Bedford, Massachusetts 01730

Mr. J. C. Romanovsky
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. August Rossano
University of Washington
Seattle, Washington 98195

Mr. Joseph D. Sableski
Control Programs Development Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Dallas Safriet
Monitoring and Data Analysis Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Victor S. Salvin
University of North Carolina at Greensboro
Greensboro, North Carolina 27408

Dr. Shahbeg Sandhu
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. Joseph P. Santodonato
Life and Material Sciences Division
Syracuse Research Corporation
Merrill Lane
Syracuse, New York 13210

Dr. Herbert Schimmel
Neurology Department
Albert Einstein Medical College
26 Usonia Road
Pleasantville, New York 10570

Dr. Carl L. Schofield
Department of Natural Resources
Cornell University
Ithaca, New York 14850

Dr. David Shriner
Environmental Sciences Division
Oak Ridge National Laboratory

Ms. Donna Sivulka
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. John M. Skelly
Department of Plant Pathology and Physiology
Virginia Polytechnic Institute
Blacksburg, Virginia 24061

Mr. Scott Smith
Biospherics, Inc.
4928 Wyaconda Road
Rockviell, Maryland 20852

Ms. Elaine Smolko
Department of Pharmacology
Duke University Medical Center
Durham, North Carolina

Dr. Frank Speizer
School of Public Health
Harvard University
Boston, Massachusetts 02115

Dr. John D. Spengler
School of Public Health
Harvard University
Boston, Massachusetts 02115

Mr. Robert K. Stevens
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. George E. Taylor, Jr.
Environmental Sciences Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830

Dr. Larry Thibodeau
School of Public Health
Harvard University
Boston, Massachusetts 02115

Dr. W. Gene Tucker
Industrial Environmental Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. D. Bruce Turner
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. James B. Upham
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. Robert Waller
Toxicology Unit
St. Bartholomew's Hospital
London, England

Mr. Stanley Wallin
Warren Spring Laboratory
Department of Industry
Stevenage, Hertfordshire SGI 2BX
England

Dr. Joseph F. Walling
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. James Ware
School of Public Health
Harvard University
Boston, Massachusetts 02115

Dr. David Weber
Office of Air, Land, and Water Use
U.S. Environmental Protection Agency
Washington, D. C. 20460

Dr. Jean Weister
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Mr. R. Murray Wells
Radian Corporation
8500 Shaol Creek Boulevard
Austin, Texas 78766

Dr. Kenneth T. Whitby
Mechanical Engineering Department
University of Minnesota
Minneapolis, Minnesota 55455

Dr. Warren White
CAPITA
Washington, University
St. Louis, Missouri 63130

Dr. Raymond Wilhour
Environmental Research Laboratory
U.S. Environmental Protection Agency
Corvallis, Oregon 97330

Dr. William E. Wilson
Environmental Sciences Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Dr. John W. Winchester
Department of Oceanography
Florida State University
Tallahassee, Florida 32306

11. RESPIRATORY DEPOSITION AND BIOLOGICAL FATE OF INHALED AEROSOLS AND SO_2*

11.1 INTRODUCTION

11.1.1 General Considerations

The respiratory airways system is the major route for exposure of people to airborne particles (aerosols) and SO_2 gas. During inhalation (and exhalation) a portion of the inhaled aerosol and gas may be deposited by contact with airway surfaces or be transferred to unexhaled air. The remainder is exhaled. The portion transferred to unexhaled air may be either deposited by contact with airway surfaces or later exhaled. These phenomena are complicated by interactions that may occur between the particles, the SO_2 gas, other gases such as biologically endogenous ammonia, and the water vapor present in the airways.

In inhalation toxicology, specific terminology is applied to these processes. The term _deposition_ refers specifically to the removal of inhaled particles or gas by the respiratory tract and to the initial regional pattern of these deposited materials. The term _clearance_ refers to the subsequent translocation (movement of material in the lung to other organs), transformation, and removal of deposited particles from the respiratory tract or from the body. It can also refer to the removal of reaction products formed from SO_2. The temporal distribution of uncleared deposited particulate materials or gas and reaction products is called _retention_. At the end of a brief aerosol or gas exposure,

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these three concepts may be described by the relationship:

RETENTION (t) = DEPOSITION - CLEARANCE (t)   (1)

where (t) refers to a function of time after deposition occurs (Raabe, 1979).

The mechanisms involved in the deposition of inhaled aerosols and gases are affected by physical and chemical properties, including aerosol particle size distribution, density, shape, surface area, electrostatic charge, hygroscopicity or deliquescence, chemical composition, gas diffusivity, and related reactions. The geometry of the respiratory airways from nose and mouth to the lung parenchyma also influences aerosol deposition; the important morphometric parameters include the diameters, lengths, and branching angles of airway segments. Physiological factors that affect deposition include breathing patterns, air flow dynamics in the respiratory tract, and variations of relative humidity and temperature within the airways. With this information, theoretical models of regional deposition have been developed to predict the fate of inhaled aerosols of various types. Carefully collected data from experiments with human volunteers provide a basis for testing these theoretical predictions.

The current state of knowledge concerning the quantification of the deposition of inhaled aerosols for both man and experimental animals is fairly well established. Important questions to be resolved concern the deposition of inhaled SO_2, especially with respect to gas-particle interaction and the extent of synergism between SO_2 and particulate materials with respect to deposition and toxicological effects. However, the fundamental factors associated with these processes have been recognized for over 20 years in that the deposition in the deep lung during inhalation and, concomitantly, the potential for biological response to SO_2 may be enhanced by the presence in

the atmosphere of certain aerosols emitted from both natural and man-made sources. Therefore one should consider the deposition, clearance, translocation, and biological response of inhaled SO_2 in conjunction with the aerosols that are present in some in the environment.

Clearance from the respiratory tract depends on many factors, including site of deposition, chemical composition and properties of the deposited particles, SO_2 reaction products, mucociliary transport in the tracheobronchial tree, macrophage phagocytosis in the deep lung, and pulmonary lymph and blood flow.

Translocation of sulfur compounds or other materials from the lung to other organs is important, since the lung can be the portal of entry for toxic agents that have effects on other organs of the body. Hence, multicompartment models of clearance from the respiratory tract to other organs can provide predictive information about the potential for injury of those other organs. Mathematical representations of lung retention and translocation require data on the various factors that affect deposition and clearance.

Since many conclusions concerning the deposition, clearance, and health impact of inhaled aerosols and SO_2 are based upon data obtained from animal experiments, care must be taken to identify differences in physiological and anatomical factors between human beings and animals that may influence these phenomena. In particular, air pollution experiments that use small rodents must be interpreted with respect to important differences between human and rodent airways, breathing patterns, flow dynamics, regional deposition, and subsequent clearance. Emphasis in the following discussion will be on the deposition and clearance that occur in the human airways, but selected comparisons are made with other mammalian species to clarify differences that may affect health impact analyses of experimental data.

11.1.2 Aerosol and SO_2 Characteristics

An aerosol may be defined as a relatively stable suspension of small liquid or solid particles in a gaseous medium. Airborne particulate materials in the environment are aerosols. Aerosols containing potentially toxic components consist of particles with a variety of physical and chemical properties. In particular, a given aerosol may include particles with a wide spectrum of physical sizes, even if all the particles have similar chemical composition. Another important property, physical density, may vary with particle size and particle type (Raabe et al., 1975). Also, the concentration of of toxic components in particles may be different for different sized particles (Natusch et al., 1974). Morphologically identical particles may have totally different chemical compositions (Pawley and Fisher, 1977). Common assumptions that particles in a given aerosol have a relatively homogeneous chemical composition, toxic potential, and physical density should not be expected to describe adequately general aerosol behavior in the atmosphere and may be seriously misleading concerning specific aerosol toxicity, especially when particles are found in combination with SO_2 gas.

It is essential for evaluation of the possible health effects associated with their inhalation that the physical and chemical properties of aerosols and gases be appropriately characterized. These properties then can provide predictive information concerning deposition and other important dosimetric factors that need to be considered if biological responses are to be fully understood.

If particles in an aerosol are smooth and spherical or nearly spherical, their physical sizes can be conveniently described in terms of their respective geometric diameters. Aerosols of solids rarely contain smooth, spherical

particles, however; various conventions for describing physical diameters have been based upon available methods of observing and measuring particle size. For example, the size of a particle may be described in terms of its projected area diameter (D_p), defined as the diameter of a circle with an area equal to the apparent cross-sectional area of the particle when lying on a collection surface and viewed with an optical or electron microscope. Other conventions for describing physical size are based on measurements of scattered light, surface area, electrical mobility, diffusional mobility, or other physical or chemical phenomena (see Mercer, 1973; Stockham and Fochtman, 1979).

Aerodynamic properties of aerosol particles depend upon a variety of physical properties, including the size and shape of the particles and their physical densities. Two important aerodynamic properties of aerosol particles are the inertial properties, which are most important for particles larger than 0.5 μm in diameter (related to the settling speed in air under the influence of the earth's gravity) and the diffusional properties, which are most important for particles smaller than 0.5 μm in diameter (related to the diffusion coefficient) (Fuchs, 1964) (see Section 11.2.1). When particles are inhaled, their aerodynamic properties, combined with various aspects of respiratory mechanics, determine their fractional deposition and the deposition location in the respiratory tract (Phalen and Raabe, 1974; Morrow, 1964a, 1974; Lippmann et al., 1971; Hamilton and Walton, 1961).

In order to avoid the complications associated with the effects of particle shape, size, and physical density upon the inertial properties of inhaled airborne particles, "aerodynamic diameters" have been defined and used to describe particles with common inertial properties with the same "aerodynamic diameter." The aerodynamic diameter most generally used is the aerodynamic

equivalent diameter (D_{ae}), defined by Hatch and Gross (1964) as "the diameter of a unit density sphere having the same settling speed (under gravity) as the particle in question of whatever shape and density." Raabe (1976) has recommended the use of an aerodynamic resistance diameter (D_{ar}), defined more directly with terms used in physics to describe the inertial properties of a particle. The relationship between these two aerodynamic diameters is given by:

$$D_{ar} = \frac{D\sqrt{[\rho C(D)]}}{\sqrt{[\rho^*]}} = D_{ae} C(D_{ae}) \tag{2}$$

with D_{ae} the aerodynamic (equivalent unit density sphere) diameter and $C(D_{ae})$, the (Cunningham) slip correction associated with a unit density ($\rho^*=1$ g/cm^3) sphere of diameter D_{ae}. The slip correction, $C(D)$, a function of physical size D, is a semiempirical factor that corrects the Stokes' Law of viscous resistance for the effect of "slip" between the air molecules when the aerosol particles are almost as small as or smaller than the mean free path of air molecules. Both of these aerodynamic diameters have been widely used in the inhalation toxicology literature. It is probably not crucial to the general properties of inhaled particles to differentiate between or be unduly concerned with these two definitions, since their difference is only 0.08 μm or less over all sizes under normal conditions at sea level. Hence, the term aerodynamic diameter can be used to refer to either or both of these two definitions. Particle characteristics described in terms of physical diameter can also be described in terms of aerodynamic diameter.

Since not all particles in an aerosol are of the same physical or aerodynamic size, the distribution of sizes must be described. If either the

physical diameter (D) or the projected aerodynamic diameter is used to characterize particles, the distribution of particle sizes in a mixed aerosol is most conveniently described as a probability density function f(D) [f(D_{ar}) or f(D_{ae})], with

$$\int_{o}^{\infty} f(D)dD = 1 \qquad (3)$$

One such generally useful function, the log-normal function, involves two parameters, the geometric mean size (or median) and the geometric standard deviation (σ_g). Environmental aerosols have size distributions that are more complicated, reflecting the production of particles in atmospheric processes, emission sources or other anthropogenic activities, and the particle dynamics. They may have several modes (Whitby, 1978). Photochemically generated aerosols create small nucleated particles that are generally smaller than 0.1 µm (the nuclei mode) while combustion and other particle generation processes usually yield relatively coarse particles larger than 2 µm. Another mode usually exists between 0.1 µm and 2 µm because of the great stability of particles in this range (see Chapters 3 and 5).

Since aerosols rarely consist of particles of a single size, they must be described in terms of parameters of size distribution functions. It has become customary in the absence of detailed data and for the sake of generalization to describe aerosols in terms of their geometric mean or median diameter and the geometric standard deviation (σ_g) of the size distribution. Hence, if the particle number is being considered, the particle size may be reported as the count median (physical) diameter (CMD) and σ_g, or the count median aerodynamic diameter (CMAD) and σ_g if aerodynamic sizes have been measured. Numerically, half the particles in an aerosol have physical sizes

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less than the CMD and half are larger. Likewise, half the particles have aerodynamic diameters smaller than the CMAD and half have larger aerodynamic diameters. Since the mass of a material is usually more relevant to its potential toxicity, the mass median (physical) diameter (MMD) or mass median aerodynamic diameter (MMAD) and σ_g is usually preferred in describing aerosols in inhalation toxicology research. Half the mass of particles in an aerosol is associated with particles smaller than the MMD and half with larger particles. Likewise, half the mass of particles is associated with particles whose aerodynamic diameters are smaller than the MMAD and half with particles having larger aerodynamic diameters. If an aerosol is radioactive or radiolabeled, mass measurements may be replaced by activity measurements yielding the activity median diameter (AMD) or activity median aerodynamic diameter (AMAD). Inter-relationships among these various ways to express the diameter of the aerosol have been examined for the log normal distribution by Raabe (1971).

In addition to particle characteristics, conditions of the gas medium influence the properties of aerosol dispersions. Such environmental conditions as relative humidity, temperature, barometric pressure, and fluid flow conditions (e.g., wind velocity or state of turbulence) affect the aerodynamics of aerosol particles. Another property that affects particle behavior is electrostatic charge. Environmental aerosols normally have some electrostatic charge distribution.

The concentration of environmental aerosols or gases affects inhalation deposition and particle dynamics. The number of particles per unit volume of gas ($\#/cm^3$) provides information indicative of the coagulation rate for an aerosol. The mass concentration (mg/m^3 or $\mu g/m^3$) or concentration of a specific potentially toxic species (mg of constituent/m^3) provides information

needed to calculate inhalation exposure levels. For SO_2, the concentration
may be expressed in parts per million (ppm) or in mass concentrations (mg/m^3);
each 1 ppm of SO_2 equals 2.62 mg/m^3 (2620 $\mu g/m^3$).

Sulfur dioxide gas is a rapidly diffusing reactive gas that is readily
soluble in water and body fluids (Aharonson, 1976). Through normal and catalyst
mediated oxidation processes in air SO_2 gas is slowly oxidized to form H_2SO_4,
leading to sulfate salts. Since NH_3 is formed in natural biological processes
including endogenously in the airways, $(NH_4)_2SO_4$ and NH_4HSO_4 are important
products of SO_2 oxidation (Charlson et al., 1978). Specific instrumental and
chemical techniques are available for SO_2 and other sulfur containing compounds
in aerosol-gas mixtures.

11.1.3 The Respiratory Tract

To evaluate the regional deposition of inhaled aerosols and sulfur dioxide,
the normal dimensions of each anatomical section of the respiratory tract from
nasal cavity to the parenchyma of the lung are needed (Figure 11-1). With
these measurements, predictive models of the deposition of inhaled particles
and gases have been devised. Although differences exist among individuals,
and variability occurs during the breathing cycle of any given individual
(Marshall and Holden, 1963), general descriptions of the anatomical features
of the respiratory tract and airflow characteristics are quite satisfactory
for general predictive models of deposition.

Morphometric measurements of the airways have been made by (a) preparation
of corrosive casts of the airspaces (Tompsett, 1970; Frank and Yaeder, 1966;
Phalen et al., 1973; Raabe et al., 1976b); (b) direct measurements in vivo,
such as by endoscopy, radiography, (Nadel, et al., 1967; Adams and Davenport, 1942;
Yeh, et al., 1975), or at autopsy (Berg, et al., 1949); or (c) two-dimensional
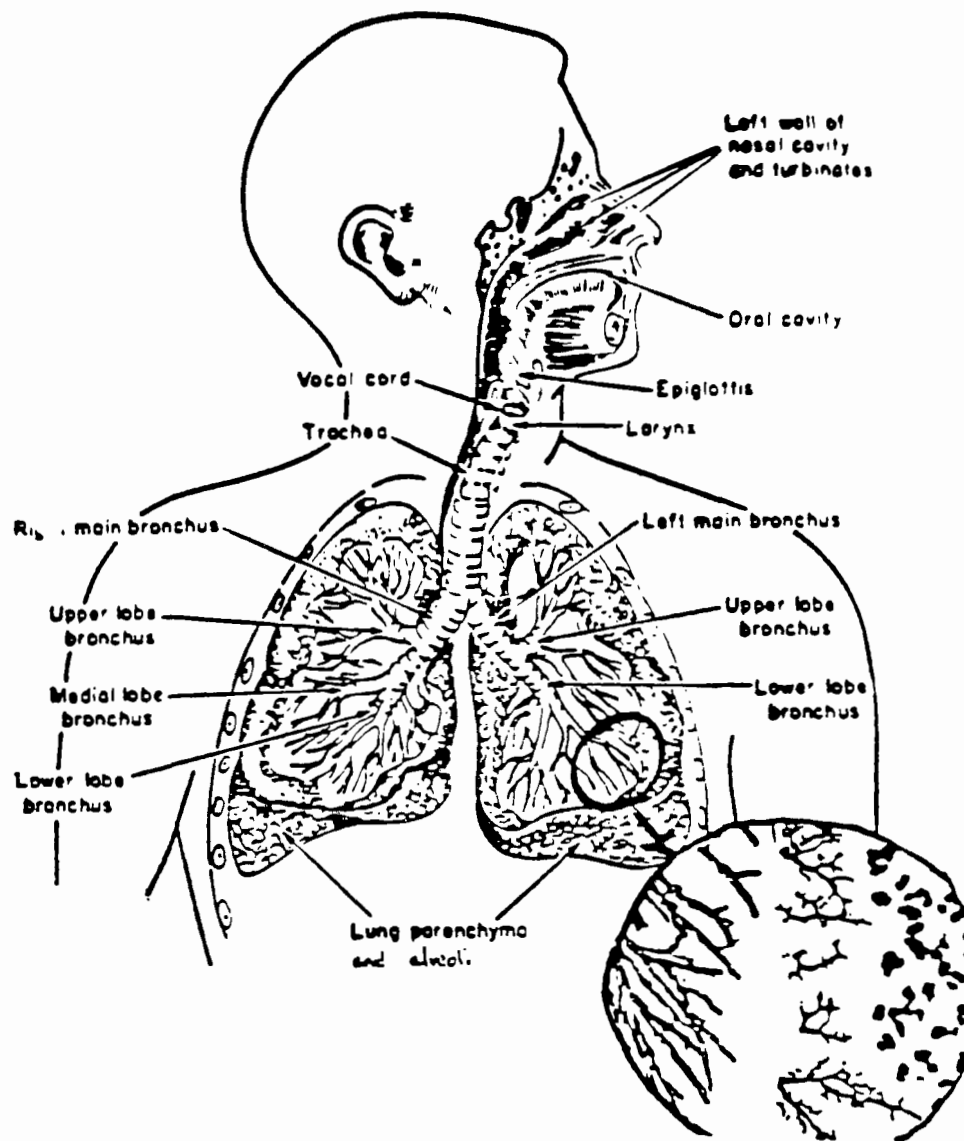
FIGURE 11-1. Features of the respiratory tract of man used in the description
of the deposition of inhaled particles and gases with insert showing
parts of a silicon rubber cast of a human lung showing some separated
bronchioles to 3 mm diameter, some bronchioles from 3 mm diameter to
terminal bronchioles, and some separated respiratory acinus bundles
(adapted from Raabe, 1970).

measurements of cross-sectional cuts of tissue either by direct observation or with the aid of light and electron microscopy (Weibel and Elias, 1967; Nagashi, 1972; Hansen ~~et al.~~ *and Ampaya* 1974; Hansen et al , 1975; Hansen and Ampaya, 1975).

The respiratory tract includes the passages of the nose, mouth, nasal pharynx, oral pharynx, epiglottis, larynx, trachea, bronchi, bronchioles, and small ducts and alveoli of the pulmonary acini. For consideration of the mechanisms associated with deposition and clearance of inhaled aerosols, the respiratory tract can be divided into three functional regions: (1) naso-pharynx (NP), the airways extending from the nares down to the epiglottis and larynx at the entrance to the trachea (the mouth is included in this region during mouth breathing); (2) tracheobronchial region (TB), the primary conduct-ing airways of the lung from the trachea to the terminal bronchioles (i.e., that portion of the lung respiratory tract having a ciliated epithelium); and (3) pulmonary region (P), the parenchymal airspaces of the lung, including the respiratory bronchioles, alveolar ducts, alveolar sacs, atria, and alveoli (i.e., the gas-exchange region). Although the anatomical and physiological divisions between these regions are gradual and difficult to distinguish, the formal separation of the ciliated from the unciliated regions has useful applications, particularly when considering particle clearance.

The NP consists primarily of hollow portions of the nose and throat. The nose is a complex structure of cartilage and muscle supported by bone and lined with mucosa (Holmes, et al., 1950). The vestibule of the nares is unciliated but contains a low-resistance filter consisting of small hairs. The nasal volume is separated into two cavities by a 2- to 7-mm thick septum. The inner nasal fossae and turbinates are ciliated, with mucus flow in the direction of the pharynx. The turbinates are shelf-like projections of bone

covered by ciliated mucous membranes with a high surface-to-volume ratio that facilitate humidification of the incoming air.

The larynx consists of two pairs of elevated mucosal folds that partially obstruct the airway. The distance from the epiglottis to below the larynx is 5 to 7 cm, with a vertical diameter of 3.6 to 4.4 cm (Snyder, 1975). Females have smaller laryngeal regions than do males.

The trachea, an elastic tube supported by 16 to 20 cartilagenous rings that circle about 3/4 of its circumference, is the first and largest of a series of conductive airway ducts (Tenney and Bartlett, 1967). The trachea divides into two major bronchi. The caliber of the trachea and major bronchi and their cross-sectional geometry is about 15 percent larger during inspiration than during expiration (Marshall and Holden, 1963; Fraser and Pare, 1971; Raabe et al., 1976b).

The lungs consist of two major parts, the left and right lungs, connected to the two major bronchi of the trachea (Figure 11-1). The left lung consists of two clearly separated lobes, the upper and lower lobes; and the right lung consists of three lobes, the upper, middle, and lower lobes. Each lobe is served by a bronchus from one of the two major bronchi. The conductive airways in each lobe of the lung consist of up to 18 to 20 dichotomous branches from the bronchi to the terminal bronchiole (Pump, 1964; Raabe et al., 1976b). Bronchial caliber correlates with body size (Thurlbeck and Haines, 1975). The caliber of the smaller conductive bronchioles may be up to 40 percent greater during inspiration than during expiration (Marshall and Holden, 1963; Hughes et al., 1972).

The pulmonary, gas-exchange region of the lung begins with the partially alveolated respiratory bronchioles. Pulmonary branching proceeds through a

few levels of respiratory bronchioles to completely alveolated ducts (Smith and Boyden, 1949; Whimster et al., 1970; Krahl, 1963) and alveolar sacs (Tenney and Remmers, 1963; Pattle, 1961b; Machlin, 1950; Frasier and Pare, 1971). Alveoli are thin-walled polyhedron air pouches which cluster about the acinus through connections with respiratory bronchioles, alveolar ducts, or alveolar sacs. The airway spaces in the respiratory zone are coated with a complex aqueous liquid containing several biochemically specialized substances, including pulmonary surfactants (Green, 1974).

Several researchers have measured the conductive airways of the lung. Weibel (1963) used a corrosion cast of the human lung prepared by Liebow and co-workers (1947) to make detailed measurements of unbroken segments to the tenth branching; he could not measure further. He used these measurements in conjunction with histological data (Weibel and Elias, 1967) on the human alveolar acinus to develop a consistent model of airway number and dimensions. Horsfield (1972), Horsfield and Cumming (1968), Horsfield and Cumming (1967), Horsfield et al. (1971), and Parker et al. (1971) also measured casts of the human conductive airways. Raabe et al. (1976[b]) used an in situ method (Phalen et al., 1973) to measure the conductive airways of several mammalian species, including man, dog, rat, and hamster. They used casts prepared at autopsy under conditions simulating end inspiration (Raabe, 1979). These replica casts purportedly were more faithful reproductions of the normal airway orientation than were those obtained with excised lungs. After determining the lengths, diameters, and branching angles for selected segments from trachea to terminal bronchioles, Raabe and co-workers (1976b) performed extensive measurements on the conductive airways of man and experimental animals. They demonstrated that the number of airway branches in the human TB region from

trachea to terminal bronchiole can range from 11 to 22. They also showed that different lobes have different average numbers of branches to terminal, with the apical or upper lobes tending to have fewer branches than the other lobes. These measurements reveal the diversity of branching angles, airway segment lengths and diameters, and branching patterns in mammalian species. Other factors, such as airway closure, changes in caliber during breathing, bronchmotor tone and constrictions can alter these dimensions (Slonim and Hamilton, 1971; Hinshaw, 1969).

The number of alveoli increases after birth until late childhood, reaching a maximum of about 300 million (Charnock and Doeshuk, 1973; Davies and Reid, 1970; Dunnill, 1962). Schreider and Raabe (1980) made acinus measurements of casts of the respiratory airways. Although the alveolus usually assumes an irregular shape because of the thin walls and close packing, alveolar size is usually described as the equivalent spherical diameter. Reported diameters range from 150 to 300 μm for man (Weibel, 1963; Davies, 1961; Crosfill and Widdicombe, 1961; Kliment, 1973; Von Hayek, 1960). The alveolar dimensions vary with degree of inflation (D'Angelo, 1972, Forrest, 1970) and hydrostatic pressure (Glazier et al., 1966, 1967).

The total surface area of the alveoli in adult man was reported by Von Hayek (1960) as 35 m^2 in expiration and 100 m^2 in deep inspiration. Weibel (1963) estimated a surface area of 70 m^2 for a human lung at three-quarters capacity. This compares with 45.5 m^2 for 16 kg dogs (Tenny and Remmers, 1963) and 1.1 m^2 for guinea pigs (Schreider, 1977).

The deep lung parenchyma includes several types of tissue, circulating blood, lymphatic drainage pathways, and lymph nodes. In man, the weight of the lung, including circulating blood, is about 1.4 percent of the total body

weight. Lung blood is equal to about 0.7 percent of total body weight (10 percent of total blood volume) (Snyder, 1975). Because a portion of lung is occupied by air, the average physical density of the parenchyma is about 0.26 g/cm^3 (Fowler and Young, 1959).

Models of the airways, which simplify the complex array of branching and dimensions into workable mathematical functions, are useful in estimation of deposition. An early idealized model of the airways of the human lung was developed by Findeisen (1935) for estimating the deposition of inhaled particles Findeisen's model assumed branching symmetry within the lung, with each generation consisting of airways of identical size. Other models based on a symmetry assumption have been proposed by Landahl (1950), Davies (1961), Weibel (1963), and Horsfield and Cumming (1968).

11.1.4 Respiration

Both the humidity and temperature of inhaled aerosols and gases, as well as the subsequent changes that occur as the aerosol-gas mixture passes through various parts of the airways, have important influences on the inhalation deposition of airborne particles. Deposition of inhaled soluble, deliquescent, and hygroscopic aerosols will depend in part on the relative humidity in the airways, since the growth of such particles (with concomitant increase in aerodynamic size) will directly affect both the site and extent of inhalation deposition.

The relative humidity of inhaled air probably reaches near saturation in the nose (Verzar et al., 1953). Since the human nose is a relatively simple and short passageway, tranquil diffusion alone cannot account for rapid humidification. Rather, convective mixing must play a role, suggesting a mechanism for enhancing SO_2 collection in the nose. The lower temperature of inhaled

air increases the effectiveness of nasal humidification by convective mixing. Unlike humidity, the temperature of the inhaled air may not reach body temperature until relatively deep in the lung. Deal et al. (1979a, b, c) measured retrocardiac and retrotracheal temperatures under different ambient temperatures and found airway cooling associated with breathing cool air. Raabe et al. (1976b) found that the temperature of the air at major bronchi in a nose-breathing dog averaged 35°C, 4°C less than the body temperature. The temperature of exhaled air at the nose of a dog averaged only 31°C (Raabe and Yeh, 1976a).

Inspiratory flow rate and depth of inhalation influence the deposition of inhaled particles. The air inspired in one breath is the tidal volume (TV). The average inspiratory flow rate, (Q), and tidal volume (Bake et al., 1974; Clement et al., 1973) affect both inertial and diffusional deposition processes (Altshuler et al., 1967). The total air remaining in the lungs at the end of normal expiration [functional residual capacity (FRC)] affects the relative mixing of inhaled particles and, when compared with total lung capacity (TLC), is indicative of the extent of aerosol penetration into the lung (West, 1974; Luft, 1958). Weibel (1972) developed relationships relating human lung capacity to body weight, and Guyton (1947a, b) and Stahl (1967) developed interspecies relationships describing respiratory volumes and patterns. An important difference between man and rodents is that small rodents breathe by inhaling shallowly and rapidly (for rats about 1.5 ml TV at 100 breaths per minute).

The inspiratory capacity (IC), the maximum volume of air that can be inhaled after a given normal expiration, is contrasted to the vital capacity (VC), which is the maximum volume of air that can be expelled from the lungs with effort after maximum forced inspiration. Air that remains in the conductive

airways (from nose to terminal bronchioles) at end expiration is considered to occupy the respiratory dead space (V_D), since the conductive airways are not involved in gas exchange (Paiva, 1973; Paiva and Paiva-Verentennicoff, 1972; Palmes, 1973).

Gas flow dynamics within the upper airways may be expected to be turbulent in humans and dogs but laminar everywhere in the airways of small rodents (Dekker, 1961; Fry, 1968; Schroter and Sudlow, 1969; Olson et al., 1973; Martin and Jacobi, 1972; West, 1961). The larynx introduces an important air flow disturbance that can influence tracheal deposition (Bartlett et al., 1973; Schlesinger and Lippmann, 1976). In the smaller human bronchi and bronchioles, where fluid flow is relatively tranquil, laminar flow prevails, but branching patterns, filling patterns (Grant et al. 1974), flow reversals with varying velocity profiles, and swirling complicate a description of flow in the small airways (Silverman and Billings, 1961; Cinkotai, 1974). Because actual flow in the respiratory airways is difficult to describe, simplifying assumptions, such as laminar or bulk flow and uniform velocity profiles, are usually incorporated into analytic descriptions.

Representative values for normal human respiratory parameters (Snyder, 1975) are frequently used for deposition and dosimetric prediction although it is understood that these values may not describe any particular person. It should be noted that considerable variability in respiratory parameters may occur among individuals in the population, particularly when healthy adults are contrasted with children, aged, and ill individuals. For a young adult weighing 70 kg with a height of 175 cm and a body surface area of 1.8 m^2, Snyder (1975) assumed a breathing rate of 12 breaths per minute with minute volume of 7.5 liters/minute. Morrow et al. (1966) assumed three sets of

representative tidal volumes, 750 ml at rest, 1450 ml during moderate activity, and 2150 ml during strenuous exercise with 15 breaths per minute for deposition calculations.

11.2 DEPOSITION IN MAN AND EXPERIMENTAL ANIMALS

11.2.1 Insoluble and Hydrophobic Solid Particles

The behavior of inhaled airborne particles in the respiratory airways and their alternative fate of either deposition or exhalation depend upon aerosol mechanics under the given physiological and anatomical condition (Yeh et al., 1976; DuBois and Rogers, 1968). To understand the basic physiological and anatomical factors influencing deposition, initial consideration must be given to nonreactive stable spherical particles whose physical properties do not vary during the breathing cycle. When deposition measurements and calculations are confirmed for these ideal insoluble particles, it is possible to develop an understanding of the more complex behavior of hygroscopic and deliquescent particles.

Figure 11-2 illustrates the five primary physical processes that lead to aerosol particle contact with the wall of the airways. Contact of particles with moist airway walls results in attachment and irreversible removal of the particle from the airstream. The contact process can occur during inspiration or expiration of a single breath or subsequently if a particle has been transferred to unexhaled lung air (Engel et al., 1973; Davies, 1972; Altshuler, 1961). Deposition increases with duration of breath holding and depth of breathing (Palmes et al., 1973; Palmes et al., 1967; Altshuler, 1961).

Electrostatic attraction of particles to the walls of the respiratory airways is probably a minor mechanism of deposition in most circumstances. Pavlik (1967) predicted that light air ions (which would include some

ELECTROSTATIC ATTRACTION

INTERCEPTION

IMPACTION

F_g

GRAVITATIONAL SETTLING

BROWNIAN DIFFUSION
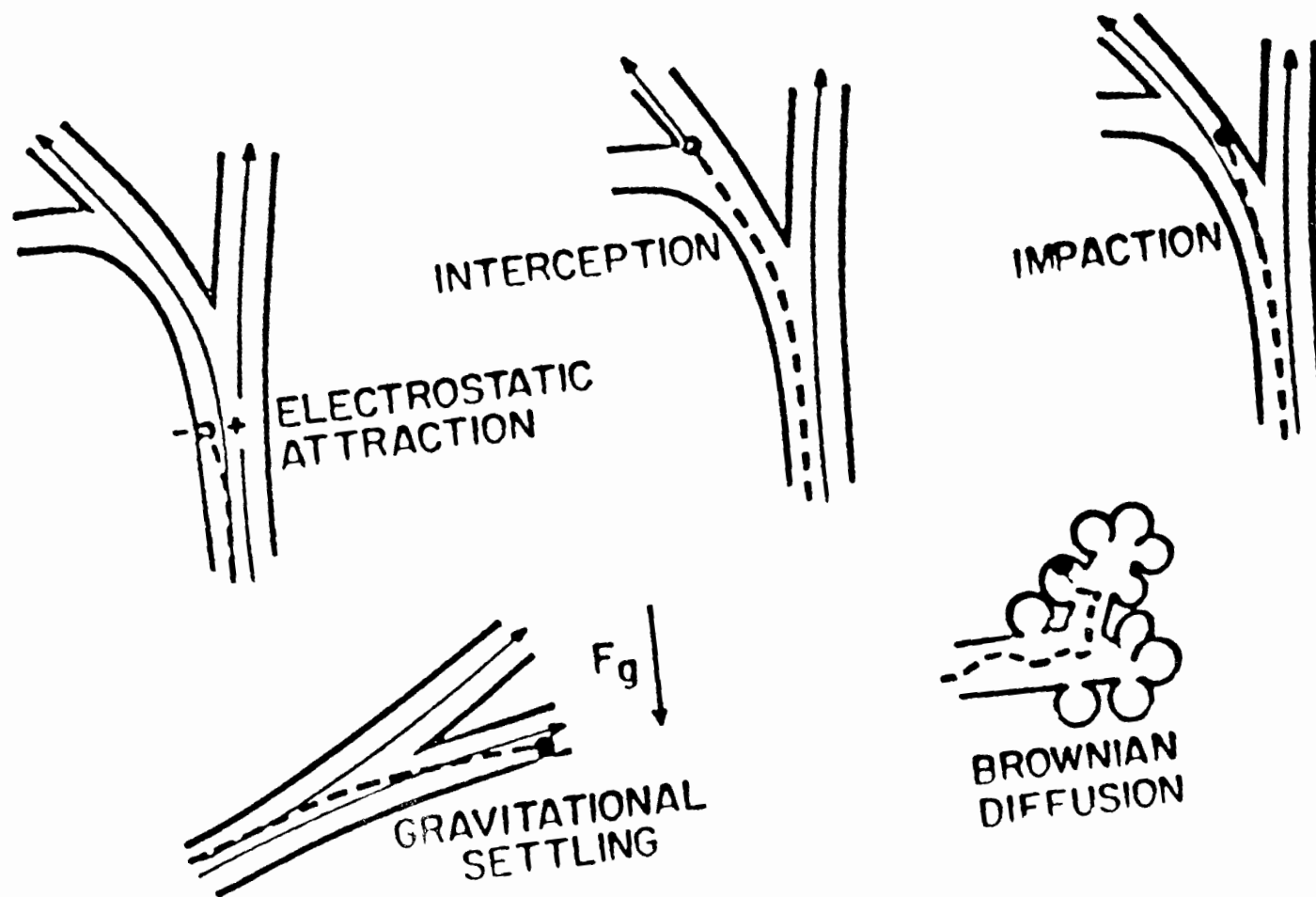
FIGURE 11-2. Representation of five major mechanisms of deposition of inhaled airborne particles in the respiratory tract (from Raabe, 1979).

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atmospheric aerosol nuclei) would be deposited by electrostatic attraction in the mouth and throat and suggested that the tonsils were naturally charged for this purpose. Fraser (1966) found that an average of 1000 electronic units of charge per aerosol particle doubled the inhalation deposition in experimental animals. Melandri et al. (1977) reported enhanced deposition of inhaled monodisperse aerosols by people when the particles were charged. Longley (1960) and Longley and Berry (1961) found the charge of the subject to have an influence on deposition. Similar observations have been made in in vitro studies (Chan et al., 1978). However, the airways are covered by a relatively conductive electrolytic liquid that probably precludes the buildup of forceful electric fields. Charged particles are therefore collected primarily by image charging as they near the wall of an airway or by mutual repulsion from a unipolarly charged cloud with a high concentration of particles (Yu, 1977). The charge-to-size ratio (and associated electrical mobility) of an aerosol particle determines the extent to which the mechanism may play a role in deposition. Hence, the role of this mechanism may depend on particle source, age, and special electrical phenomena in the environment. It is reasonable to expect this mechanism to have a small role, if any, in the deposition of atmospheric environmental aerosols.

Interception consists of noninertial incidental meeting of a particle and the lining of the airway and thus depends on the physical size of the particle. This process would have a zero probability if the particles were only points rather than extended bodies. It is important primarily for particles with large aspect ratios, such as long fibrous particles of asbestos (Harris and Fraser, 1976). Interception may be expected to play a negligible role in the inhalation deposition of most environmental aerosols.

Impaction dominates deposition of particles larger than 3 μm D_{ar} in the nasopharyngeal and tracheobronchial regions (Pattle, 1961a; Bohning et al., 1975). In this process, changes in airstream direction or magnitude of air velocity streamlines or eddy components are not followed by airborne particles because of their inertia. For example, if air is directed toward an airway surface (such as a branch carina) but the forward velocity is suddenly reduced because of change in flow direction, inertial momentum may carry larger particles across the air streamlines and into the surface of the airway. Impaction at an airway branch has been likened to impaction at the bend of a tube, providing theoretical estimates of the impaction probability (P_I) (Johnston and Muir, 1973; Yeh, 1974; Cheng and Wang, 1975). Aerodynamic separation of this type is satisfactorily characterized in terms of the particle aerodynamic diameter. If impaction in the airways is likened to collection of aerosols in a round-jet impactor, the 50 percent collection efficiency would occur at a particle aerodynamic diameter of 18 μm D_{ar} for the human trachael bifurcation for a volumetric flow rate of 45 liter/minute and would have little effect on particles smaller than 6 μm D_{ar}. However, the airflow in the trachea and major bronchi in man is turbulent and disturbed by the larynx so that turbulent impaction plays a role in deposition in these larger airways (Schlesinger and Lippmann, 1976). Breathing patterns involving higher volumetric flow rates would tend to impact smaller particles. In contrast, the passages of the nose contain smaller airways, and the convective mixing spaces of the nasal turbinates would be expected to collect some particles as small as 1 or 2 μm D_{ar} by impaction. Hence, impaction is an important process affecting the inhalation deposition in the human airways of environmental aerosol particles greater than 1 μm in aerodynamic diameter.

Gravitational settling occurs because of the influence of the earth's gravity on small particles. Deposition of particles by this mechanism can occur in all airways except those very few that are vertical. The probability of gravitational deposition (P_s) is usually estimated with equations describing gravitational settling of particles in an inclined cylindrical tube of diameter (d) under laminar flow conditions (Wang, 1975; Heyder and Gebhart, 1977). This deposition depends on the particle concentration distribution in the airway segments, the incline angle with respect to gravity, and the aerodynamic resistance diameter (D_{ar}) of the particle. Deposition by gravitational settling is therefore characterized in terms of the particle aerodynamic diameter. This mechanism has an important influence on the deposition of particles larger than 0.5 μm D_{ar}. Settling has an important role in the deposition of environmental aerosols in the distal region of the bronchial airways. Settling plays an equally important role in the pulmonary deposition and is responsible for part of the deposition of particles in this region during mouth breathing.

Deposition by diffusion results from the random (Brownian) motion of very small particles caused by bombardment of the gas molecules in air. The magnitude of this motion can be described by the diffusion coefficient for a given physical particle diameter. Since larger particles have relatively small diffusional mobility compared with inertia, diffusion primarily affects deposition of particles with physical diameters smaller than 1 μm. For a 0.5 μm particle with a physical density of about 1 g/cm^3, the influences of inertial properties and diffusional properties on lung deposition are about equal. Accurate calculation of the diffusional deposition of aerosols in the airways requires information concerning the three-dimensional velocity profile of air flow in each airway segment. If the flow of a given segment is laminar and

approximately Poisueille, the probability of deposition by diffusion (P_D) might be approximated using the Gormley-Kennedy (1949) equation for a cylindrical pipe. However, this assumes the aerosol is mixed at the entrance of the cylinder and it might overestimate deposition in lung segments where there is minimal mixing between branches and laminar flow between segments.

It is important to note that the diffusivity, electrical mobility, and interception potential of a particle depend on its physical size, while the inertial properties of settling and impaction depend on its aerodynamic diameter. These two measures of size may be quite different, depending on particle shape and physical density. Because the main mechanism of deposition is diffusion for particles whose physical (geometric) size is less than 0.5 μm D and impaction and settling above 0.5 μm D_{ar}, it is convenient to use 0.5 μm as the boundary between two regions. Although this convention may lead to confusion in the case of very dense particles, most environmental aerosols have densities below 3 g/cm^3, and the deposition probability tends to have a minimum plateau between 0.5 μm and 1 μm D_{ar} (the equivalent sizes for a spherical particle with physical diameter 0.5 μm and D_{ar} with density 3 g/cm^3, respectively). Of course, a comparison of deposition probabilities is desirable between the aerodynamic diameter and physical diameter of submicrometer particles.

Thus, it is possible to use the available information concerning breathing patterns and respiratory physiology, the anatomical and geometrical characteristics of the airways, and the physical behavior of insoluble spherical particles to develop theoretical models of regional deposition (Landahl, 1963; Findeisen, 1935; Beeckmans, 1965; Landahl et al., 1951). In these models, deposition of inhaled aerosols in a given region of the respiratory tract or in the entire

tract is expressed as a fraction of inhaled particles. Deposition fraction is the ratio of the number or mass of particles deposited in the respiratory tract to the number or mass of particles inhaled. The undeposited fraction represents those particles that are exhaled after inhalation. For example, pulmonary deposition (sometimes called alveolar deposition) is the ratio of the number or mass of particles deposited in the unciliated small airways and gas exchange spaces of the parenchyma of the lung to the number or mass of particles entering the nose or mouth. The fraction not deposited in the pulmonary region is either deposited in some other region or exhaled. Similarly, deposition fractions can be defined for the nasopharyngeal and tracheobronchial regions of the respiratory airways.

The theoretical probability of deposition can be calculated as the difference between unity and the product of the probabilities of transmission through a given duct or series of ducts. Hence, the probability of deposition for a monodisperse aerosol of a given particle size for the combination of impaction, settling, and diffusion for a single segment region is given by:

$$P = 1 - (1 - P_I)(1 - P_S)(1 - P_D) \qquad (4)$$

where P is the combined deposition probability, P_I is the impaction deposition probability, P_S is the settling deposition probability, and P_D is the diffusion deposition probability.

Most model calculations treat the various mechanisms of deposition as independently occurring phenomena. However, such processes as Brownian diffusion and gravitational settling will interfere with each other when their effects are of comparable magnitude, and that interference can reduce the combined deposition to less than the sum of the separate depositions (Goldberg et al., 1978). Taulbee and Yu (1975a) have developed a theoretical deposition

model which allows for the combined effects of the primary deposition mechanisms and features an imaginary expanding tube model of the airway system (Weibel 1963) based on cross-sectional areas and airway lengths.

The most widely used models of regional deposition versus particle size were developed by the International Commission on Radiological Protection Task Group on Lung Dynamics under the chairmanship of P. E. Morrow (Morrow et al., 1966). Although the purpose of these models was to determine radiation exposure from inhaled radioactive aerosols, the ICRP aerosol deposition and clearance models are broadly applicable to environmental aerosols. The ICRP Task Group used the anatomical model and general methods of Findeisen (1935) and Landahl (1950, 1963) for calculating deposition in the tracheobronchial and pulmonary regions. The Gormley-Kennedy (1949) equation for cylindrical tubes was used for calculating diffusional deposition. Particles were assumed to be insoluble, stable, and spherical with physical densities of 1 g/cm^3. Regional deposition was calculated for a breathing rate of 15 breaths per minute (BPM) for three tidal volumes (TV): (a) TV 750 ml, at rest (Figure 11-3), (b) TV 1450 ml, moderate activity (Figure 11-4), and (c) TV 2150 ml, fairly strenuous activity.

The ICRP Task Group used the calculated deposition fractions for individual particle sizes to predict deposition of log-normally distributed aerosols consisting of unit density spherical particles with geometric standard deviations (σ_g) as high as 4.5. When the results were expressed in terms of the mass median diameter (MMD) for these various sized distributions of unit density of aerosols (equivalent to the MMAD), the loci of the expected deposition values spanned relatively narrow limits (Figure 11-5).

The ICRP Task Group on Lung Dynamics (Morrow et al., 1966) compared the calculated regional and total deposition fractions for inhaled particles with the available human data. Those data were primarily total deposition values
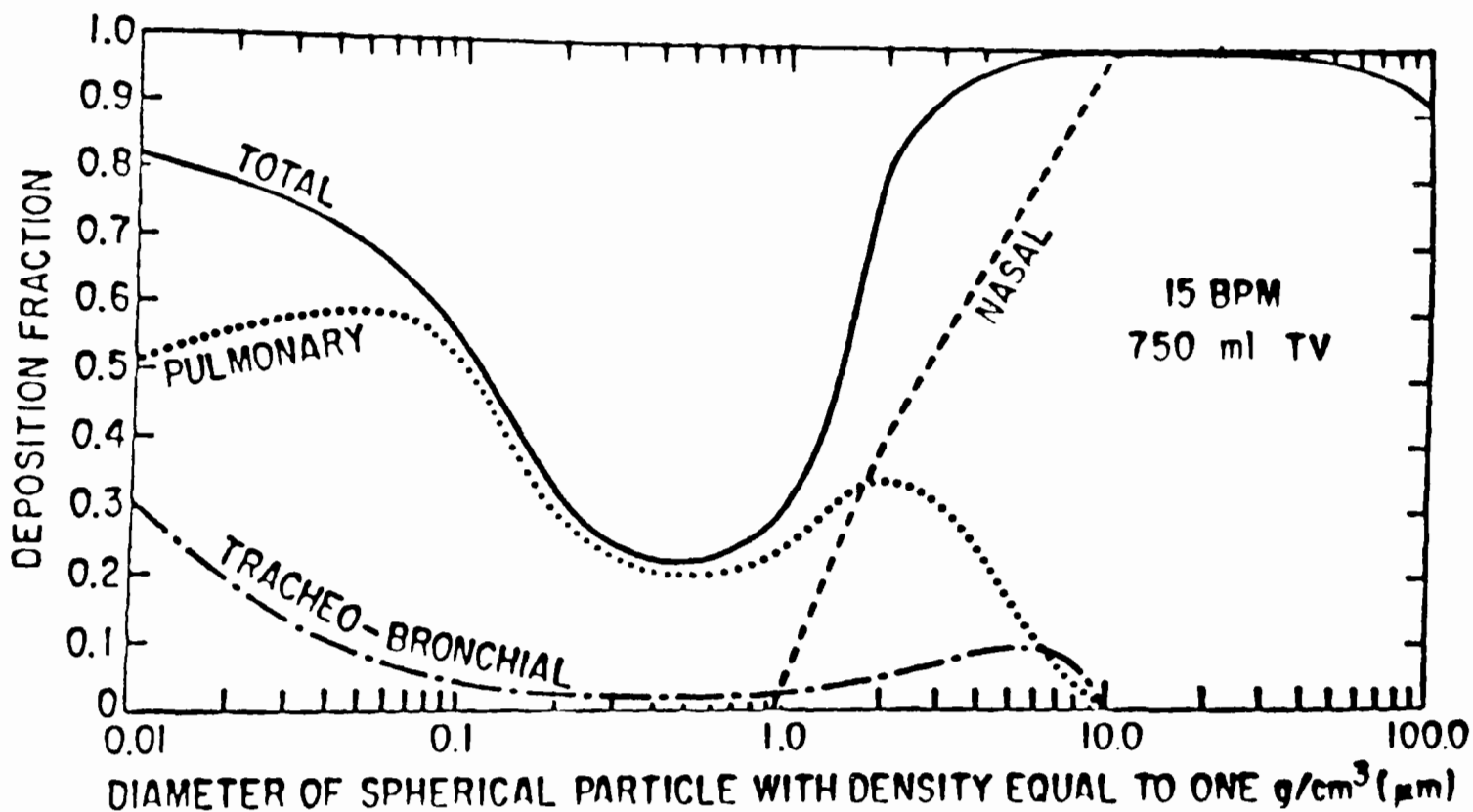
FIGURE 11-3. Total and regional deposition fractions in the human respiratory tract for various sizes of inhaled airborne spherical particles with physical density of one g/cm³ as calculated by the ICRP Task Group on Lung Dynamics (Morrow et al., 1966) for breathing rate of 15 breaths per minute (BPM) and a tidal volume (TV) of 750 ml (from Raabe, 1979).
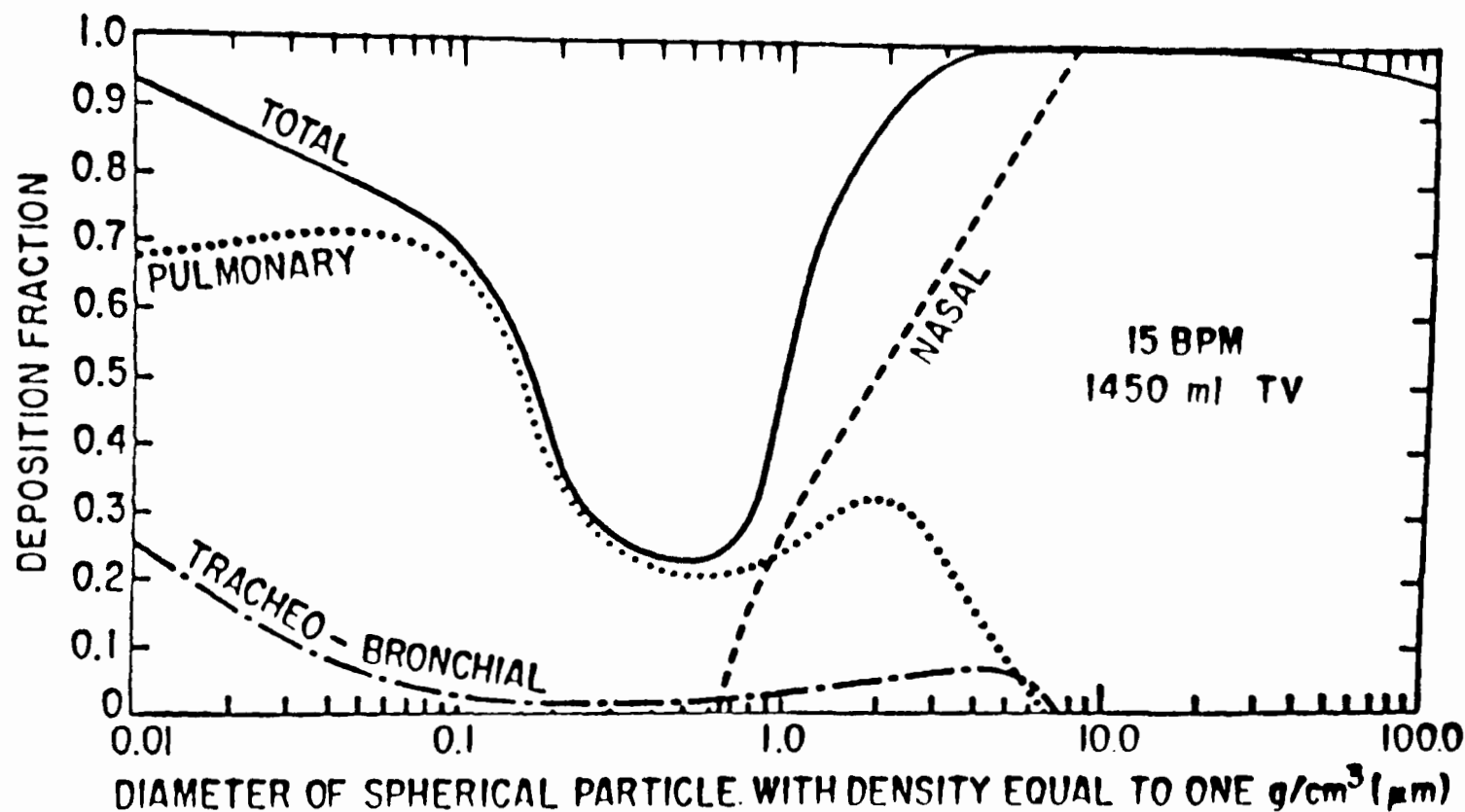
FIGURE 11-4. Total and regional deposition fractions in the human respiratory tract for various sizes of inhaled airborne spherical particles with physical density of one g/cm^3 as calculated by the ICRP Task Group on Lung Dynamics (Morrow et al., 1956) for a breathing rate of 15 breaths per minute (BPM) and a tidal volume (TV) of 1450 ml (from Raabe, 1979).
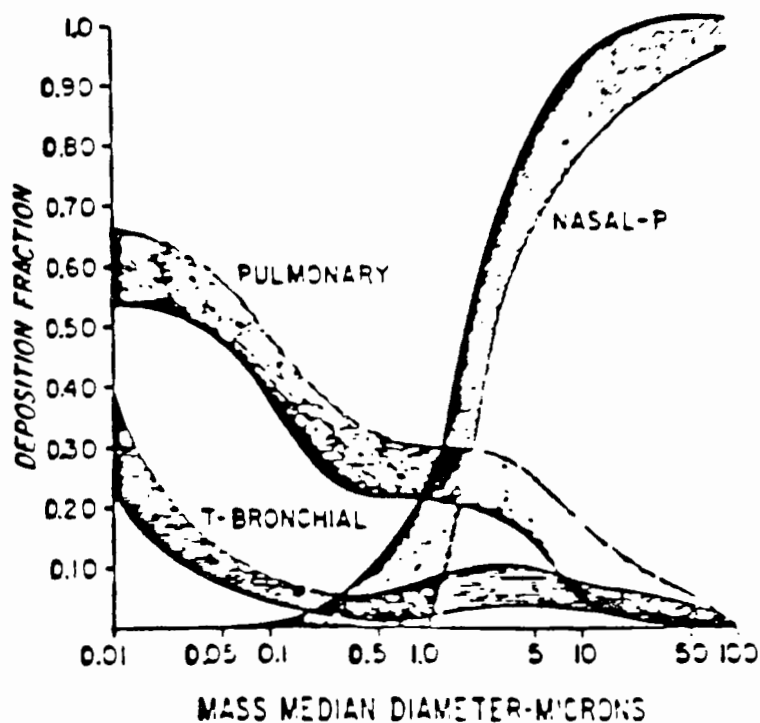
FIGURE 11-5. The range of regional deposition fractions (shaded areas) for log-normally distributed spherical aerosols in human nose breathing at 15 BPM and 1450 ml TV. Geometric standard deviation ranges between 1.2 and 4.5; particle physical density is one g/cm³ so that MMD = MMAD (Morrow et al., 1966)

for polydisperse and sometimes unstable aerosols (Morrow, 1970b; Landahl and Herrmann, 1948; Davies, 1964b; Van Wijk and Patterson, 1940; Brown et al., 1950; Dautrebande and Walkenhurst, 1966; Morrow et al., 1958; Landahl and Black, 1947; Landahl and Hermann, 1948). Since then, the deposition in humans of monodisperse insoluble, stable aerosols of different sizes has been measured under different breathing conditions. The most extensive of these studies are those of Lippmann and Albert, (1969), Heyder et al. (1975), and Giacomelli-Maltoni et al. (1972). Additional useful data are reported by Palmes and Wang (1971), Shanty (1974), George and Breslin (1967), Altshuler et al. (1967), Hounam et al. (1971a and 1971b), and Foord et al. (1976), among others (Pavia et al., 1977; Muir and Davies, 1967; Taulbee et al., 1978; Hounam, 1971; Heyder, 1971; Heyder and Davies, 1971; Fry and Black, 1973.)

These human deposition data have been collected from volunteers inhaling test aerosols through either mouthpieces or nose tubes. Differences between those artificially controlled inhalations and normal, spontaneous mouth breathing or nose breathing are possible. Also, the particular breathing rate (BPM), respiratory functional residual capacity (FRC), and tidal volume (TV) used in the experiments affect deposition.

If the quantity of aerosol exhaled is compared with that inhaled, the data can be expressed as total deposition, but regional involvement cannot be distinguished (Heyder et al., 1975). By tagging the test aerosols with radio-labels, investigators can separate deposition by region, beginning with either nasopharyngeal deposition for nose breathing or pharyngeal deposition for mouth breathing (Albert et al., 1967a). The measurement of clearance of the radiolabeled aerosol from the thorax can be used to separate early clearance,

indicative of tracheobronchial (TB) deposition, from more slowly cleared pulmonary (P) deposition (Lippmann and Albert, 1969).

Selected portions of the available data on total and regional aerosol deposition have been compared with the calculated deposition values of the ICRP Task Group on Lung Dynamics (Morrow et al., 1966) (Figures 11-6 to 11-10). In these comparisons, the predicted values either agree well with or represent the upper limit of the observed deposition values. The greatest overall discrepancy between actual and calculated values occurs for particles smaller than 0.2 μm; fractional pulmonary deposition measured for those particles during mouth breathing is about 0.1 to 0.2, compared with the predicted 0.3 to 0.6. However, actual data for these smaller particles are based on few experiments.

The most extensive and generally useful comparison of the effects of respiratory parameters on aerosol deposition have been conducted by Heyder and coworkers (1975, 1980) in systematic experiments comparing deposition of different sized monodisperse aerosols in human volunteers at different tidal volumes, flow rates, and breathing frequencies. For particles between 0.1 μm and 4.0 μm in diameter, Heyder et al. (1975) measured only total respiratory deposition during either nose or mouth breathing. They sequentially maintained a given tidal volume and tested different selected breathing rates, inspiratory flow rates, and particle sizes. They then maintained a fixed breathing rate and studied deposition at different tidal volumes and inspiratory flow rates. Likewise, they held respiratory flow rates constant and measured deposition at different tidal volumes and breathing rates. They demonstrated several important features of aerosol deposition in the human respiratory airways. With volumetric flow rate held at 15 liter/minute, the particle size yielding

TOTAL DEPOSITION FOR NASAL BREATHING
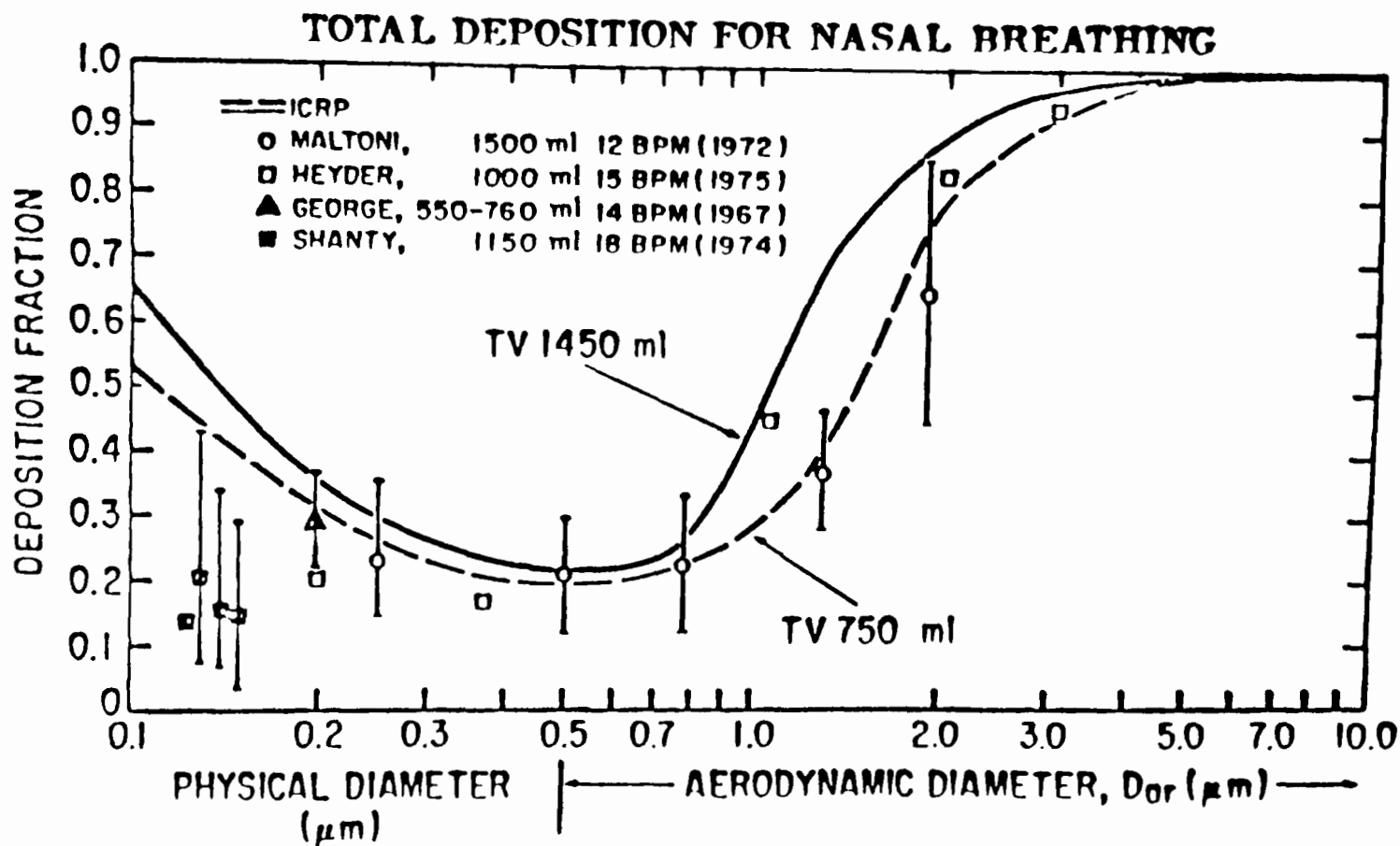
FIGURE 11-6. Selected data (Giacomelli-Maltoni et al., 1972; Heyder et al., 1975; George and Breslin, 1967; Shanty, 1974) reported for the deposition in the entire respiratory tract of monodisperse aerosols inhaled through the nose by people are compared with predicted values calculated by the ICRP Task Group on Lung Dynamics (Morrow et al., 1966) (from Raabe, 1979).

TOTAL DEPOSITION FOR MOUTH BREATHING
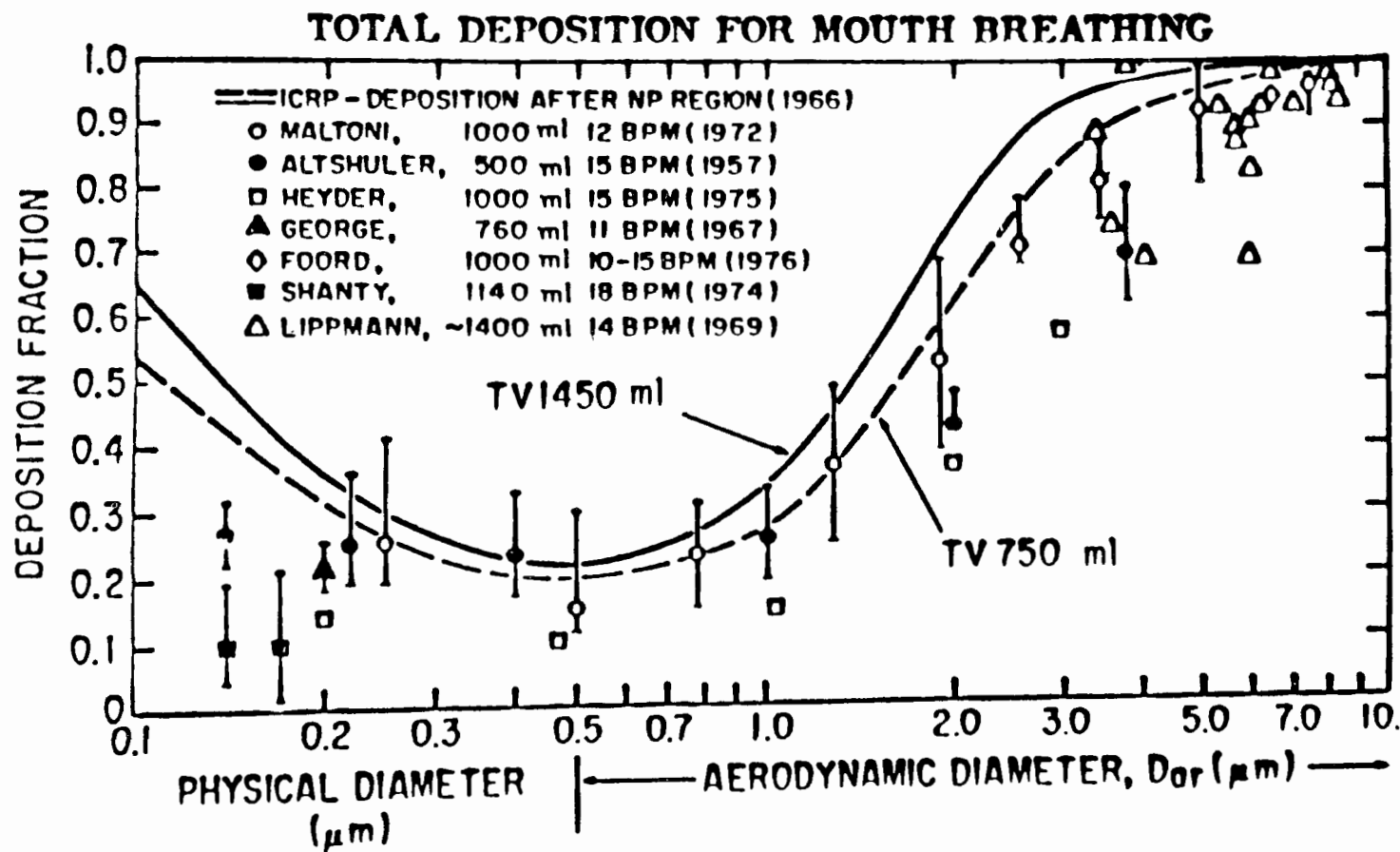
FIGURE 11-7. Selected data (Giacomelli-Maltoni et al., 1972; Altshuler et al., 1957; Heyder et al., 1975; George and Breslin, 1967; Foord et al., 1976; Shanty, 1974; and Lippmann and Albert, 1969) reported for the deposition in the respiratory tract of monodisperse aerosols inhaled through the mouth by people are compared with predicted values calculated by the ICRP Task Group on Lung Dynamics (Morrow et al., 1966) (from Raabe, 1979).

NASOPHARYNGEAL (NP) DEPOSITION
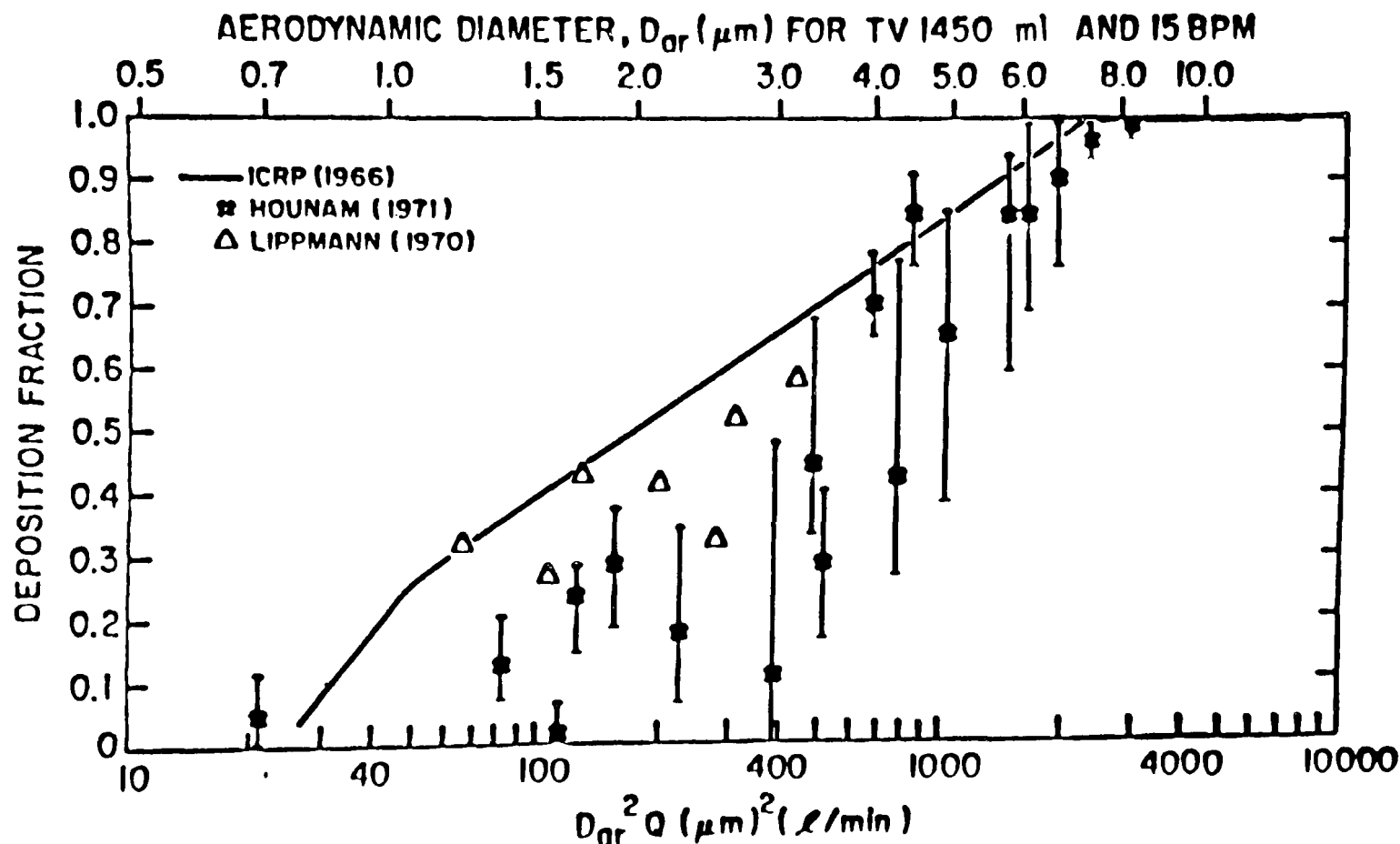
FIGURE 11-8. Selected data (Hounam et al., 1971; Lippmann, 1970[a]) reported for the deposition fraction of monodisperse aerosols in the human nasopharyngeal (NP) region of the respiratory tract are plotted against the characteristic term (D_{ar}^2Q, where Q is the average inspiratory flow in l/min) that controls inertial impaction; for reference, the calculated value (Morrow et al., 1966) is shown for 15 BPM at 1450 ml TV (from Raabe, 1979).

TRACHEOBRONCHIAL (TB) DEPOSITION
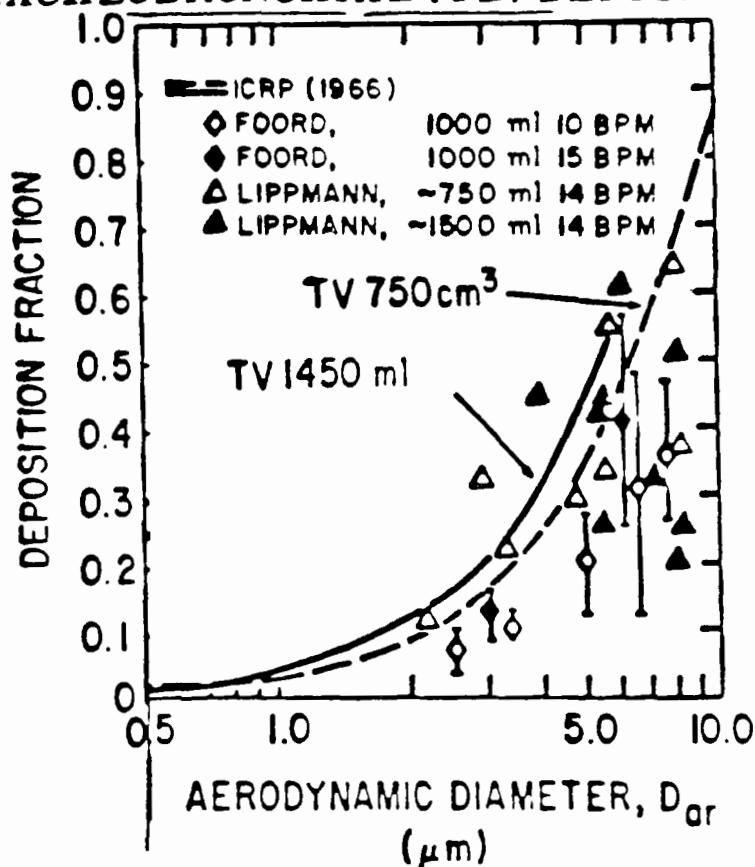
FIGURE 11-9. Selected data (Foord et al., 1976; Lippmann and Albert, 1969) reported for tracheobronchial (TB) deposition*of monodisperse aerosols inhaled through the mouth by people are compared with predicted values calculated by the ICRP Task Group on Lung Dynamics (Morrow et al., 1966) (from Raabe, 1979).
*(expressed as fraction of particles entering trachea)

PULMONARY (P) DEPOSITION FOR MOUTH BREATHING

DEPOSITION FRACTION

ICRP—FOR PARTICLES ENTERING TRACHEA (1966)
● ALTSHULER, 500 ml 15 BPM (1967)
▲ GEORGE, 760 ml 11 BPM (1967)
◇ FOORD, 1000 ml 15 BPM (1976)
■ SHANTY 1140 ml 18 BPM (1974)
△ LIPPMANN, 1400 ml 14 BPM (1969)

TV 1450 ml

TV 750 ml

PHYSICAL DIAMETER (μm)

AERODYNAMIC DIAMETER, D_{or} (μm)
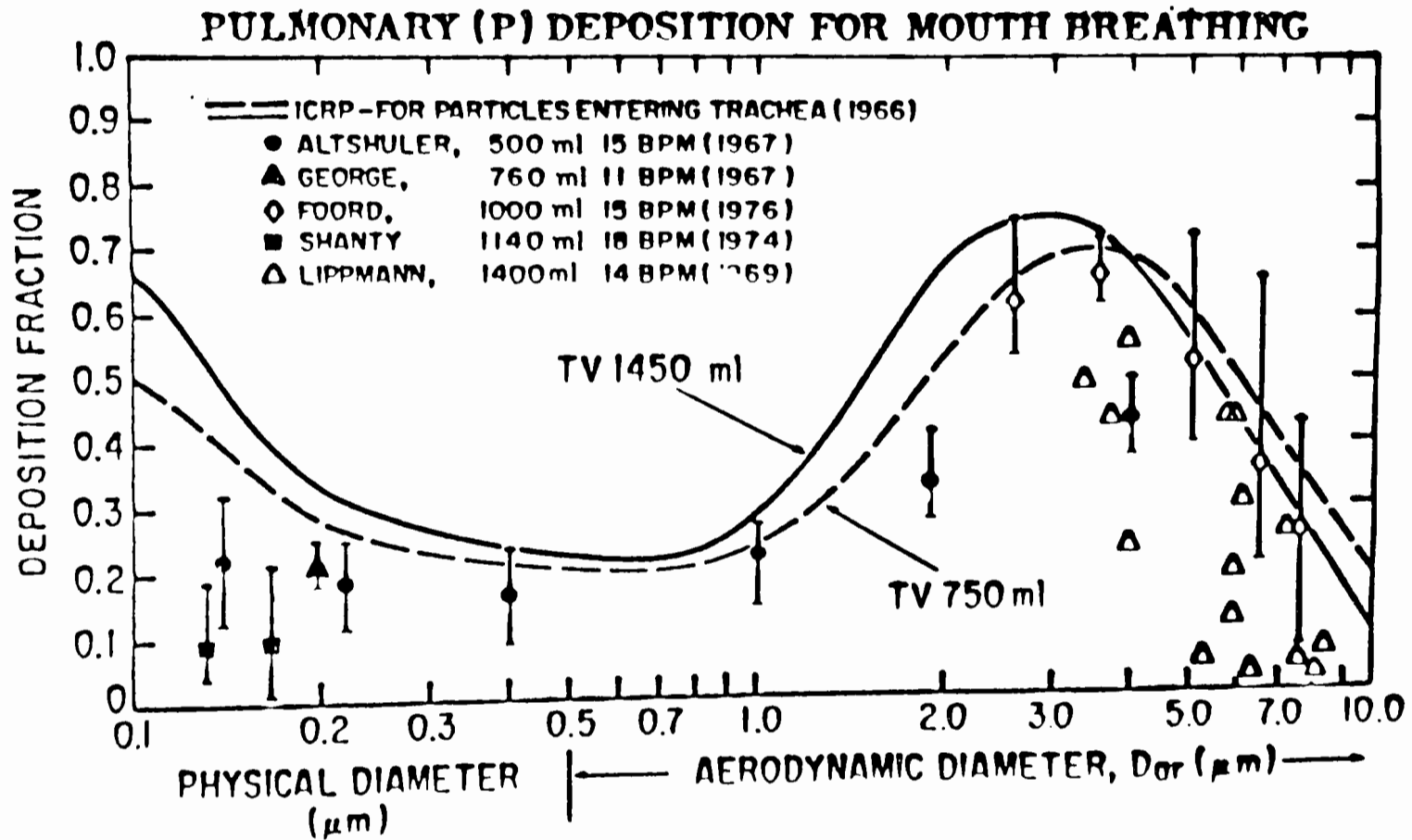
FIGURE 11-10. Selected data (Altshuler et al., 1967; George and Breslin, 1967; Foord et al., 1976; Shanty, 1974; Lippmann and Albert, 1969) reported for pulmonary (P) deposition of monodisperse aerosols inhaled through the mouth by people are compared with predicted values calculated for tidal volumes (TV) of 750 ml and 1450 ml by the ICRP Task Group on Lung Dynamics (Morrow et al., 1966) (from Raabe, 1979).

the lowest deposition changed from 0.66 µm at TV 250 ml to 0.46 µm at TV 2000 ml. Breathing at TV 1000 ml changed this minimum deposition size from 0.58 µm at 30 BPM to 0.46 µm at 3.75 BPM. Hence, the particle size of minimum deposition was reduced with increased residence time of particles in the lung and the net deposition for all particles was increased. In fact, as the breathing rate went from 3.75 BPM to 30 BPM, the deposition at 1 µm D_{ar} went from 0.08 to 0.4, an increase of a factor of 5.

When Heyder et al. (1975) kept the breathing frequency constant while changing the flow rate, the deposition for particles smaller than 1 µm remained essentially unchanged, indicating that inertial impaction was of little importance in the deposition of submicrometer aerosols. On the other hand, the deposition of particles larger than 1 µm D_{ar} was enhanced at high flow rates, indicating the influence of inertial impaction on the deposition of larger particles.

Alveolar and total deposition of particles for mouth breathing was evaluated by Heyder et al. (1980) as a function of their aerodynamic diameter for two breathing patterns. Keeping the mean volumetric flow rate constant at 250 ml/sec and allowing the mean residence time to vary between 2 and 8 sec, they observed a decrease of the particle size for maximum alveolar deposition from 4 mm to 3.2 mm as the mean residence time increased. With this mean flowrate particles smaller than about 2.3 mm aerodynamic diameter were exclusively deposited in the alveolar region, indicating their inertia was not sufficiently high for impaction loses. When the mean flow rate was increased to 750 ml/sec and the mean residence time was 2 sec, particles with an aerodynamic diameter smaller than about 1.5 mm were exclusively deposited in the alveolar region of the respiratory tract. From the data of Heyder et al.

(1980) it can also be seen that alveolar deposition and the particle size for maximum deposition decrease as the mean flow rate increases. In the above studies the maximum of alveolar deposition was shifted from 3.5 mm to 3 mm in aerodynamic diameter.

Considering the limitations of the models used by the ICRP Task Group on Lung Dynamics (Morrow et al., 1966) and the inherent variability between individuals, their results for deposition of insoluble hydrophobic particles provide generally useful guidance for environmental assessment purposes, especially since they do not underestimate deposition fraction for the chosen respiratory conditions. These models may represent other breathing conditions as well, considering that individuals can exhibit differences in deposition depending on the physiological parameters and the influence of cigarette smoking and lung disease alterations (Lippmann, 1977).

When aerosols are inhaled through the nose the relatively efficient filtration action of the nasopharyngeal region eliminates the passage of particles larger than 10 μm D_{ar} to the lung and markedly limits the pulmonary deposition of particles between 2 μm D_{ar} and 10 μm D_{ar} (Figures 11-3-11-5). An active person breathing at 15 BPM and a tidal volume of 1450 ml (Figure 11-4) would be expected to deposit in the deep lung about 35 percent, 25 percent, 10 percent, and close to 0 percent of inhaled aerosols of unit density spherical particles of 0.2 μm, 1.0 m, 5.0 μm, and 10 μm, respectively, during nose breathing. Likewise, the tracheobronchial deposition would be expected to be about 2 percent, 3 percent, 6 percent, and 0 percent for these sizes, respectively.

Mouth breathing markedly alters the deposition of inhaled particles in humans (Lippmann, 1977; Miller et al., 1979; Heyder et al., 1980) in that

larger particles can enter both the tracheobronchial region (Figure 11-9) and the pulmonary region (Figure 11-10). The deposition in the deep lung would be expected to be about 35 percent, 30 percent, 55 percent, and 10 percent for inhaled aerosols of unit density spherical particles of 0.2 μm, 1 μm, 5 μm, and 10 μm, respectively, for a person breathing at 15 BPM with a tidal volume of 1450 ml. This demonstrates the greater importance of the pulmonary depositions of larger particles during mouth breathing. In addition, some larger particles that normally are all collected in the nasopharyngeal region during nose breathing may pass the glottis and deposit in the upper part of the tracheobronchial tree during mouth breathing (Figure 11-9; Morrow et al., 1966; and Lippmann, 1977). Lippmann (1977) calculated that about 10 percent of particles as large as 15 μm unit density spheres might enter the tracheo-bronchial tree during mouth breathing (Q = 30 liter/minute). The rest and larger particles are deposited in the mouth and oral pharynx. Miller et al. (1979) used this finding in suggesting that an "inhalable" particle sampling procedure consider particles as large as 15 μm aerodynamic diameter, capable of penetrating to the tracheobronchial region.

Since much information concerning inhalation toxicology is collected with beagles or small rodents, it is important to consider the comparative regional deposition in these experimental animals. Cuddihy et al. (1973) measured the regional deposition of polydisperse aerosols in beagles with TV about 170 ml at about 15 BPM and expressed the results as mass deposition percentage versus mass median aerodynamic resistance diameter ($MMAD_{ar}$) that ranged from 0.42 μm to 6.6 m with geometric standard deviation σ_g = 1.8. These results are summarized in Figure 11-11 and compared with the Task Group Values for man with TV 1450 ml, integrated to account for a σ_g = 1.8.
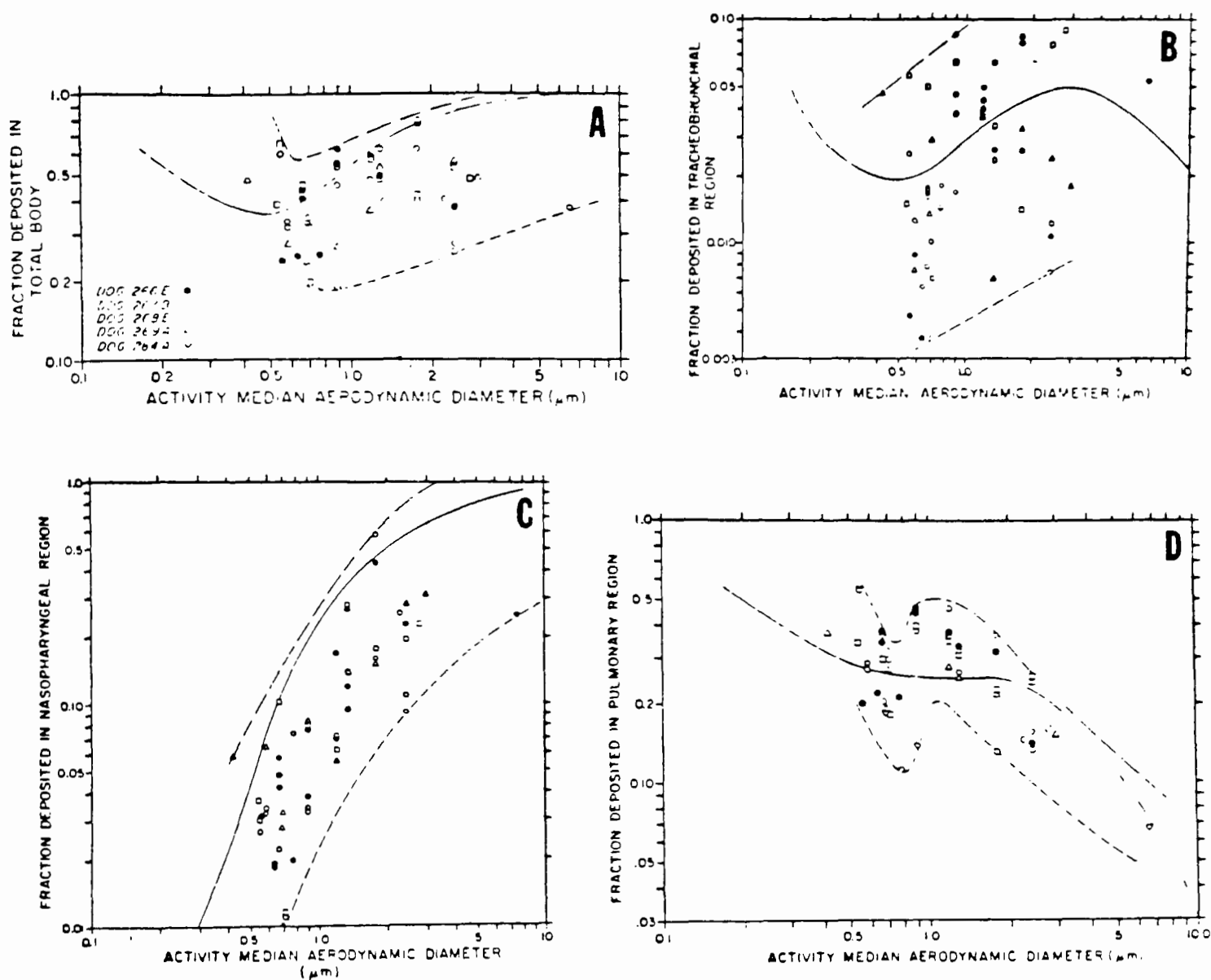
FIGURE 11-11. Deposition of inhaled polydisperse aerosols of lanthanum oxide (radiolabeled with ^{140}La) in beagle dogs exposed in a nose-only exposure apparatus showing (a) the deposition fraction in the total dog, (b) the deposition fraction in the tracheobronchial region, (c) the deposition fraction in the nasopharyngeal region, and (d) the deposition fraction in the pulmonary region (from Cuddihy et al., 1973). The dashed lines indicate the range of observed values.

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Raabe et al. (1977) have measured the regional deposition of 0.1 μm to 3.15 m D_{ar} monodisperse aerosols in rats (TV about 2 ml, 70 BPM) and Syrian hamsters (TV about 0.8 ml at about 40 BPM). Their results are summarized in Figure 11-12. The deposition of particles 3 μm D_{ar} or less in small rodents is about one-half the ICRP (Morrow et al., 1966) estimates for humans, although some comparable deposition values have been reported for humans by Heyder et al. (1975). The distributions among the respiratory regions during nose breathing follow a pattern that is very similar to human regional deposition during nose breathing. The use of rodents or dogs in inhalation toxicology research for extrapolation to humans does not seem to entail significant problems associated with differences in regional deposition of inhaled aerosols based on particle sizes less than 3 μm D_{ar} for inert insoluble particles during nose breathing.

Deposition calculations usually group lung regions without regard to nonuniformity of the pattern of deposited particles within the regions. Schlesinger and Lippmann (1978) found that nonuniform deposition in the trachea could be caused by the air flow disturbance of the larynx. Bell and Friedlander (1973) and Bell (1978) observed and quantified particle deposition as it occurs at a single airway bifurcation and found it to be highly nonuniform and heaviest around the carinal arch. Raabe et al. (1977) observed that the relative lobar pulmonary deposition of monodisperse aerosols was up to 60 percent higher in the right apical lobes of small rodents (corresponding to the human right upper lobe) and that the difference was greater for 3.15 μm and 2.19 μm D_{ar} particles than for smaller particles. In addition, Raabe et al. (1977) showed that these differences in relative lobar deposition were related to the geometric mean number of airway bifurcations between trachea
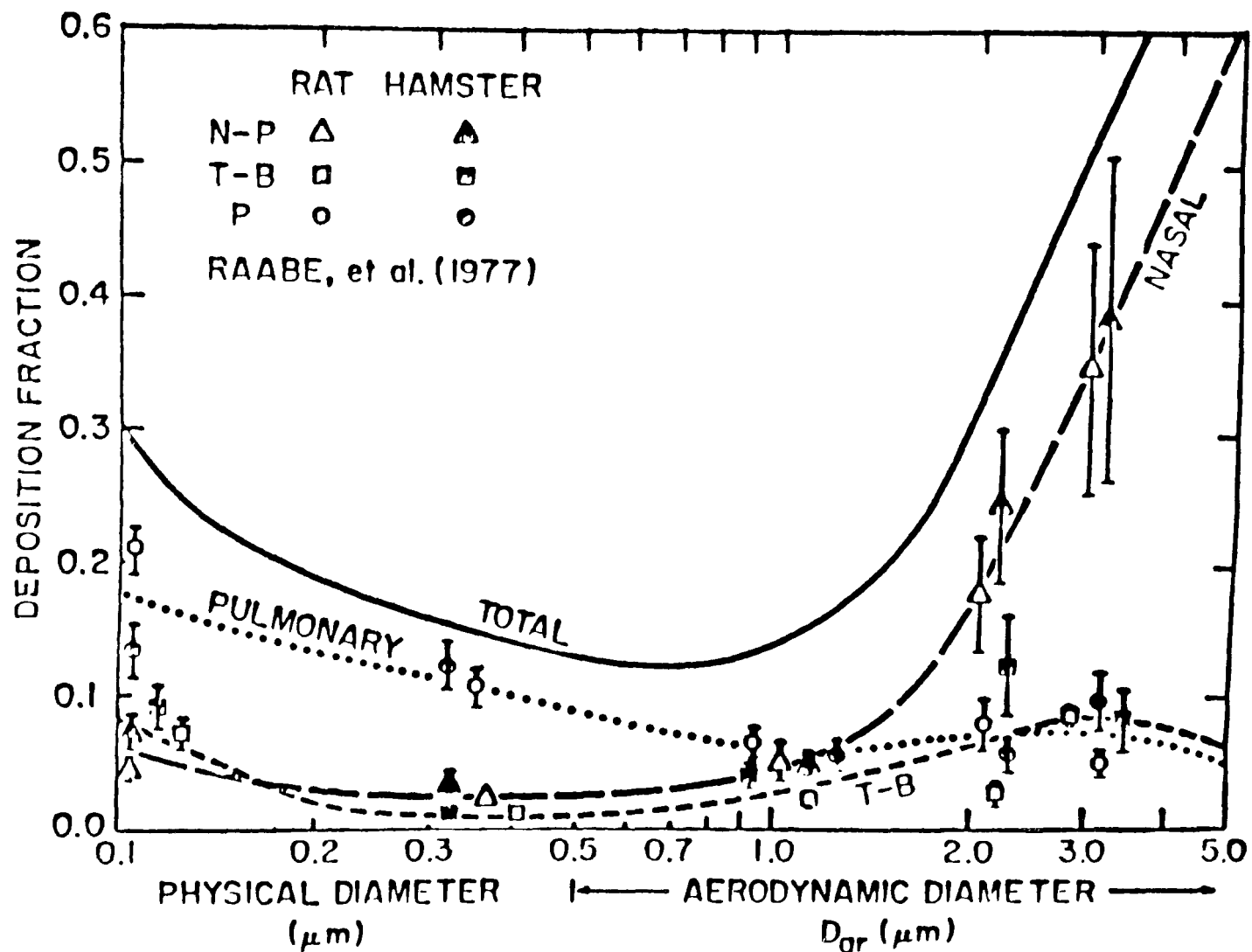
FIGURE 11-12.   Deposition of inhaled monodisperse aerosols of fused aluminosilicate spheres in small rodents showing the deposition in the nasopharyngeal (nasal) region, the tracheo-bronchial (T-B) region, the pulmonary region and in the total respiratory tract based upon Raabe et al. (1977).

and terminal bronchioles in each lobe for rats and hamsters. Since similar morphometric differences occur in human lungs, nonuniform lobar deposition should also occur. Schlesinger et al. (1977) found nonuniform deposition in the lobar branches of a hollow model of the tracheobronchial airways with enhanced carinal deposition and were able to demonstrate a correlation of higher lobular deposition and the reported incidence of bronchogenic carcinoma in different human lung lobes.

11.2.2 Soluble, Deliquescent, and Hygroscopic Particles

Most deposition studies and models tend to focus on insoluble and stable test aerosols whose properties do not change during the course of inhalation and deposition. However, environmental aerosols usually consist of deliquescent or hygroscopic particles that may grow in the humid respiratory airways. That growth will affect deposition (Scherer et al., 1979). The ICRP Task Group on Lung Dynamics (Morrow et al., 1966) addressed this problem by considering the equilibrium diameter for deliquescent materials at relative humidities near, but less than, 100 percent. However, the residence times in the respiratory tract may be too short for large particles to reach their equilibrium size (Nair and Vohra, 1975; Charlson et al., 1978). Also, environmental aerosols may consist of a combination of components, including complex mixtures that may not behave like pure substances.

Ferron (1977) has described the factors affecting soluble particle growth in the airways during breathing. Basically, his results suggest that particles 1 μm in aerodynamic diameter will increase by a factor of three to four in aerodynamic diameter during passage through the airways. Nasopharyngeal, tracheobronchial, and pulmonary deposition of the enlarged particles would be greater than the deposition expected for the original particle size. Submicronic particles, including those as small as 0.05 μm, will grow by a factor

of two in physical diameter, with relatively little effect on deposition; particles smaller than 0.3 μm D_{ar} may even have some reduced pulmonary deposition with growth because of reduced diffusivity.

Acid sulfates and sulfuric acid formed by the oxidation of SO_2 in the environment may be reduced in acidity by naturally occurring ammonia (NH_3) to form ammonium sulfate ($(NH_4)_2SO_4$ and ammonium bisulfate (NH_4HSO_4). Larson et al. (1977) made short-term measurements that suggest that endogenously generated ammonia (NH_3) gas in the human airways may rapidly and completely neutralize sulfuric acid aerosols in the concentrations that are normally encountered in the ambient environment. Further, it is useful to note that ammonia is generated from food and excreta in inhalation chambers used to expose experimental animals to sulfuric acid (H_2SO_4) so that some neutralization of sulfuric acid in these test atmospheres may also occur.

Because of SO_2 oxidation, most environmental aerosols have a major ammonium sulfate ($(NH_4)_2SO_4$ or NH_4HSO_2 constituent and possibly some hygroscopic H_2SO_4, especially in the submicrometer size range. Growth of these particles will occur in the respiratory airways during breathing. This growth involves chemical dilution of the electrolyte or acid with absorbed water. A particle growing a factor of three in physical diameter must absorb a volume of water equal to 26 times its original particle volume. Also, the increased size will enhance losses by inertial mechanisms, including impaction in the upper airways A 1 μm D_{ar} particle of H_2SO_4 or $(NH_4)_2SO_4$ may grow to nearly 3 μm D_{ar} in the nasal region, increasing both nasal deposition and tracheobronchial deposition by a factor of 2 or more over the deposition expected for a 1 μm D_{ar} particle, with the net result that pulmonary deposition is reduced (see Figure 11-3). Particle growth in the airways may be a protective mechanism, since (a) the

deposition in the upper airways is probably less potentially harmful than in the pulmonary regions; and (b) the reduced electrolyte or acid concentration will probably reduce the level of local toxicity.

11.2.3 Surface Coated Particles

Some environmental particles may consist of a relatively insoluble core coated with various chemical species including metallic salts, $(NH_4)_2SO_4$, $(NH_4)HSO_4$, H_2SO_4, organic compounds including polynuclear aromatic hydrocarbons (PAH), and small particles of other sparingly soluble materials. Some surface growth due to water adsorption may occur in the airways but will be limited by the availability of deliquescent or hygroscopic components on the particle surface. In general, the increase in aerodynamic diameter that may occur would be much less for coated particles than for more pure forms.

Important examples of coated particles are the fly ash, soot, or other residual solid particle aerosols released to the environment by fossil fuel combustion. The exact chemical form of the relatively inert core of these particles will vary from nearly pure fused aluminosilicate particles produced during the combustion of coal to carbonaceous or metal oxide particles produced by internal combustion engines. Volatile trace metal compounds and organic compunds condense on these particles during the cooling of the effluent stream in the power plant smoke stack or engine exhaust line and during release to the atmosphere. In addition, gases such as SO_2 can adsorb to the particle surfaces or finer aerosols can aggregate onto the particle surfaces. If these processes are diffusion limited, the condensation and coagulation will be quantitatively proportional to particle diameter for particles larger than 0.5 µm D and to particle surface for smaller particles. In either case the

fractional mass of the surface coating material will be greater on smaller particles than on larger ones. In other words, the condensed material coats the particles with a relative mass concentration that increases with decreasing particle size. Important elements such as Se, Cd, As, V, Zn, Sb, and Be have been found to exhibit this size dependence in coal fly ash aerosols (Davison et al., 1974; Natusch et al., 1974; Gladney et al., 1976). Therefore, the growth of such surface-coated particles in the airways should be expected to be much less than for pure deliquescent particles. Such growth should be only a minor influence on the deposition of large particles. On the other hand, small submicrometer coated particles may be principally composed of a deliquescent surface coating and subject to more extensive relative growth. (See also Chapters 3, 5, and 6.)

11.2.4 Gas Deposition

The major factors affecting the uptake of gases in the respiratory tract are the morphology of the respiratory tract, the physicochemical properties of the mucous and surfactant layers, the route of breathing and the depth and rate of airflow, physicochemical properties of the gas, and the physical processes which govern gas transport. A brief discussion of these factors serves to illustrate their general role in the deposition of gases and convey some aspects specific to the uptake of SO_2.

The complex morphological structure of the human respiratory tract has been discussed in section 11.1.3. The nature and structure of the respiratory tract in man and animals critically influences the deposition of gases since the relative contribution of gas transport processes varies as a result of this morphology. The human tracheobronchial tree is more symmetric, with

respect to diameter ratios and branching angles, than that of dogs, rats, or hamsters, but is closest to that of the dog (Phalen et al., 1974). The structure of the tracheobronchial tree is variable from species to species, from lobe to lobe within a given lung, and from one depth to another in the lung.

The amount of a gas acting on a given area of the respiratory tract is reflected by the airway concentration at that level. In general, the more soluble a gas is the higher it is removed in the respiratory tract. However, the resultant tissue dose and observed toxicity do not necessarily correlate with this removal. The gas must first come in contact with the mucous or surfactant layer lining the airway, depending upon which level of the respiratory tract the gas has reached. Chemical reactions with components in these layers can occur, thereby increasing the total absorption of the gas, but can also reduce the amount of the gas penetrating to the tissue. Thus, knowledge of the biochemical composition of the mucous and surfactant layers is needed to identify components of these fluids which may react with the gas, influencing deposition and the resulting toxicity

Various reviews are available on the physical and chemical properties of bronchial secretions (Barton and Lourenco, 1973; Charman et al., 1974) on the structure and function of tracheobronchial mucosa (Kilburn, 1967). on the surface lining of lung alveoli (Pattle, 1965), and on the chemical mechanisms of action of gases, such as O_3 and NO_2, in biological systems (Menzel, 1976).

Although respiratory surface area differs greatly among various vertebrate species, the amount of surfactant correlates well with the amount of dipalmitoyl lecithin in lung parenchyma and with alveolar surface area (Clements et al , 1970 1969). Dipalmitoyl lecithin has been found to constitute 90-95 percent of

recoverable lipid (Balis et al., *1971* ~~1970~~; Hurst et al., 1973). Thus, the alveolar region is normally lined with saturated lecithin and is mostly free of other lipids, proteins and carbohydrates. Ecanow et al. (1967) suggested a possible role of alveolar surfactants in the uptake of inhaled gas related to the formation upon inspiration of micelles which can readily solubilize non-polar gases or inhaled anaesthetics. With release of pressure during expiration, the micelles return to the subphase, disaggregate, and release the anaesthetic or molecular gases for absorption by the blood stream.

Physicochemical properties of a gas relevant to respiratory tract deposition are its solubility and diffusivity in mucus, surfactant, and water and its reaction-rate constants in mucus, surfactant, water, and tissue. Henry's law relates the gas-phase and liquid-phase interfacial concentrations and is a function of temperature and pressure. The solubility of most gases in mucus and surfactant is not known. However, Henry's law constant for many gases in water is known, the value for SO_2 being 59.7 mole fraction in air per mole fraction in water at $37^{o}C$ and one atmosphere of pressure (Washburn, 1928). The diffusivities of most gases in mucus, surfactant, tissue, and water are also unknown, thereby complicating efforts to model gas uptake in the respiratory tract. Diffusivity may be much smaller in a viscous mucous fluid than in water, but ciliary activity effectively increases the diffusion coefficient. In the general case, transport rates of the gas across the mucus-tissue interface, tissue layer, and the tissue-blood interface are needed to fully understand the absorption and desorption of gases in the respiratory tract. However, knowledge on the biochemical mechanisms of action of a given gas may enable one or more of these compartments to be ignored.

The major processes affecting gas transport involve convection, diffusion, and chemical reactions. The bulk movement of inspired gas in the respiratory tract is induced by a pressure gradient and is termed convection. Molecular diffusion due to local concentration gradients is superimposed on this bulk flow at all times, with the transport of the gas being accomplished by the coupling of these two mechanisms. Convection can be decomposed into the processes of advection and eddy dispersion. Advection is the horizontal movement of a mass of air that causes changes in temperature or in other physical properties, while eddy dispersion occurs when air is mixed by turbulence so that individual fluid elements transport the gas and generate the flux. Due to the morphology of the respiratory tract and respiratory airflow patterns, the relative contribution of the various processes to transport and deposition is a function of location.

During the respiratory cycle, the volumetric flow rate of air varies from zero up to a maximum (dependent upon tidal volume, breathing frequency, and breathing pattern) and then back to zero. Usually expiration is longer than inspiration, and intervening pauses may occur. The net result of these variables is to impart complicated flow patterns and turbulence in some portions of the respiratory tract.

The complex anatomical structure of the nose is well suited for humidification, regulation of temperature, and removal of many particles and gases. The air deflecting channels of the posterior nares cause impaction of large airborne particles and create turbulent air flow conditions. As the cross-sectional area expands beyond the entrance flow separation occurs. This results in turbulence and eddies which continue as the air traverses the passages around the turbinates. Proctor and Swift (1971) studied the flow of

water through a clear plastic model of the walls of the nasal passages and constructed charts of the direction and linear velocity of airflow in the model. With a steady inspiratory flow of 0.4 l/sec, they found that the linear inspiratory velocity at the nasal entrance reached at least 4.5 - 5 m/sec and at most 10 - 12 m/sec, values which are significantly greater than the 2 m/sec peak linear velocity in the tracheobronchial tree during quiet breathing.

Schroter and Sudlow (1969) studied a wide variety of flow patterns and rates in large scale symmetrical models of typical tracheobronchial tree junctions. For both inspiration and expiration and irrespective of entry profile form, they observed secondary flows at all flow rates in their single bifurcation model. When a second bifurcation was added a short distance downstream of the first, the entering flow profile was found to influence the resulting flow patterns. Also different results were obtained depending upon the plane in which the second bifurcation was located relative to the first bifurcation.

Olson et al. (1973) studied convective airflow patterns in cast replicas of the human respiratory tract during steady inspiration. They showed that the effect of the larynx is such that flow patterns typical of smooth bifurcating tubes do not occur until the lobar bronchi are reached. Small eddies were observed as far down as the sublobar bronchi with 200 ml/s flows in the trachea. In man the glottis of the larynx acts as a variable orifice since the position of the vocal cords changes. During inspiration a jet of turbulent air enters the trachea and is directed against its ventral wall imparting additional turbulence over that associated with the corrugated walls and length of the trachea.

In the tracheobronchial tree with its many branches, changes in caliber and irregular wall surfaces, it is difficult to establish exactly where flow is laminar, turbulent, or transitional. Viscous forces predominate in laminar flow and streamlines persist for great distances, while with turbulent flow there is rapid and random mixing downstream. As the flow rate increases, unsteadiness develops and separation of the streamlines from the wall can occur leading to the formation of local eddies. This type of flow is termed transitional. The Reynolds number, the ratio of inertial to viscous forces, is useful in describing whether flow is laminar or turbulent. Values between approximately 2000 and 4000 are ascribed to transitional flow with smaller Reynolds numbers reflecting laminar flow and larger ones turbulent flow. Fully developed laminar flow probably only occurs in the very small airways; flow is transitional in most of the tracheobronchial tree, while true turbulence may occur in the trachea, especially during exercise when flow velocities are high (West, 1977).

Turbulence will gradually decay in any branch in which the Reynolds number is less than 3000 (Owen, 1969). Decays of 15 percent, 16 percent, and 10 percent are predicted to occur in the first three generations of bifurcation respectively, using the theory of Batchelor (1953) for the change in turbulent energy at regions of rapid flow contraction. While these decay calculations neglect the possible effects of the strong secondary flows generated at the bifurcation, their validity is supported by the data of Pedley et al.(1971) which shows that the boundary layer remains laminar in the daughter-tube for Reynolds numbers in the parent-tube up to at least 10,000. Hence, the turbulent eddies are localized in the core.

Flow oscillations in the segmental bronchi attributed to beating of the heart are only detectable during breathholding or during pauses between inspiration and expiration (West, 1961). A peak oscillatory flow rate of 0.5 l/min was measured, which is about 20 percent of the peak flow rate in the segmental bronchi during quiet breathing. Gas mixing is improved by these oscillations.

Diffusion in the lung normally involves at least three gases and the governing laws are Stefan-Maxwell equations rather than the more familar Fick's law (Hirschfelder et al., 1954). In a multicomponent mixture, the transfer of one component is a function of its own concentration as well as of the concentration of the other components; in the binary case diffusivity is dependent on the total pressure and temperature of the mixture, the molecular weights of the two species and is independent of the composition of the mixture. Toor (1957) showed that a ternary gas mixture may exhibit one of the following phenomena: 1) diffusion barrier - when a component gas diffusion rate is zero even though its concentration gradient is not zero, 2) osmotic diffusion - when a component gas diffusion rate is not zero even though its concentration gradient is zero, and 3) reverse diffusion - when a component gas diffuses against the gradient of its concentration. An exact solution to the Stefan-Maxell equation is extremely difficult to obtain and in respiratory physiology, diffusion in the lung has always been assumed mathematically to be binary. Chang et al. (1975) used a simple gas film model to examine differences between binary and ternary diffusion. Their results indicate that for air breathing under normal conditions, gas transport diffusion problems in the lungs may be examined using binary laws. However, significant errors may occur if binary laws are used to examine diffusion involving gases, such as helium, or high pressures.

In studying the nature of gas mixing in the tracheobronchial tree and its effects on gas transport there have been numerous modeling efforts utilizing an approach in which all pathways from the mouth or trachea to the alveoli are combined into one effective pathway whose cross-sectional area is equal to the summed cross-sectional area of all bronchial tubes at a given distance from the mouth or trachea (Davidson and Fitz-Gerald, 1974; Paiva, 1973; Pedley, 1970; Yu, 1975; Scherer et al., 1972). In this formulation, the mechanical mixing imparted by tube bifurcations, turbulence, and secondary flows and the mixing due to molecular diffusion are represented by the function form of the effective axial diffusion coefficient (Scherer et al, 1975). Thus, this coefficient of diffusion incorporates the effect of axial convection. The effective axial diffusion coefficient is a constant equal to the molecular diffusivity only in the alveolar region where gas velocity is very small. However, in other regions of the tracheobronchial tree, the local average gas velocity and the tube geometry will jointly determine the value. Various functional forms have been proposed in the studies cited above for an appropriate expression for the effective axial diffusion coefficient.

Utilizing two dimensionless parameters, Wilson and Lin (1970) showed that pure convection is the dominant mechanism of gas transport through the 7th generation of branching in the human lung. Based upon their analyses they suggested that roughly between generations 8 and 12 Taylor laminar diffusivity (Taylor, 1953) for parabolic flow in a straight tube would apply. For this type of diffusion, radial diffusion and axial convection are coupled to produce an effective block flow with axial diffusion. Block flow convection with axial diffusion dominates in generations beyond the 12th. Turbulent pipe flow diffusivity (Taylor, 1954) has been used in the case where flow is turbulent

over part of the bronchial tree (Davidson and Fitz-Gerald, 1974; Pedley, 1970).

By constructing individual streamline pathways from the trachea to the alveoli, Yu (1975) derived an expression for the effective axial diffusion coefficient which equalled the algebraic sum of the molecular diffusion coefficient and an apparent diffusion coefficient. The apparent diffusion coefficient arises from two independent mechanisms: 1) the nonhomogeneous ventilation distribution in the lung, and 2) the interaction of nonuniform velocity and concentration profiles due to Taylor's mechanism in individual airways. Using an average standard deviation of airway lengths based upon the data of Weibel (1963) and various flow theory limiting values, Yu (1975) demonstrated that Taylor diffusion is everywhere in the tracheobronchial tree dominated by the apparent diffusion due to nonhomogeneous distribution of ventilation, rather than being a major mechanism for gas transport in some airways as claimed by Wilson and Lin (1970).

In all of the previously described studies the diffusivity expressions used assume fully developed flow in straight pipes to describe gas mixing, a condition not truly applicable over most of the tracheobronchial tree. Since flow patterns at tube bifurcations are different for inspiration and expiration (Schroter and Sudlow, 1969), the mixing process and hence the effective diffusivities are different. To obtain diffusivities applicable to the tracheo-bronchial tree, Scherer et al. (1975) used airway lengths and diameters from Weibel (1963) and branching angles from Horsfield and Cumming (1967) to construct a five-generation symmetrical branched tube model and to experimentally determine effective axial diffusivity for laminar flow of a gas as a function of mean axial velocities up to 100 cm/s in the zeroth generation tube. The

relationship was approximately linear and diffusivities for expiration were about one-third those for inspiration. The values obtained by Scherer et al (1975) for steady flow can be applied to oscillating flow in the tracheo-bronchial tree provided the oscillating flow can be considered quasi-steady, i.e., steady at any instant of time. This condition should hold in the first ten generations whenever flow rates are approximately greater than 0.1 l/s (Jaffrin and Kesic, 1974).

As computational models of gas transport, such as that of Pack et al. (1977), become more refined to include effective diffusion, fluctuating lung dimensions, etc., one can obtain a better understanding of the effects of various factors affecting the transport and removal in the lung of gases, such as SO_2. The deposition of SO_2 in the respiratory tract depends upon the transfer of the gas from the air to the liquid coating or mucus membrane surfaces of the airways and subsequent reaction of the sulfite anion with constituents of body fluids or cells. Since SO_2 dissolves readily in water at or near neutral pH, the moist walls of the airways should readily collect SO_2 and diffusion to the surface of the airways from inhaled air should be an irreversible and efficient process (Balchum et al., 1960). The rate at which SO_2 comes in contact with the walls of the airways is therefore controlled by the diffusion (Aharonson, 1976).

The theoretical diffusivity of SO_2 at body temperature (sea level) is 0.20 cm^2/sec. This diffusivity in combination with high solubility in body fluids is responsible for high deposition in the nasopharyngeal region and upper airways. Frank et al. (1969) surgically isolated the upper airways of anesthetized dogs with separate connections for the nose and mouth. Sulfur dioxide labeled with ^{35}S was passed through this isolated nasopharyngeal

region for 5 min, and nearly complete removal was observed for concentrations of 2.62 mg/m^3 to 131 mg/m^3 (1 to 50 ppm) at a flow rate of 3.5 liter/minute through the nose. Uptake of the mouth averaged more than 95 percent at 3.5 liter/minute with SO$_2$ levels of 2.62 mg/m^3 and 26.2 mg/m^3 (1 and 10 ppm). Strandberg (1964) made similar measurements for rabbits with tracheal cannulas He observed 95 percent absorption in the respiratory tract at 524 mg SO$_2$/mg^3 (200 ppm) but at 0.13 mg SO$_2$/m^3 (0.05 ppm) absorption was lowered to about 40 percent during inspiration, demonstrating an apparent concentration effect. Absorption of SO$_2$ at expiration was 98% in the 524 mg/m^3 (200 ppm) studies compared to 80% for experiments using 0.13 mg/m^3 (0.05 ppm). Dalhamn and Strandberg (1961) found that rabbits exposed to 262-786 mg SO$_2$/m^3 (100 - 300 ppm) absorbed 90% - 95% of the SO$_2$. They noted that absorption was to some extent dependent upon the technique whereby tracheal air samples were obtained.

Corn et al. (1976) studied the upper respiratory tract deposition of SO$_2$ in cats and computed mass transfer coefficients which can be used with surface area data to calculate the amount of SO$_2$ removed in various parts of the respiratory tract. Utilizing a theoretical approach, their own empirical data, and information available from the literature, Aharonson et al. (1974) examined the effect of respiratory airflow rate on nasal removal of soluble vapors. The only assumption made regarding factors affecting local uptake was that there was no back pressure in the blood. Hence, whether the rate of uptake is limited by diffusion through the gas phase, diffusion through the tissue, chemical reactions in the tissue, or local blood flow in the tissues, the analytical approach is valid, as long as the rate of uptake is proportional to the gas phase

pressure of the vapor. Their analysis for acetone, ether, ozone, and sulfur dioxide showed tha. the uptake coefficient, which defines the average flux of soluble vapors into the nasal mucosa per gas-phase unit partial pressure, increases with increasing airflow rate.

In experiments described by Brain (1970) there was a 32-fold increase in the amount of SO_2 present in the trachea of dogs when the air flow-rate was increased 10-fold. However, had the uptake coefficient not changed with the flow rate, Aharonson et al. (1974) pointed out that penetration would have increased 500-fold. If the uptake coefficient for SO_2 is concentration dependent, as the data of Strandberg (1964) suggests, increasing airflow rate may increase uptake due to higher levels of SO_2 being present along the center of the inspired airstream for the same input levels.

The deposition and clearance of sulfur dioxide also has been studied in in vitro and model systems. In a model of the tracheobronchial airways lined with a simulated airway fluid (bovine serum albumin dissolved in saline), it was observed that SO_2 was primarily absorbed in the upper third of the simulated airway with only a small fraction of the SO_2 reaching the simulated alveolar or bronchiolar regions (Kawecki, 1978).

Uptake and release of SO_2 in the nose of human subjects breathing 42.2 mg/m^3 (16.1 ppm) through a mask during a 30 minute exposure period was studied by Speizer and Frank (1966). During inspiration the concentration of SO_2 had dropped 14% at a distance 1-2 cm within the nose and was too small to detect at the pharynx with the analytical method used. Expired gas in the pharynx was also virtually free of SO_2, but

in its transit through the nose the expired air acquired SO_2 from the nasal mucosa. The expired SO_2 concentration at the nose was 5.2 mg/m^3 (2.0 ppm), or about 12% of the original mask concentration. In most subjects the nasal mucosa continued to release small amounts of SO_2 during the first 15 minutes after cessation of the SO_2 exposure.

Melville (1970) exposed humans to SO_2 levels ranging from 4 mg/m^3 to 9 mg/m^3 (1.5 ppm to 3.4 ppm) for periods up to 10 min. Extraction of SO_2 during nose breathing was significantly greater (p < 0.01) than during mouth breathing (85% versus 70%, respectively) and was independent of the inspired concentration of SO_2. Andersen et al. (1974) found that at least 99% of 65.5 mg SO_2/m^3 (25.0 ppm) was absorbed in the nose of subjects during inspiration. Values obtained after one to three hours of exposure were not different from those obtained after four to six hours of exposure, thereby indicating there was no saturation effect during this period of time.

11.2.5 Aerosol-Gas Mixtures

Gases readily diffuse to the surface of aerosol particles and can participate in a variety of surface interactions. Surface absorption related to temperature and gaseous vapor pressure occurs if residence sites for the gas molecules are present on the particles. Such physical adsorption can be described by the Longmuir or more complex isotherms (Gordieyeff, 1956). In addition chemical adsorption can occur involving chemical transformations and bonds that enhance transfer of gaseous materials to the particulate phase. Such transformations can include both inorganic and organic vapors (Natusch, 1978). In addition aerosols of liquid droplets can collect and carry volatile

are dissolved in the droplets. In these cases, aerosols can serve as vectors carrying molecules of various substances deeper into the airways than would occur if the substances were in their gaseous forms.

Since SO_2 is found in the gas phase in various environmental aerosols, the reactions that occur between SO_2 and aerosols, and the gas-to-particle conversions that may occur, can greatly influence the regional deposition of biologically active chemical species. Since SO_2 is highly soluble in water, droplet aerosols, including those formed by delinquescent particles, will collect dissolved SO_2 and can carry the resulting sulfurous acid deep into the lung. The presence of certain sulfite species formed by such reactions in environmental aerosols has been suggested (Eatough et al., 1978). SO_2 is also known to be converted to sulfate by reactions catalyzed by some aerosols, including those containing iron or manganese. The simple adsorption of SO_2 to aerosol surfaces by chemical reaction may lead to the aerosol's acting as a vector for transporting SO_2 to the deep lung. These types of SO_2-aerosol behaviors are apparently responsible for the so-called synergism in biological response found in experiments using SO_2 in combination with certain aerosols (Goetz, 1960; Frank et al., 1962). However, in a study in which rabbits were exposed to a mixture of SO_2 and carbon particles that adsorbed SO_2 on their surface, the presence of carbon particles in the SO_2 mixture did not affect absorption in the respiratory tract to any appreciable extent (Dalhamn and Strandberg, 1963).

The deposition of the aerosol and gaseous fractions of the sulfur species can be predicted from the properties of these fractions. Hence, the problem of estimating deposition (and subsequent biological effects) requires an

understanding of the proportion of sulfur species associated with the aerosol fraction and their chemical properties. Since these reactions are dynamic processes, the rate and mechanics of the gas-particle chemical reactions, especially as they may occur in the airways, must be understood.

11.3 TRANSFORMATIONS AND CLEARANCE FROM THE RESPIRATORY TRACT

Particulate material deposited in the respiratory tract may eventually be cleared by the tracheobronchial ciliary mucus conveyor or nasal mucus flow to the throat and is either expectorated or swallowed. Other deposited material may be cleared by either the lymphatic system or transfer to the blood. SO_2 probably reacts rapidly with biological constituents to produce S-sulfonate (Gunnison, 1971). The role of clearance as a protective mechanism for the respiratory tract depends on the physicochemical characteristics of the particles (or gaseous species), the site of deposition, and respiratory physiology If the particles are soluble in body fluids, their deposition in the nasal turbinates with subsequent absorption into the blood may be more important than pulmonary deposition, and total deposition of soluble particles may be more important than regional deposition. For relatively inert and insoluble particles, deposition in the pulmonary region, where they may be tenaciously retained, would be more hazardous. The deposition by dissolution of SO_2 in the nasopharyngeal region may be protective, since it probably involves less serious biological effects than deposition in the bronchial or pulmonary airways. Mouth breathing would eliminate the nasal absorption and increase the SO_2 levels entering the lung. If the particles or SO_2 chemically react with body fluids, transformations of the material can affect clearance. In all respiratory regions, the dissolution of particles competes with other clearance processes.

11.3.1 Depor .ted Particulate Material

Because clearance from the three respiratory tract regions (NP, TB, and P) is physiologically and temporally different, by region of deposition and characteristic chemical classes of particles (i.e., by relative solubility in body fluids) (Morrow et al., 1966). An understanding of regional deposition is requisite to an evaluation of respiratory clearance and a description of the retention of deposited particulate materials. In addition, there may be significant differences between the relative importance of clearance mechanisms in different mammalian species.

Particle deposition in the nasopharyngeal (NP) region is limited primarily to the larger particles deposited by inertial impaction. Deposition of various aerosol particles may lead to specific biological effects associated with this region. For particles that do not quickly dissolve or that react with body fluids, clearance from this region is mechanical. The anterior third of the human nose (where most particles >5 μm may deposit) does not clear except by blowing, wiping, sneezing, or other extrinsic means, and particles may not be removed until 1 or more days after deposition (Proctor and Swift, 1971; Proctor et al., 1969; Proctor and Wagner, 1965 and 1967; Proctor et al., 1973).

The posterior portions of the human nose, including the nasal turbinates, have mucociliary clearance averaging 4 to 6 mm/min with considerable variation among individuals (Proctor et al./, and Wagner 1965; ~~Proctor and Wagner, 1967~~; Ewert, 1965; van Ree and van Dishoeck, 1962). Particles are moved with this mucus to the throat and are swallowed or expectorated. Various reactions can occur in the gastrointestinal tract, and some assimilation into the blood is possible even for particles that were relatively insoluble in the nose. The ICRP Task

Group (Morrow et al., 1966) adopted a 4-minute half-time for physical clearance from the human NP region by mucociliary transport to the throat and subsequent swallowing.

Soluble particles or droplets are readily assimilated by the mucous membranes of the NP region directly into the blood. Solubility is graded from extremely insoluble to instantly soluble, and the dissolution rate constant for the particles must be considered for each aerosol.

Since the tracheobronchial region includes both very large and very small conductive airways, particles of various sizes can be deposited. If deposited in sufficient quantity over a sufficiently long period, some of these particles can lead to biological responses in the bronchial airways (Ulmer, 1967; Nadel et al., 1967). The retention of deposited materials in this region can differ markedly among individuals and can be affected by such factors as cigarette smoking, pathological abnormalities, or responses to inhaled air pollutants. Clearly, the more rapid the clearance, the less time available for untoward responses or latent injury. In mouth breathing of aerosols, such as during smoking or under physical exertion, the beneficial filtering of large particles in the NP region is lost, and a greater fraction of these large particles can be deposited in the TB region.

An important characteristic of the TB region is that it is both ciliated and equipped with mucus-secreting cells. Mucociliary clearance mechanisms has been reviewed by Schlesinger (1973). For relatively insoluble and inert particles, the primary clearance mechanism for the TB region is mucociliary transport to the glottis, with subsequent expectoration or swallowing and passage through the gastrointestinal tract. Mucus flow influences the ciliary mucus conveyor (Van As and Webster, 1972; Besarab and Litt, 1970; Dadaian et al, 1971,

The rate of mucus movement is slowest in the finer, more distal airways and greatest in the major bronchi and trachea. In addition, coughing can accelerate tracheobronchial clearance by the mucociliary conveyor. The size distribution of particles affects their distribution in the tracheobronchial tree. The clearance of small particles, usually deposited deep in the lung, is slower than for larger particles, which tend to deposit in the larger airways (Albert et al., 1967b; Albert et al., 1973; Camner et al., 1971; Luchsinger et al., 1968).

The clearance of material in the TB compartment cannot be described by a single rate. Data from experimental studies imply that the larger airways clear with a half-time of about 0.5 hours, intermediate airways with a half-time of 2.5 hours, and finer airways with a half-time of 5 hours (Morrow et al., 1967a; Morrow, 1973). There is also considerable variability among individuals (Camner et al., 1972a, 1972b, Camner et al. 1973a, 1973b; Albert et al., 1967b). Material with slow dissolution rates in the TB compartment will usually not persist for longer than about 24 hours in healthy humans. Cigarette smoking has been reported under various conditions to either increase decrease, or have little effect on the efficiency and speed of TB clearance (Camner ~~et al.~~ *and Philipson*, 1972a; LaBelle et al., 1966; Bohning et al., 1975; Albert et al., 1974; Thomson *and Davies* 1973).

Particles smaller than about 10 μm D_{ar} are deposited to some extent in the pulmonary region of the lung upon inhalation (Figures 3, 4, and 10), although the deposition of particles much smaller than 0.01 μm may be quite limited because of the competing diffusional deposition in the NP and TB regions. Particles that deposit in the pulmonary region land on surfaces kept moist by a complex liquid containing pulmonary surfactants (Blank et al.,

1969; Balis et al., 1971; Pattle, 1961b; Kott et al., 1974; Henderson et al., 1975). There are no ciliated cells in the epithelium of this region, and flow of liquid from pulmonary airspaces into the tracheobronchial region is minimal in humans (unlike murine species; Gross et al., 1966). Insoluble materials that deposit in the human pulmonary region are usually retained for extended periods.

A description of the clearance of particles from the pulmonary region should characterize particle distribution and redistribution. Usually, relatively insoluble particles are rapidly phagocytized by pulmonary macrophages (LaBelle and Brieger, 1961; Sanders and Adee, 1968; Green, 1971; Green, 1974; Ferin, 1965; Camner et al., 1973a; Camner et al., 1974; Camner et al., 1973b; Chapman and Hibbs, 1977). Smaller particles may not be as efficiently or rapidly collected as larger particles (Hahn et al., 1977); some particles may enter the alveolar interstitium by pinocytosis (Strecker, 1967). Chemotoxic processes have been identified in phagocytosis (Metzger, 1968), and some particles may be cytotoxic to macrophage cells (Allison et al., 1967). Migration and grouping of macrophages laden with particles can lead to redistribution of evenly dispersed particles into clumps and focal aggregations of particles in the deep lung. Some macrophages containing particles may enter the boundary region between the ciliated bronchioles and the respiratory ducts and then can be carried with the mucociliary flow of the TB region.

Some insoluble particles deposited in the lung are eventually trapped in the pulmonary interstitium (Strecker, 1967), impeding mechanical redistribution or removal (Felicetti et al., 1975). Only the very smallest particles (smaller than 10 nm in physical diameter) can readily diffuse through pores directly into the blood, passing intact through the air-to-blood cellular

barrier of the gas-exchange regions of the lung (Raabe et al., 1978a; Raabe et al., 1978b; Gross, 1954; Raabe, 1979).

Another possible clearance route for migrating particles and particle-laden macrophages is the pulmonary lymph drainage system with translocation to the tracheobronchial lymph nodes (Thomas, 1968; Lauweryns and Baert, 1977; Leeds et al., 1971). Little information is available about the clearance rates for transfer from lung to lymph nodes in man, but half-times of 1 to 2 years have been estimated from data on dogs and monkeys (Leach et al., 1970). Like transfer to the TB region with clearance by the mucociliary escalator, transfer to lymph nodes may affect only a portion of the material deposited in the lung.

Waligora (1971) studied the pulmonary clearance of extremely insoluble and inert particles of zirconium oxide radiolabeled with ^{95}Nb. Although his results were not precise, the biological clearance half-life in man was about 1 year, a value about the same as for beagles. By contrast, murine species have a more rapid pulmonary clearance (Morgan et al., 1977). Leach et al. (1970, 1973) exposed experimental animals to insoluble UO_2 (MMAD of about 3.5 μm) and observed lung retention half-times of 19.9 months for dogs and 15.5 months for monkeys. Ramsden et al. (1970) measured the retention of accidentally inhaled, relatively insoluble $^{239}PuO_2$ (plutonium dioxide) in a man's lungs and found the clearance half-time to be about 240 to 290 days; some of that material was dissolved into blood and excreted in the urine. Pulmonary clearance half-times as long as 1000 days have been reported for extremely insoluble particles of plutonium dioxide in dogs (Raabe and Goldman, 1979). Cohen et al. (1979) reported an apparent half-time of about 100 days for nonsmokers and about 1 year for smokers for pulmonary clearance of magnetite particles.

Because of the slow clearance by the various mechanical pathways, dissolution and associated physical and biochemical transformations are often the dominant mechanisms of clearance from the pulmonary region (Morrow, 1973). The term "dissolution" is taken in its broadest context to include whatever processes cause material in a discrete particle to be dispersed into the lung fluids and the blood (Green, 1975). Many chemical compounds deposited in the lung in particulate form are mobilized faster than can be explained by known chemical properties at the normal lung fluid pH of about 7.4 (Kanapilly, 1977). Raabe et al. (1978a) suggested that the apparent dissolution of highly insoluble PuO_2 actually may be due to fragmentation into particles small enough to move readily into the blood, rather than to true dissolution.

Mercer (1967) developed an analysis of pulmonary clearance based on particle dissolution under nonequilibrium conditions. If the dissolution rate constant (k) is known for a material, the time required to dissolve half the mass of (monodisperse) particles of initial physical diameter (D_0) is given by:

$$T_{1/2} = 0.618 \; \alpha_v \; \rho D_0 / \alpha_s k \tag{5}$$

with ρ the physical density of the particles and α_v and α_s the volume and surface shape factors, respectively (for spherical particles $\alpha_s / \alpha_v = 6$). The particles would be expected to be completely dissolved at a time, t_f, given by:

$$t_f = 3\alpha_v \; \rho \; D_0 / \alpha_s k \tag{6}$$

Mercer (1967) also calculated the expected dissolution half-time for poly-disperse particles when their mass median (physical) diameter in the lung is known:

$$T_{1/2} = 0.6 \, \alpha_v \, \rho(MMD)/\alpha_s k \qquad (7)$$

Further, he showed that the resulting apparent lung retention function R(t) could be described as the sum of two exponentials of the form:

$$R(t) = M/M_0 = f_1 e^{-\lambda_1 \beta} + f_2 e^{-\lambda_2 \beta} \qquad (8)$$

where $f_1 = (1-f_2)$, $\beta = \alpha_s Kt/\alpha_v \rho(MMD)$ and f_1, f_2, λ_1, and λ_2 are functions of the geometric standard deviations as defined by Mercer (1967). Therefore, for dissolution-controlled pulmonary clearance, smaller particles will exhibit proportionately shorter clearance half-times. When the dissolution half-times are much shorter than the half-times associated with the translocations of particles to the TB region or to lymph nodes (i.e., much less than 1 year), dissolution will dominate retention characteristics. Materials usually thought to be relatively insoluble (such as glass) may have high dissolution rate constants and short dissolution half-times for the small particles found in the lung; the dissolution half-time for 1 μm D glass spheres is about 75 days (Raabe, 1979). Changes in structure or chemical properties, such as by heat treatment of aerosols (Raabe, 1971), can lead to important changes in dissolution rates and observed pulmonary retention.

Since respiratory tract clearance may begin immediately after the initial deposition, the dynamics of retention can become quite complicated when additional deposition is superimposed on clearance phenomena. Extended or chronic

exposures are the rule for environmental aerosols, and particulate material may accumulate in some portions of the lung (Davies, 1963; Walkenhorst, 1967; Davies, 1964a; Einbrodt, 1967).

Usually the retention time of material in the respiratory tract is measured (such as with radiolabeled aerosols) rather than the clearance rates (Sanchis et al., 1972; Camner et al., 1971; Edmunds et al., 1970; Luchsinger et al., 1968; Aldas et al., 1971; Ferin, 1967; Barclay et al., 1938; Morrow et al , 1967a; Morrow et al., 1967b; Friberg and Holma, 1961; Holma, 1967; Kaufman and Gamsus, 1974). The lung burden or respiratory tract burden can be represented by an appropriate retention function with time as the independent variable (Morrow, 1970a; Morrow, 1970b). For models based on simple first-order kinetics the lung burden (y) at a given time during exposure is controlled by the instantaneous equation (Raabe, 1967):

$$\frac{dy}{dt} = E - \lambda_1 y \qquad (9)$$

where E is the instantaneous deposition rate of particulate material deposited in the lung per unit time during an inhalation exposure and λ_1 is the fraction of material in the lung cleared from the lung per unit time. For an exposure that lasts a time t_e, the lung burden from the exposure is given by:

$$y_e = (E - Ee^{-\lambda_1 t_e})/\lambda_1 \qquad (10)$$

where E is the average exposure rate. After the exposure ends, the clearance is governed by:

$$\frac{dy}{dt} = -\lambda_1 y \qquad (11)$$

and the lung burden is given by:

$$y = y_e \ e^{-\lambda_1 t} \tag{12}$$

where y_e is the lung burden at the end of the exposure period (t_e). Hollinger et al. (1979) used this simple model to describe the deposition and clearance of inhaled submicronic ZnO in rats (Figure 11-13) where the concentration of zinc (as Zn) in the lungs (as described by Equations 10 and 12) is superimposed on the natural background concentration of zinc in lung tissue. The normally insoluble zinc has only a 4.8-hour dissolution half-time ($\lambda_1 = 0.21 \ h^{-1}$) for this aerosol. Of course, environmental aerosol exposures continue so that a steady state lung burden may be expressed by:

$$y_{ss} = E/\lambda_1 \tag{13}$$

If several deposition and clearance regions, subregions, or special pools are involved, a more complicated multicompartmental model may be required to describe lung or respiratory tract buildup and retention of inhaled aerosols. If each compartment can be described by first order kinetics, as given in Equations 10 and 12, the lung burden during exposure is given by:

$$y_e = \sum_{i=1}^{n} y_i = \sum_{i=1}^{n} (E_i - E_i e^{-\lambda_i t_e})/\lambda_i \tag{14}$$

where the subscript i is the index associated with each of the n different clearance compartments. The steady state value for environmental aerosols is:
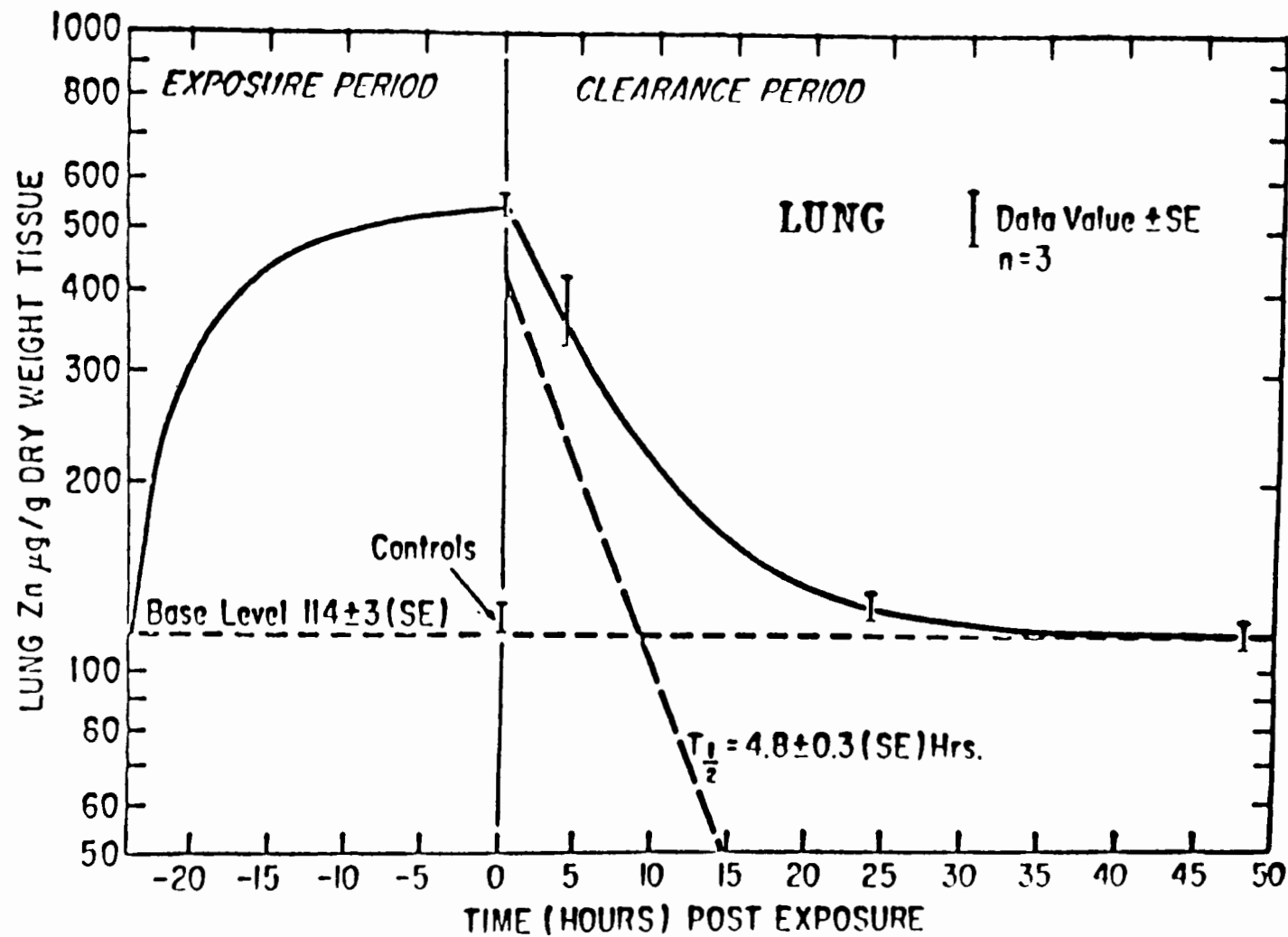
FIGURE 11-13. Single exponential model, fit by weighted least-squares, of the buildup (based on text equation 10) and retention (based on text Equation 12) of zinc in rat lungs (data from Hollinger et al. 1979).

$$y_{ss} = \sum_{i=1}^{n} E_i/\lambda_i \qquad (15)$$

Likewise, the retention, when exposure ends, is given by (Raabe, 1967):

$$y = \sum_{i=1}^{n} (y_i e^{-\lambda_i t}) \qquad (16)$$

where each of the λ_i values translates to a clearance rate for each of the compartments given by half-time $T_{1/2} = \ln 2/\lambda_i$ (Figure 11-14).

For chronic exposures where the several pools are in complex arrays of change, a simple power function may serve as a satisfactory model of pulmonary retention (Downs et al., 1967). In such a model, the pulmonary region is treated as one complex, well-mixed pool into which material is added and removed during exposure, as given by the instantaneous equation:

$$\frac{dy}{dt} = E - \lambda_p y/t \quad [y = 0 \text{ at } t = 0] \qquad (17)$$

where y is the total lung burden at a given time (t), E is the average deposition rate of inhaled particulate material in the lung, and λ_p is the fraction of available lung burden being cleared. Unlike the λ_i of the exponential retention models, λ_p is dimensionless. The time coordinate is not arbitrary; time is taken as zero only at the beginning of the inhalation exposure,
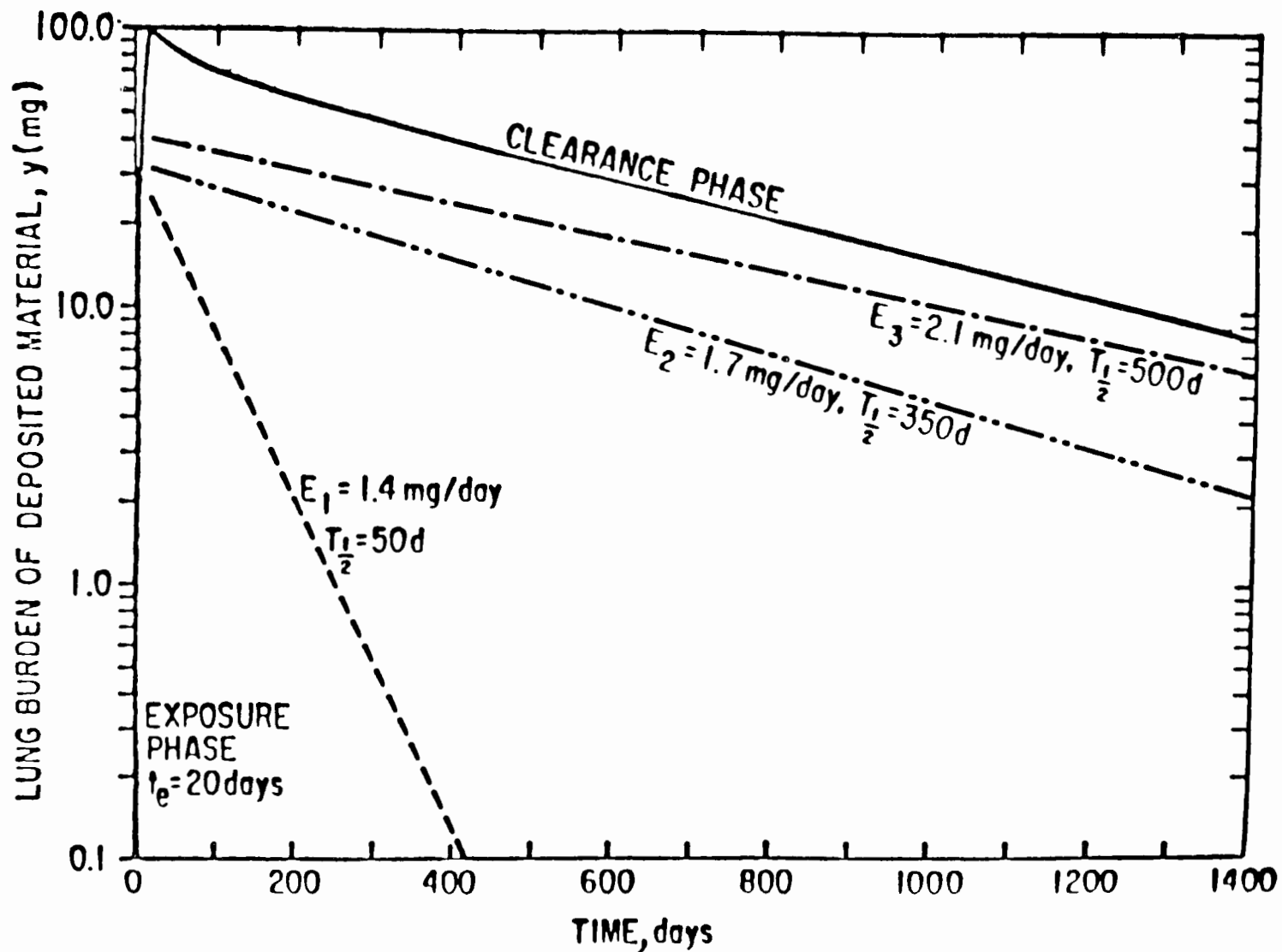
FIGURE 11-14. Example of the use of the sum of exponential models for describing lung uptake during inhalation exposure (Equation 14) and retention (clearance phase) after exposure ends (Equation 16) for three lung compartments with half-lives 50 d, 350 d, and 500 d, and twenty-day exposure rates of 1.4 mg/d (E_1), 1.7 mg/d (E_2), and 2.1 mg/d (E_3), respectively (from Raabe, 1979).

when the lung burden is nil. Thus, during an exposure lasting until time (t_e), the pulmonary burden (y_e) is given by (Raabe, 1967):

$$y_e = Et_e/(\lambda_p + 1) \tag{18}$$

On this basis, no steady-state concentration is reached even though clearance is progressing and the lung concentration continues to increase during chronic exposures to environmental aerosols. This model is therefore not applicable to relatively soluble species. The lung burden (y) after the exposure ends is given by (Raabe, 1967):

$$y = y_e \, t_e^{\lambda_p} \, t^{-\lambda_p} = At^{-\lambda_p} \; [t = t_e + t_p] \tag{19}$$

where time (t) is reckoned from the beginning of exposure and is equal to the sum of the exposure time (t_e) and the time after exposure (t_p). This model is illustrated in Figure 11-15.

Deposited particulate material cleared from the lung is usually transformed chemically and transferred to other tissues of the body. The injurious properties of a toxic material translocated from the lung may therefore be expressed in other organs. Identification of the potential hazards associated with inhalation exposures to toxicants is compounded when the respiratory tract is not the only target for injury but still serves as the portal of entry into the body. The metabolic behavior and excretion of inhaled toxicants after deposition in the lung could define the probable target organs and indicate potential pathogenesis of resulting disease.

Multicompartmental models that describe biological behavior can become extremely complex. Each toxicant or component of aerosol particles deposited
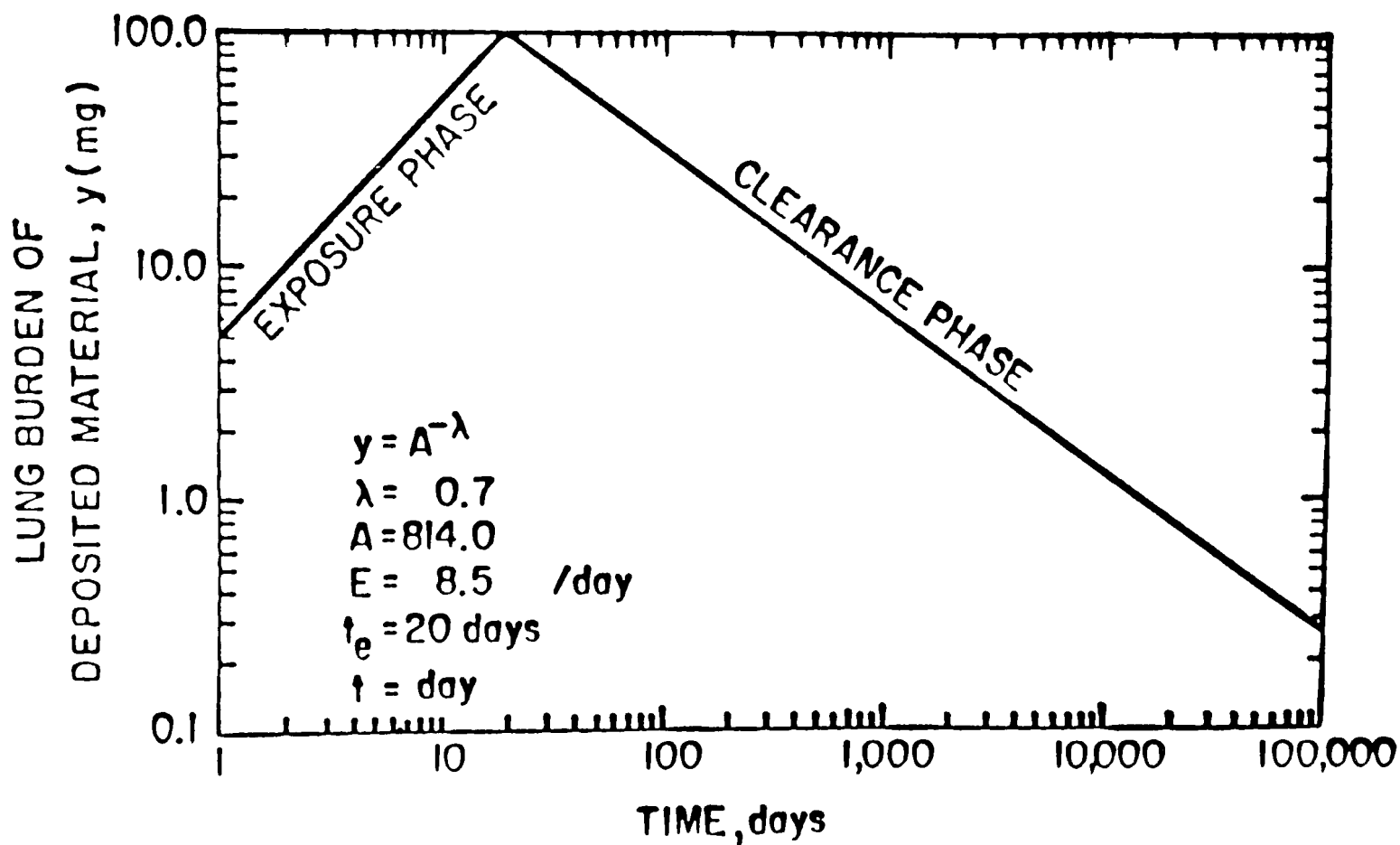
FIGURE 11-15. Example of the use of the power function model for describing lung uptake during inhalation exposure (text Equation 18) and retention (clearance phase) after exposure ends (text Equation 19) for a twenty-day exposure at 8.5 mg/d (E) (adapted from Raabe 1967).

in the respiratory tract may need to be described by a separate rate constant and pool or compartment. A general model of the metabolic behavior of inhaled particles (Figure 11-16) shows 39 different places where rate constants may need to be determined. In this general model, the pulmonary region of the lung is visualized as consisting of three independent clearance compartments, and the particles are presumed to be converted from their original particulate state to some other physicochemical form or transformed state prior to clearance from the respiratory tract. Such a transformed state can be used to describe, for example, the behavior of hydrolytic aerosols in the respiratory tract.

A more specific model of the systemic metabolism of inhaled aerosols is shown (Figure 11-17) for cerium trichloride (^{144}CeCl$_3$) contained in particles of cesium chloride (CsCl) with a MMAD$_{ar}$ of about 2 μm (Boecker and Cuddihy, 1974). The resultant pattern of combined uptake and retention in various organs after inhalation exposure is illustrated in Figure 11-18. In this case, the exposure is acute; the fate of relatively insoluble materials in chronically inhaled environmental aerosols may involve more complex relationships.

11.3.2 Absorbed SO$_2$

SO$_2$ coming in contact with the fluids lining the airways (pH 7 4) should dissolve into the aqueous fluid and form some bisulfite (HSO$_3$-) and considerable sulfite (SO$_3^{2-}$) anions. Because of the chemical reactivity of these anions, various reactions are possible, leading to the oxidation of sulfite to sulfate.

Clearance of sulfite from the respiratory tract may involve several intermediate chemical reactions and transformations. Gunnison (1971) has identified S-sulfonate in blood as a reaction product of inhaled SO$_2$. The reaction rate is rapid, if not nearly instantaneous, so that there is no
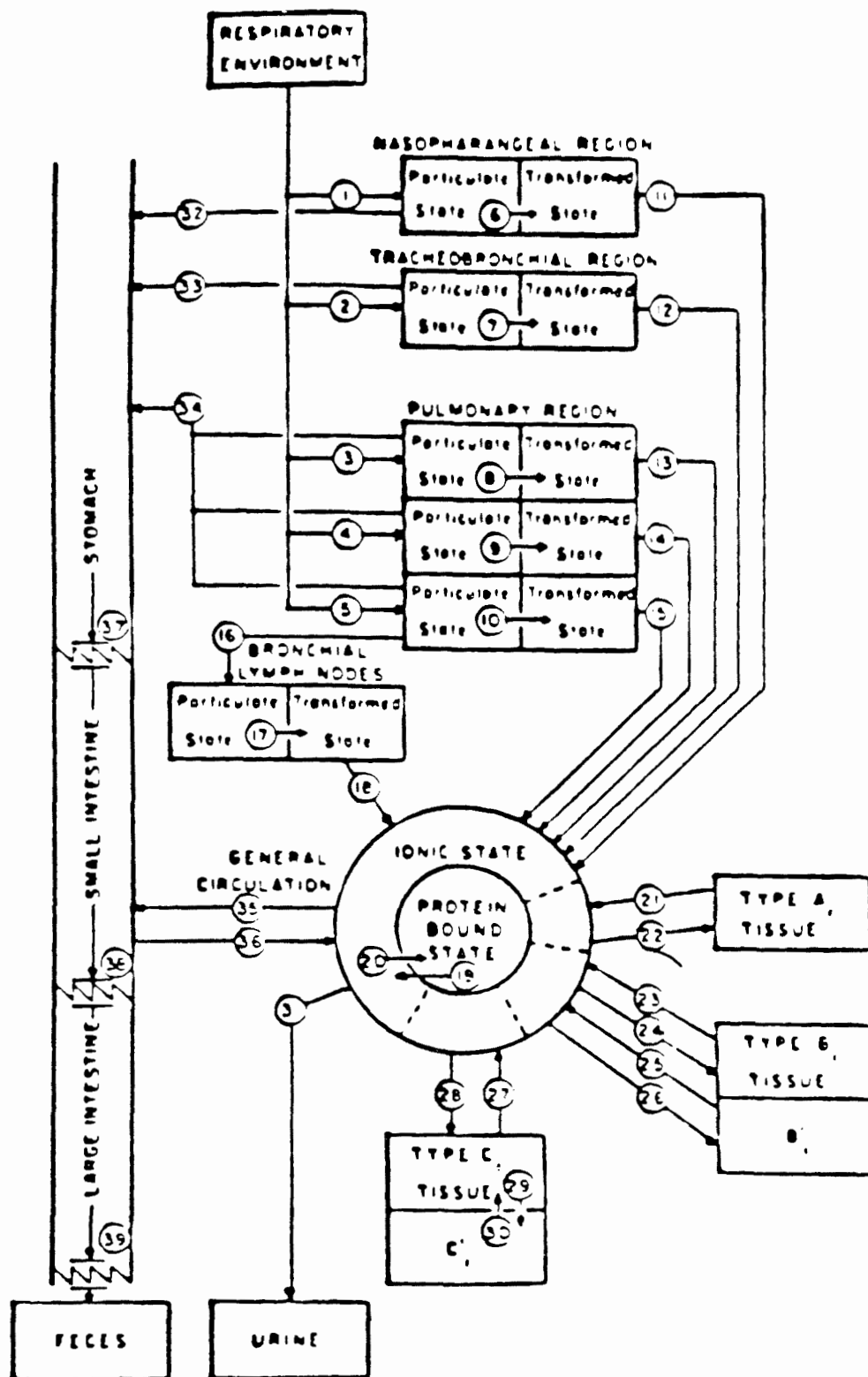
FIGURE 11-16. Model of the multicompartmental deposition, clearance, retention translocation, and excretion of inhaled particulate material in the respiratory tract and tissues of the body; the numbered circles represent the transfer rate constants (from Cuddihy, 1969).
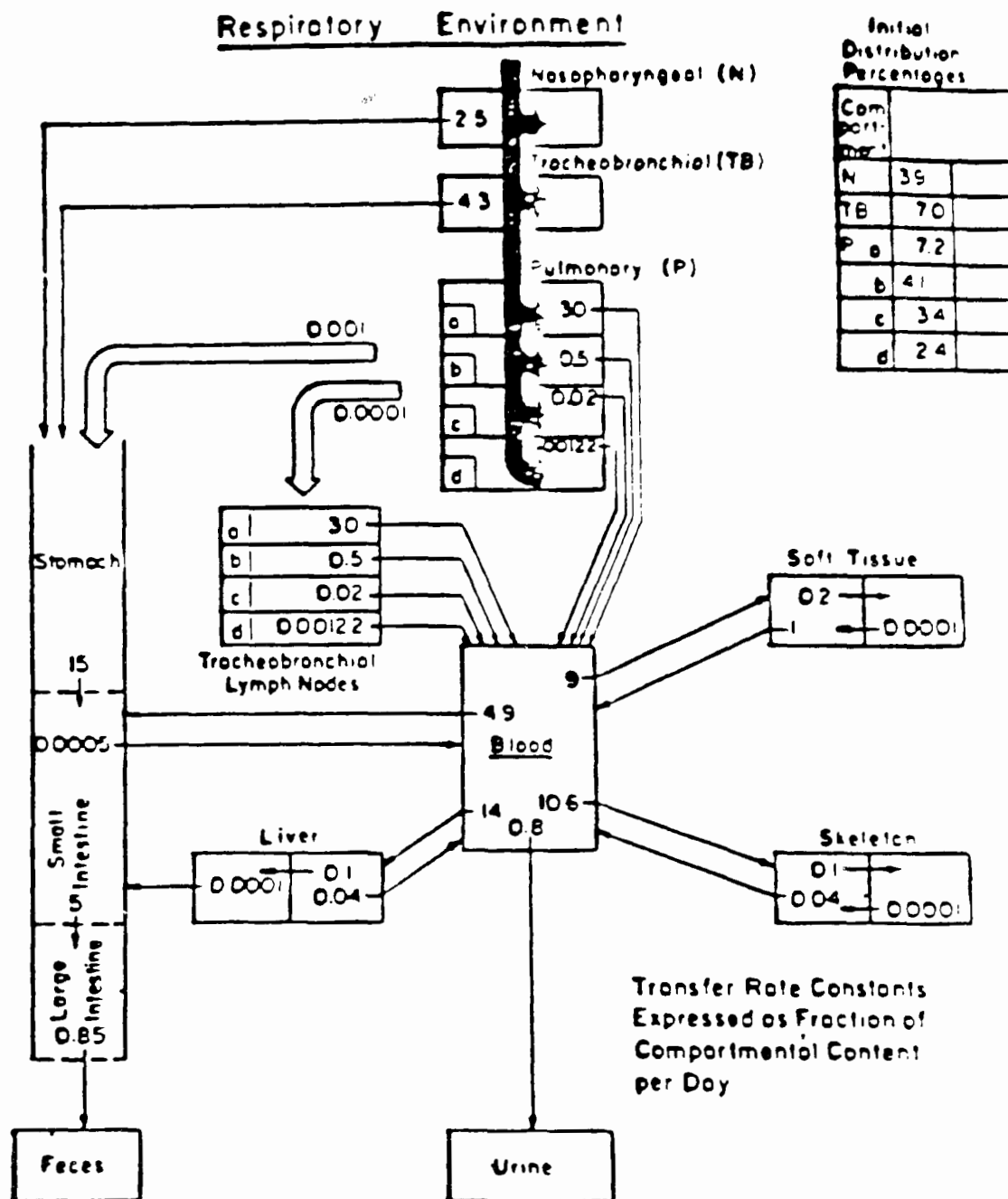
FIGURE 11-17. Multicomponent model of the deposition, clearance, retention, translocation and excretion of an example sparingly soluble metallic compound (^{144}CeCl$_3$ continued in CsCl particles) inhaled by man or experimental animals; the rate constants are based upon first order kinetics as in text Equation 11 (from Boecker and Cuddihy, 1974).
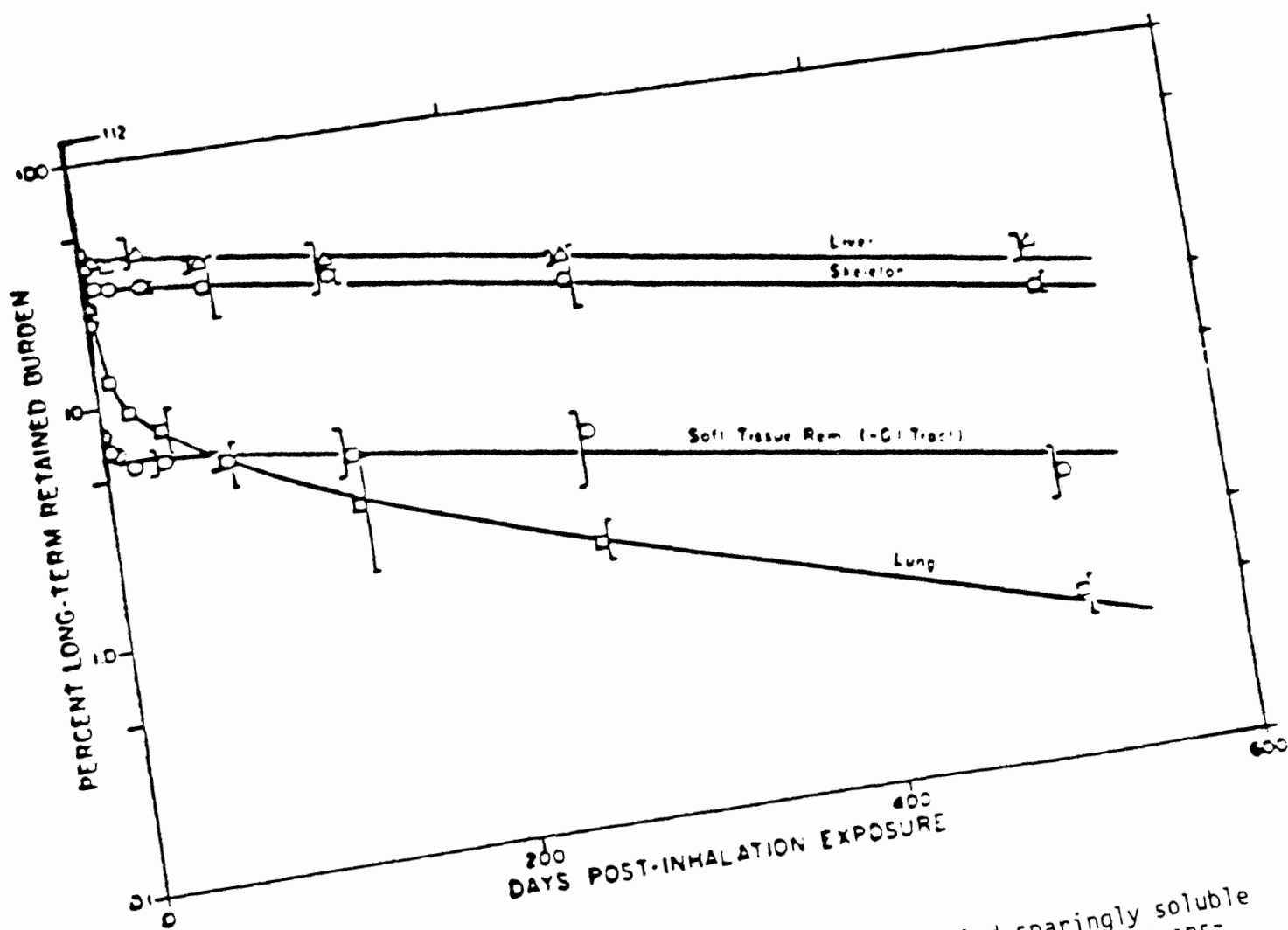
FIGURE 11-18. Example of the organ retention of an inhaled sparingly soluble metallic compound assuming a single acute exposure demonstrating the translocation from lung and build-up and clearance from other organs (from Boecker and Cuddihy, 1974).

11-77

long-term clearance to characterize. However, intermediate and potentially toxic products may be formed. These products may have residence times that are long enough to demonstrate an elevation of the sulfur content of the lung. Potentially detrimental reactions are most likely to be of biological concern when they occur in the pulmonary and bronchial regions of the lung.

Desorption from the upper respiratory tract may be expected whenever the partial pressure of SO_2 on mucosal surfaces exceeds that of the air flowing by. Desorption of SO_2 from mucosal surfaces was still evident after 30 minutes of flushing with ambient air the airways of dogs which had breathed 2.62 mg/m^3 (1.0 ppm) for 5 min. (Frank et al., 1969). Frank et al. (1967) reported SO_2 in the lungs of dogs that apparently was carried by the blood after nasal deposition. In human subjects breathing 42.2 mg/m^3 (16.1 ppm) through a mask for 30 minutes, 12% of the SO_2 taken up by the tissues in inspiration reentered the air stream in expiration and another 3% was desorbed during the first 15 minutes after the end of SO_2 exposure (Speizer and Frank, 1966). Thus, during expiration, SO_2 was desorbed from the nasal mucosa in quantities totaling approximately 15% of the original inspired concentration.

The effects of SO_2 on tracheobronchial clearance in 9 healthy, nonsmoking adults was studied by Wolff et al. (1975). Technetium Tc 99m albumin aerosol (3 µm MMAD, σ_g = 1.6) was inhaled as a bolus under controlled conditions. A three hour exposure to 13.1 mg SO_2/m^3 (5.0 ppm) had no significant effect on mucociliary clearance in resting subjects, except for a small transient increase (p < 0.05) after 1 hour. A significant decrease in nasal mucus flow rates during a six hour exposure of 15 young men to 13.1 mg SO_2/m^3 (5.0 ppm) and 65.5 mg SO_2/m^3 (25.0 ppm), but not 2.62 mg SO_2/m^3 (1.0 ppm), was observed by Andersen et al. (1974). Decreases were greatest in the anterior nose and in

subjects with initially slow mucus flow rates. Newhouse et al. (1978) assessed the effect of oral exposure to SO_2 on bronchial clearance of a radio-active aerosol (3 μm MMAD) in healthy nonsmoking males and females who exercised periodically during exposure at an exertion level sufficient to keep the heart rate at 70% - 75% of the predicted maximum. After a 2 hour exposure to 13.1 mg SO_2/m^3 (5.0 ppm), clearance was increased.

11.3.3 Particles and SO_2 Mixtures

The presence of adsorbed SO_2 or other sulfur compounds on aerosol surfaces may alter the clearance processes of both. Chemical reactions involving sulfur compounds on particle surfaces may enhance the apparent solubility of the aerosol particles. These aerosol particles may also undergo reaction with sulfite or other species upon contact with body fluids.

The formation of sulfate anions by oxidation of SO_2 to SO_3 may be catalyzed by manganese, iron, or other aerosol components. The SO_3 reacts immediately with water to form sulfuric acid that can react with other materials, such as metal oxides on fly ash aerosols, to produce sulfate compounds. Since sulfate is a normal constituent of body fluids (Kanapilly, 1977), the clearance of sulfate anions probably involves simple dissolution and diffusional dilution into body fluids.

11.4 DISCUSSION AND SUMMARY

When aerosols or SO_2 are inhaled by man or experimental animals, different fractions of the inhaled materials deposit by a variety of mechanisms in various locations in the respiratory tract. Particle size distribution, particle chemical properties, SO_2 diffusivity, respiratory tract anatomy, and airflow patterns all influence the deposition. The predicted regional

deposition percentages for man given by the Task Group on Lung Dynamics are in reasonable agreement with available experimental measurements and provide useful general guidelines for estimating particle deposition for environmental assessment. Nose breathing and mouth breathing provide somewhat contrasting deposition patterns. During nose breathing nearly all particles larger than 8 μm in aerodynamic diameter are usually collected in the nasopharyngeal region, while this natural filtration can be circumvented during mouth breathing so that some particles as large as 15 μm aerodynamic diameter may enter the tracheobronchial region. After deposition, the inhaled material will be translocated by processes that depend on the character of the particles and their site of deposition. If the material is quite soluble in body fluids, it will readily enter the bloodstream. Relatively insoluble material that lands on ciliated epithelium, either in the nasopharyngeal region or tracheobronchial airways, will be translocated with mucus flow to the throat and will be swallowed or expectorated. Depending on particle size, relatively insoluble material that deposits on nonciliated surfaces in the pulmonary region may be phagocytized, may enter the interstitium and remain in the lung for an extended period, or may be translocated by lymphatic drainage. Some material from the pulmonary region may enter the TB region and be cleared by the mucociliary conveyor.

Both deposition and retention play roles in determining the effects of inhaled particulate toxicants and SO_2. Everyone is environmentally exposed to a variety of dusts, fumes, sprays, mists, smoke, photochemical particles, and combustion aerosols, as well as SO_2 and other potentially toxic gases. The particle size distribution and chemical and physical composition of airborne particulate material require special attention in toxicological evaluations

since a wide variety of physicochemical properties may be encountered in both experimental and ambient inhalation exposures. Sulfur dioxide may deposit directly in the airways or enter into a variety of gas-to-particle conversions or gas-particle chemical and physical reactions. SO_2 must be considered with aerosol behavior in the atmosphere and during inhalation deposition, as well as in relation to respiratory responses.

The three functional regions (NP, TB, and P) of the respiratory airways can each be characterized by major mechanisms of deposition and clearance (Table 11-1). Besides being a target of inhaled particles and gases, the respiratory tract is also the portal of entry by which other organs may be affected. An understanding of the mechanisms and patterns of translocation to other organ systems is required for evaluation of the potential for injury or response in those organs.

TABLE 11-1. SUMMARY OF THE RESPIRATORY DEPOSITION AND CLEARANCE
OF INHALED AEROSOLS (FROM RAABE, 1979)

REGION	DEPOSITION	CLEARANCE
NP NASOPHARYNGEAL	IMPACTION DIFFUSION INTERCEPTION ATTRACTION	MUCOCILIARY SNEEZING BLOWING DISSOLUTION
TB TRACHEOBRONCHIAL	IMPACTION DIFFUSION SETTLING INTERCEPTION ATTRACTION	MUCOCILIARY COUGHING DISSOLUTION
P PULMONARY	DIFFUSION SETTLING ATTRACTION INTERCEPTION	DISSOLUTION PHAGOCYTOSIS LYMPH FLOW

A fundamental principle in inhalation toxicology is that it is the deposition of inhaled particulate materials in sensitive regions of the respiratory tract or subsequent transformations and translocations to sensitive organs or cells that leads to potentially deleterious biological responses. Particles (or gases) that deposit neither in sensitive regions of the airways nor in regions conducive to translocation to sensitive organs are cleared with relatively low probability of causing injury or disease (Morrow, 1964). For example, large insoluble particles that deposit almost exclusively in the nose are prevented from reaching the lung during nose breathing and are less likely to lead to injury than smaller particles having appreciable lung deposition.

This principle was early observed in coal mining in Europe; it was found that the air concentration of dust in mines didn't necessarily correlate to the incidence of respiratory disease. However, a meaningful comparison was possible when samples were aerodynamically fractionated to provide a separate measure of the respirable dust levels. This led to the use of "respirable" dust samples in the coal mining industry (Walton, 1954). Further, the repeated practice of collecting respirable dust samples is necessary, since there is variability in the aerodynamic size distribution of dust depending on age and source.

On this basis the principle of "respirable" dust sampling was developed (Lippmann, 1970b). In this context the word "respirable" means broadly "fit to be breathed." The objective is to collect samples that have been purposely biased in favor of the smaller, more respirable sizes. Only the smaller size fraction is measured to yield the "respirable" aerosol concentration. No specific "cut-size" was defined, since it is clear that there is no size for

which all particles smaller are respirable and all larger are not. Instead, weighting functions were defined that simulated the size classification normally afforded by the human naso-pharyngeal deposition during nose breathing. Another factor involved in describing a respirable fraction was the availability of a simple instrument that would provide a practical means for collection of these size-classified samples.

Two weighting functions have been generally used as criteria for respirable dust sampling (Fig. 11-19). The first originated in 1952 when the British Medical Research Council adopted the horizontal elutriator (Walton, 1954) as the respirable dust sampler. Particles that pass the elutriator are collected on a filter or by some other means. The second criteria originated with researchers working for the U. S. Atomic Energy Commission who needed to establish a basis for size classification of radioactive insoluble aerosols; these recommendations came from a meeting held at Los Alamos Scientific Laboratory (LASL), New Mexico, and are commonly referred to as the LASL criteria (Fig. 11-19). A small cyclone separator was chosen as the respirable dust sampler, since massive samples as obtained with the horizontal elutriator were not necessary for analysis of radioactive aerosols. Only the particles that pass the sampler, namely, the smaller size fraction, are collected and used to provide a measure of the respirable aerosol concentration.

Neither the BMRC nor the LASL criteria for respirable aerosol sampling agrees exactly with the ICRP Task Group recommendations concerning naso-pharyngeal deposition but tend to include more of the particles which are less than 7 μm in aerodynamic diameter. This is probably fortuitous, since it tends to compensate for aerosols deposited in the deep lung in a combination of mouth and nose breathing. Hence, the 3 μm particles that are more
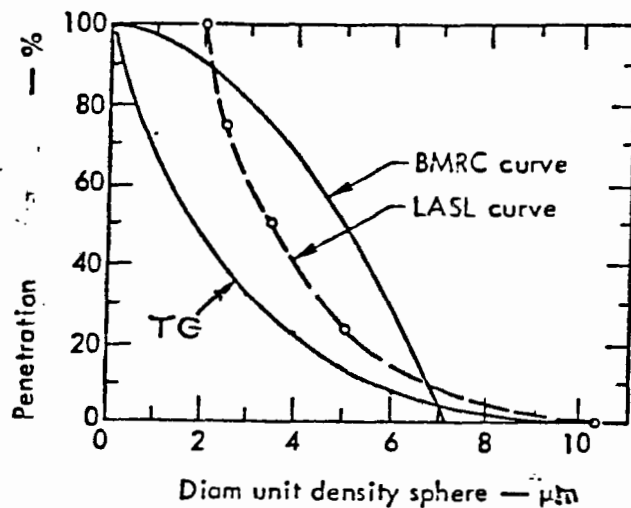
FIGURE ~~20~~ 11-19

Respirable aerosol sampling criteria for penetration of
repirable aerosols through a size-classifier to provide for
collection of particles that have the greatest potential for
pulmonary deposition if inhaled (from Raabe,1979).

efficiently deposited in the pulmonary region during mouth breathing (Fig. 12)
than during nose breathing (Fig. 11-3) are weighted more than would be justified
by the ICRP Task Group nose breathing models.

It is important to note that the "respirable" dust sample is thus not
intended to be a measure of the lung deposition but only a measure of aerosol
concentration for particles that are the primary candidates for lung deposi-
tion. Clearly, the respirable dust sample is only biologically relevant for
aerosols whose upper respiratory deposition is not expected to be of major
health impact. Soluble aerosols of toxic substances can enter the blood
directly from the nasal mucosa or the gastrointestinal tract during clearance
from the nose, and the deposition of particles as large as 100 μm or even
larger in the nose may be the primary hazard for such aerosols.

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11. RESPIRABLE AEROSOL SAMPLING

A fundamental principle in inhalation toxicology is that it is the deposition of inhaled particulate materials in sensitive regions of the respiratory tract or subsequent transformations and translocations to sensitive organs or cells that leads to potentially deleterious biological responses. Particles (or gases) that deposit neither in sensitive regions of the airways nor in regions conducive to translocation to sensitive organs are cleared with relatively low probability of causing injury or disease (Morrow, 1964). For example, large insoluble particles that deposit almost exclusively in the nose are prevented from reaching the lung during nose breathing and are less likely to lead to injury than smaller particles having appreciable lung deposition.

This principle was early observed in coal mining in Europe; it was found that the air concentration of dust in mines didn't necessarily correlate to the incidence of respiratory disease. However, a meaningful comparison was possible when samples were aerodynamically fractionated to provide a separate measure of the respirable dust levels. This led to the use of "respirable" dust samples in the coal mining industry (Walton, 1954). Further, the repeated practice of collecting respirable dust samples is necessary, since there is variability in the aerodynamic size distribution of dust depending on age and source.

On this basis the principle of "respirable" dust sampling was developed (Lippmann, 1970b). In this context the word "respirable" means broadly "fit to be breathed." The objective is to collect samples that have been purposely biased in favor of the smaller, more respirable sizes. Only the smaller size fraction is measured to yield the "respirable" aerosol concentration. No specific "cut-size" was defined, since it is clear that there is no size for

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Chapter 11 - PM/SO$_2$
Errata
REFERENCE LIST CORRECTIONS

Page	Par/Line	Delete	Insert
11-86	After 8th Ref.	-	Clements, J. A., J. Nellenbogen, and H. J. Trahan. Pulmonary surfactant and evolution of the lungs. Science 169: 603-604, 1970.
11-93	After 11th Ref.	-	Kawecki, J. M. Emmission of Sulfur-Bearing Compounds from Motor Vehicle and Aircraft Engines, A Report to Congress. EPA-600/9-78-028, U. S. Env. Prot. Agency. Aug. 1978.
11-96	After 5th Ref.	-	Menzel, D. B. The role of free radicals in the toxicity of air pollutants (nitrogen oxides and ozone). In: Free Radicals in Biology. Vol. II, Academic Press, New York, 1976. pp. 181-202.

12. TOXICOLOGICAL STUDIES

12.1 INTRODUCTION

This chapter describes in vitro and in vivo studies of sulfur oxides and particulate matter. The toxic effects of sulfur oxides and of atmospheric aerosols overlap because a major component of atmospheric aerosols are salts of sulfuric acid (ammonium sulfate, sodium sulfate, zinc ammonium sulfate, and related compounds) (see Chapters 3 and 5). The toxicology of all forms of sulfur oxides must be considered as a whole. For example, in the ambient air sulfur dioxide (SO_2) may interact with aerosols, may be absorbed on particles, or may be dissolved in liquid aerosols. To a lesser degree, similar interactions may occur in the air within the respiratory tract. Sulfuric acid aerosols may react with ammonia forming ammonium sulfate [$(NH_4)_2SO_4$] and ammonium bisulfate (NH_4HSO_4) in the ambient air, the animal exposure chamber atmosphere before inhalation, or to a lesser degree simultaneously upon inhalation. Biological interaction can also occur, resulting in a situation where the effect of a mixture of pollutants has additive, synergistic, or antagonistic health effects compared to the effects of the single pollutants.

This chapter will also present brief discussions of the toxicology of organic compounds so far detected as atmospheric particulates. Unfortunately, our knowledge of the exact chemical nature and health effects of these materials is incomplete. A more complete treatment of this subject can be found in the health assessment document on polycyclic organic matter (POM).[164] A similar overview is provided for heavy metals. Individual documents and reviews have covered this topic in more detail.[275-283]

Because of the relative toxicity of various particles and their interaction with SO_2, this Chapter should be taken as a whole and not as artificially segregated major topics. Discussions of the deposition and clearance are limited; the reader, therefore, should be familiar with the content of Chapter 11 which presents this subject in detail.

12.2 EFFECTS OF SULFUR DIOXIDE

12.2.1 Biochemistry of Sulfur Dioxide

Much of the discussion under 12.2.1 relates to in vitro experiments. In vitro studies are those in which the potential target (i.e., cells, enzymes, other molecules, etc.) is exposed to the toxicant outside the body. In such a culture system, some homeostatic or repair mechanisms are absent. In some cases, pollutants act by indirect mechanisms. For example, the pollutant affects target A which in turn alters target B. Thus, if only target B were present, the effect would not be observed. In addition, the dosimetric relationships of in vitro studies to in vivo studies are not defined. Therefore, effective concentrations cannot be extrapolated from in vitro to in vivo studies. For the above reasons, there is some controversy as to whether these in vitro reactions can be extrapolated to mechanisms of toxicity. Nonetheless, sound in vitro investigations can show whether a given pollutant has the potential of altering a given target. In vitro studies are best used to provide guidance for in vivo investigations or when in vivo results have been observed. In the latter case, the relatively simplified in vitro system can sometimes elucidate the potential mechanisms of toxicity. To these ends, they can be useful.

Knowledge of the chemistry of sulfurous acid and SO_2 is necessary to understand the physiological and toxicological properties of SO_2. Sulfur

dioxide is the gaseous anhydride of sulfurous acid. It dissolves readily in water; and at physiological pH near neutrality, hydrated SO_2 readily dissociates to form bisulfite and sulfite ions as illustrated by Equations 12-1 and 12-2. The rate of hydration of SO_2 is very rapid; the rate constant of hydration, k_1, is 3.4×10^6 M^{-1} sec^{-1}, and the rate constant of the reverse reaction is 2×10^8 M^{-1} sec^{-1} at 20°C (Equation 12-1).[1] The dissociation constants of sulfurous acid are 1.37 and 6.25 (in dilute salt solutions),[1] so at pH 7.4 sulfite ions are present at about 14 times those of bisulfite, but in rapid equilibrium. Hence, SO_2 can be treated as bisulfite/sulfite and conversely.

$$SO_2 + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} H_2SO_3 \qquad\qquad 12\text{-}1$$

$$H_2SO_3 \overset{pK_a = 1.37}{\rightleftharpoons} H^+ + HSO_3^- \overset{pK_a = 6.25}{\rightleftharpoons} H^+ + SO_3^= \qquad 12\text{-}2$$
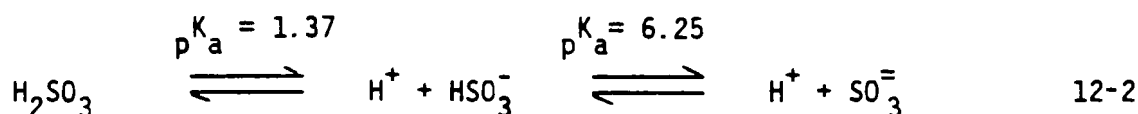
Sulfur dioxide reacts readily with all major classes of biomolecules. Reactions of SO_2 or bisulfite with nucleic acids, proteins, lipids, and other biological components have been repeatedly demonstrated in vitro.

12.2.1.1 Chemical Reactions of Bisulfite with Biological Molecules-- The chemical reactions of bisulfite with biological molecules are discussed in detail in Appendix I. Briefly, there are three important reactions: sulfonation, autoxidation, and addition to cytosine.

Sulfonation results from the nucleophilic attack of bisulfite on disulfides:

$$RSSR' + HSO_3^- \rightleftharpoons RSSO_3^- + R'SH \qquad\qquad 12\text{-}3$$

This reaction is also known as sulfitolysis. The products of the reaction are S-sulfonates ($RSSO_3^-$) and thiols (R'SH). Direct evidence for the formation of plasma S-sulfonates has been found.[69] Any plasma protein containing a disulfide group could react to form an S-sulfonate. Small molecular weight disulfides, such as oxidized glutathione, can also be reactants. Generally, analyses of plasma S-sulfonates have been restricted to diffusable (dialyzable or small molecular weight) and nondiffusable (nondialyzable or protein) S-sulfonates. The exact molecular species has not been determined. S-sulfonates can react with thiols, either reduced glutathione or protein thiol groups, to form sulfite and disulfide. Since this reverse reaction is facile, S-sulfonates are hypothesized as being transportable forms of bisulfite within the body (see Appendix I, Section 1.0).

Similar reversible nucleophilic addition of bisulfite to a variety of biologically important molecules has been reported (see Appendix I). The toxicological importance of these chemical species is uncertain. It is not likely, for example, that the reactions of bisulfite with pyridine nucleotides (NAD or NADP), reducing sugars, or thiamine are important to the toxicity of bisulfite or SO_2.

Autoxidation of bisulfite occurs through a multistep chain reaction (see Appendix I, Section 2.0). These reactions may be important because they produce hydroxyl ($\cdot OH$) and superoxide ($\cdot O_2^-$) free radicals as well as singlet oxygen ($\cdot O_2$). These chemical species of oxygen are highly reactive and are also produced by ionizing radiation. Hydroxyl free radicals are theoretically responsible for the lethal effects of ionizing radiation. Autoxidation of bisulfite could lead to increased concentrations of these reactive chemical species within the cell and could hypothetically lead to similar adverse

effects. The reactive forms of oxygen can also initiate peroxidation of the lipid bilayer of cells. Peroxidation of cellular lipids, especially plasma membrane lipids, is thought to be highly deleterious.[31] (See Appendix I, Section 3.0.) No direct evidence has been presented to support peroxidation of cellular lipids as a mechanism of toxicity of SO_2.

Bisulfite addition to cytosine can result in deamination to form uracil. The result would be a DNA conversion of GC to AT sites and could be mutagenic. Transamination of cytosine can occur through reaction of an amine with cytosine-sulfite adduct. Since the nucleus is rich in polyamines, transamination is a likely event. Deamination of cytosine occurs most readily in high (1 M) concentrations of sulfite; transamination also requires high sulfite and amine concentrations. The decomposition of the cytosine-sulfite adduct is the rate limiting step in both reactions.

12.2.1.2 <u>Potential Mutagenic Effects of Sulfite and SO_2</u>--At the present time, no clear evidence exists for mutagenicity caused by SO_2 or sulfite. However, because of the reactivity of sulfite with cytosine, the potential mutagenic properties of sulfite and SO_2 have been examined. Such experiments are detailed in Appendix I, Section 6.0. To date, microbial experiments with high concentrations of sulfite in acid solutions <u>in vitro</u> have produced mutations. These conditions would be similar to those favoring deamination of cytosine. Experiments conducted at low concentrations and neutral pH are less convincing. For example, the microbial assays were not done with strains of <u>Salmonella</u> known to be sensitive to mutagens (Ames Assays). Negative experiments have been reported when insects (Drosophila) and mammals (mice) were exposed. Cytotoxicity, rather than mutagenicity, appears when cultured animal and human cells are

exposed to sulfite. (See Table 12-1 for summary; details in Appendix I, Section 6.0.)

12.2.1.3 Metabolism of Sulfur Dioxide

12.2.1.3.1 Integrated Metabolism. There are several studies of the metabolism of exogenously supplied SO_2, sulfite, or bisulfite. Quantitative differences exist between inhaled and ingested SO_2 with regard to the rate of clearance of the key intermediary in sulfite metabolism, plasma S-sulfonates,[69] but no qualitative differences exist in the metabolism of inhaled SO_2 and injected or ingested bisulfite or sulfite. The importance of the appearance of plasma S-sulfonates lies in tneir potential ability to serve as a circulating poc' of sulfite molecules. Plasma S-sulfonates represent both protein-bound and small molecular weight thiol-bound forms of sulfite (Reaction 1 in Figure 12-1). Continuous inhalation of 26.2 mg/m^3 (10 ppm) SO_2 resulted in the attainment of 38 ± 15 nmole of plasma S-sulfonates/ml in rabbits after about 4 days.[69] The clearance of plasma S-sulfonates generated by either inhalation of SO_2 or ingestion of sulfite in the drinking water was exponential, exhibiting only a single compartment in most rabbits. The half-life was 4.1 days for S-sulfonates generated by inhalation vs. 1.3 days for those generated by ingestion.[69] The mechanism for this quantitative difference in clearance rates has not yet been found. An integrated scheme is shown in Figure 12-1.

Inhaled SO_2 quickly penetrates the nasal mucosa and airways as shown by the rapid appearance of ^{35}S in the venous blood of dogs inhaling [35]SO_2.[44] A significant fraction of the blood ^{35}S was probably in the form of plasma S-sulfonates ($RSSO_3^-$). Gunnison and Palmes[69] have shown that this compound accumulates on long-term inhalation of SO_2 as well as on ingestion or injection of sulfite solutions in rabbits. These researchers suggest that tissue or

TABLE 12-1. POTENTIAL MUTAGENIC EFFECTS OF SO_2/BISULFITE

Concentration SO_2	Bisulfite	Organism	End Point	Response	Comments	Reference
	0.9 M HSO_3^- pH 5.0	Phage T4-R11 System	GC→AT or deamination of cysocine	+		Summers and Drake[200]
	3 M HSO_3^- pH 5-6	Phage T4-R11 System	deamination of cytocine	±	Poor dose response	Hayatsu and Miura[201] Iida et al.[202]
	1 M HSO_3^- pH 5.2	E. coli K12 & K15	GC→AT or deamination of cytocine	+		Mukai et al.[203]
	5×10^{-3} M HSO_3^- pH 3.6	S. cerevisiae	Point Mutation	+	-	Dorange and Dupuy[204]
	0.04 or 0.08 M	D. melanogaster	Point Mutation	-	May not be bioavailable	Valencia et al.[205]
1310 mg/m^3 (500 ppm)		Hela cells (Human)	Cytotoxicity	+		Thompson and Pace[207]
13.1 - 105 mg/m^3 (5 - 40 ppm x 3 min)		Mouse fibroblasts & Peritoneal macrophages				Nulsen et al.[208]

TABLE 12-1. POTENTIAL MUTAGENIC EFFECTS OF SO_2/BISULFITE

Concentration SO_2	Bisulfite	Organism	End Point	Response	Comments	Reference
	0.9 M pH 5.0	Phage T4-R11 System	GC→AT or deamination of cysocine	+		Summers and Drake[200]
	3 M pH 5-6	Phage T4-R11 System	deamination of cytocine	±	Poor dose response	Hayatsu and Miura[201] Sida et al.[202]
	1 M pH 5.2	E. coli K12 & K15	GC→AT or deamination of cytocine	+		Mukai et al.[203]
	5×10^{-3} M pH 3.6	S. cerevisiae	Point Mutation	+		Dorange and Dupry[204]
	0.04 or 0.08 M	D. melanogaster	Point Mutation	-	May not be bioavailable	Valencia et al.[205]
1310 mg/m^3 (500 ppm)		Hela cells (Human)	Cytotoxicity	+		Thompson and Pace[207]
13.1 - 105 mg/m^3 (5 - 40 ppm x 3 min)		Mouse fibroblasts & Peritoneal macrophages				Nulsen et al.[208]

TABLE 12-1. (Continued)

Concentration SO_2	Bisulfite	Organism	End Point	Response	Comments	Reference
14.9 mg/m^3		Human lymphocytes	Point Mutation Chromosomal aberrations Cytotoxicity	- - +		Kikigawa and *Iizuka* [209] ~~Sizuka~~
	0.0001M 0.01M	Human lymphocytes	Inhibition of mitosis	+	Dose related response	Harman et al. [213]
	0.0001M	Mouse oocytes	Inhibition of meiosis	+	Observed fuzziness of	Jagiello et al. [212]
	0.0040M	Ewe oocytes	Inhibition of meiosis	+	chromosomes may be due to cytotoxicity	
	0.0025M	Cow oocytes	Inhibition of meiosis	+		
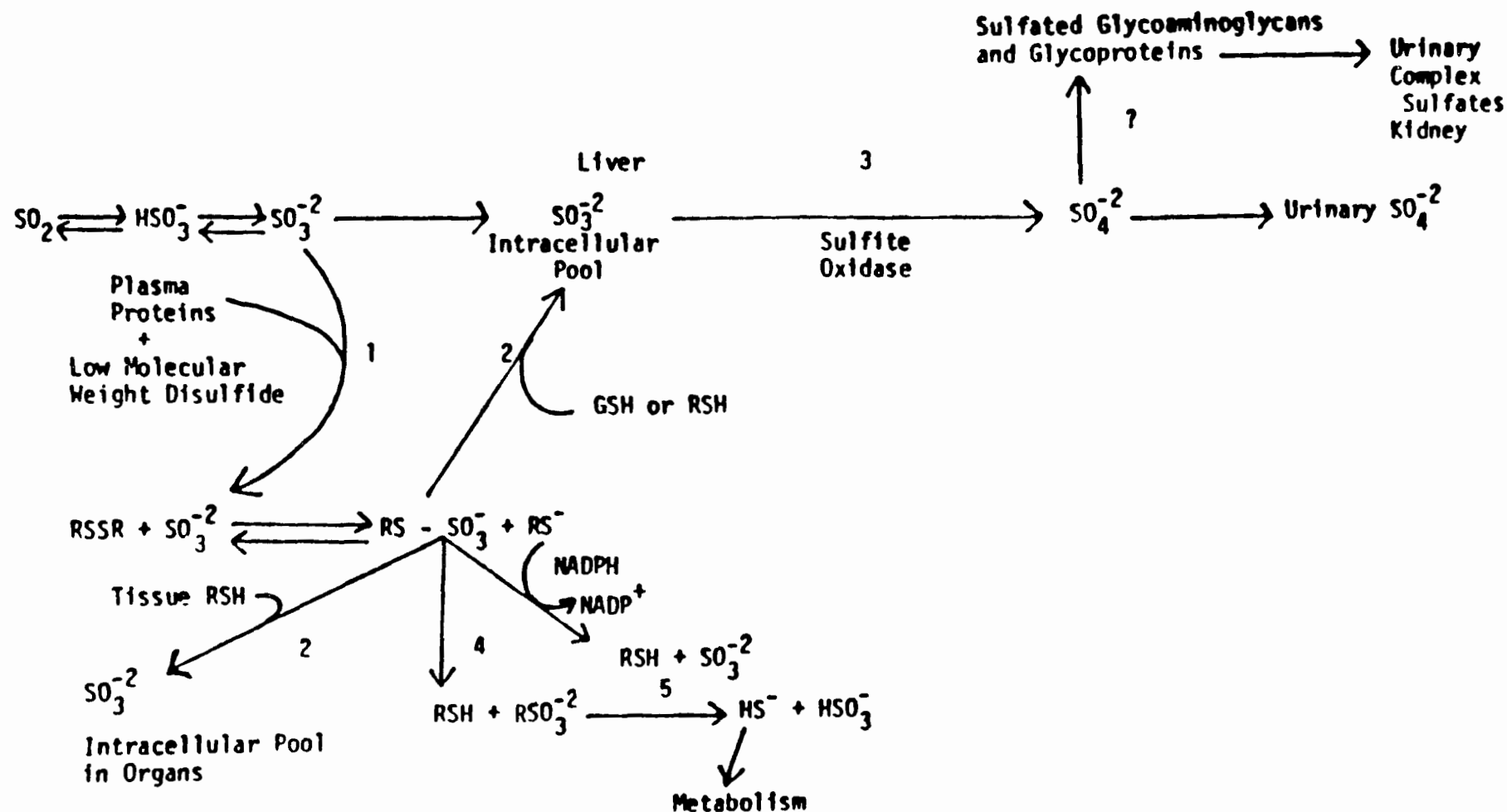
Figure 12-1. An integrative scheme for metabolism of sulfur dioxide in mammals.

plasma sulfhydryl compounds can react with plasma S-sulfonates to reverse the reaction, leading to the establishment of an intracellular pool of sulfite. Thus, intracellular concentrations of sulfite can occur over a prolonged period after a single inhalation of SO_2. Such a mechanism may explain the observation that inhaled $^{35}SO_2$ leads to the presence of ^{35}S in various other organs in dogs besides the lung (e.g., the ovaries).[77] Distribution of a mobile source of sulfite through the blood is particularly important because of the variety of reactions of SO_2, sulfite and bisulfite, and because of the implication that toxic effects are also possible in nonpulmonary organs.

Frank et al.[77] found exhaled ^{35}S in the breath of dogs exposed to $^{35}SO_2$ through the surgically isolated head and upper airways. Presumably, the breath ^{35}S was in the form of $^{35}SO_2$ and could have occurred through nasal absorption of SO_2 and distribution through the circulation. Breath SO_2 could have come either from the desorption of hydrated SO_2 (bisulfite or sulfite) or through reversal of the equilibrium of sulfite and plasma proteins with plasma S-sulfonates. Since plasma S-sulfonates are the dominant form of exogenously supplied SO_2 in the blood, the reversal of Reaction 1 (Figure 12-1) seems to occur easily and rapidly during the early phases of exposure.

Most of the inhaled SO_2 is presumed to be detoxified by the sulfite oxidase pathway in the liver, forming sulfate which is excreted in the urine (Reaction 3, Figure 12-1). The dominance of this reaction has been supported by studies of sulfite oxidase inhibition[32] which are discussed below and by the appearance of about 85 percent of the inhaled $^{35}SO_2$ as urinary sulfate in dogs.[44] Once oxidized by sulfite oxidase, most of the inhaled ^{35}S derived from $^{35}SO_2$ appears in the urine as ^{35}S-sulfate.[44] A small fraction (10 to 15 percent) of the urinary ^{35}S was in the form of sulfuric acid esters and

ethers.[44] Sulfate arising from the oxidation of sulfite can enter the sulfate

pool and could be incorporated into sulfate macromolecules including

glycosaminoglycans and glycoproteins. These macromolecules are actively

synthesized by the respiratory mucosa and could account for the presence of

radiolabeled sulfur in the respiratory tract following inhalation of $^{35}SO_2$.[44]

Most of the nondialyzable ^{35}S detected by Yokoyama et al.[44] was bound to the

α-globulin fraction of plasma. The chemical form of the ^{35}S was not

determined. Yokoyama et al.[44] speculated that the ^{35}S present in the

α-globulin fraction was in the form of sulfonated carbohydrates. The problem

is in need of further clarification. According to Gunnison and Palmes,[69]

plasma S-sulfonated proteins may also have contained the ^{35}S. They have

suggested that the slow clearance of plasma S-sulfonates is an important

factor in determining toxicity. They have not reported, however,

intracellular levels of S-sulfonates or sulfite.

Reductive cleavage of S-thiosulfates to a thiol and thiosulfate

(Reaction 4, Figure 12-1) has been reported.[77] Thiosulfate can be reduced to

hydrosulfide (Reaction 5, Figure 12-1) by rhodonase and reduced lipoate or by

thiosulfate reductase and reduced glutathione.[72-74]

12.2.1.3.2 <u>Sulfite Oxidase</u>. The biochemistry of sulfite oxidase will be

discussed because of its importance as a mechanism of detoxification of

sulfite. Genetic deficiency of sulfite oxidase occurs in humans.[167-169]

Dietary factors can, however, alter the enzymatic activity.[42] Sulfite oxidase

(EC 1.8.3.1) is a metallo-hemo protein with molybdenum and protoheme as the

prosthetic groups.[32] It exists in animals,[32-37] bacteria,[38] and plants.[39-41]

In both plants and animals, the enzyme is located in the mitochondria.

Purified sulfite oxidase can utilize either cytochrome c or oxygen as the

electronic receptor.[34] When coupled with cytochrome $\underline{c}$ to the mitochondrial respiratory chain, sulfite oxidase reduces molecular oxygen to water (Equation 12-24), whereas during oxygen reduction, the product formed is hydrogen peroxide (Equation 12-25).

$$SO_3^{-2} \Big\rangle \Big(\begin{array}{c} 2 \text{ Cyt c (Fe}^{3+}) \\ \\ 2 \text{ Cyt c (Fe}^{2+}) \end{array} \Big\rangle \Big(\begin{array}{c} H_2O \\ \\ 1/2 \ O_2 \end{array} \qquad \text{12-24}$$

$$SO_3^{-2} + H_2O + O_2 \rightarrow SO_4^{-2} + H_2O_2 \qquad \text{12-25}$$
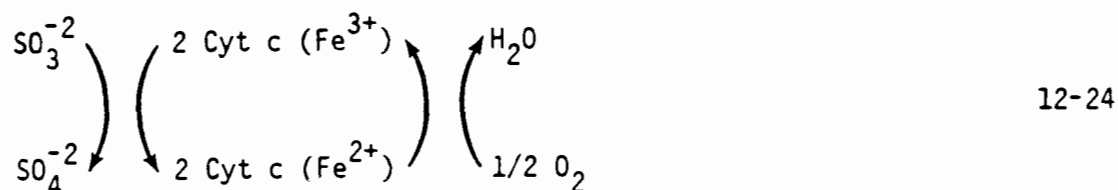
Direct reduction of molecular oxygen by sulfite oxidase is prevented in the presence of ferric cytochrome $\underline{c}$. In intact mitochondria, therefore, sulfite oxidation occurs through the interaction of sulfite oxidase with the respiratory chain of the mitochondria, producing 1 mole of ATP/mole of sulfite oxidase.

Sulfite oxidase is presumed to be necessary for the detoxification of sulfite. In three reported cases in humans, a genetic defect in this enzyme resulted in severe neurological problems.[167-169] Cohen et al.[42] suggested that sulfite oxidase is the principal mechanism for detoxifying bisulfite and SO_2. This is supported by a study which showed that dogs exposed to $^{35}SO_2$[44] excreted 80 to 90 percent of the inhaled ^{35}S in the urine. Because sulfite oxidase requires molybdenum, Cohen et al.[42] were able to deplete rats of sulfite oxidase by feeding them a low molybdenum diet and treating them with 100 ppm of sodium tungstate in drinking water. Tungsten competes with molybdenum and essentially abolishes the activity of sulfite oxidase and xanthine oxidase (EC 1.2.3.2), the two major molybdo-proteins of rat liver.

Similar decreases were observed in the lung and other organs. The LD50 for interperitoneally injected bisulfite was found to be 181 mg $NaHSO_3$/kg in the sulfite oxidase deficient animals compared to 473 mg/kg in the nondeficient rats.

The effect of inhaled SO_2 on lethality was more complex.[42] High levels were used in all cases and two effects of inhaled SO_2 were observed. At 1,546 or 2,424 mg/m^3 (590 or 925 ppm) SO_2 or less, the principal effect in control animals was respiratory insufficiency resulting in death by asphyxiation. At 6,157 mg/m^3 (2,350 ppm) SO_2 or greater (up to 1.3×10^6 mg/m^3, 1,310,000 ppm), the principal effect appeared to be mediated by the central nervous system (CNS) resulting in seizures and prostration followed by death. A direct effect of bisulfite on the CNS has been suggested.[42] Interperitoneally injected bisulfite[42] also produced CNS effects. Mortality was observed in both the control and tungsten-treated animals exposed to greater than 1,554 mg/m^3 (593 ppm) SO_2 for 4 hr. Most of the deaths occurred within 48 hr of exposure, and no further mortality occurred during the subsequent 2 wk period. Time before death, however, appeared to be much shorter for those rats treated with tungsten than for control animals. To test this finding, rats were exposed continuously to 1,546, 2,424, or 6,157 mg/m^3 (590, 925, or 2,350 ppm) SO_2. At 6,157 mg/m^3 (2,350 ppm) and 2,424 mg/m^3 (925 ppm), but not at 1,546 mg/m^3 (590 ppm), a clear difference existed between the tungsten-treated (i.e., deficient in sulfite oxidase) and control animals, with the tungsten-treated animals dying earlier. Cohen et al.[42] suggest that these differences in survival times are due to the inability of the tungsten-treated animals to detoxify inhaled SO_2 to sulfate. Of those animals exposed to 2,424 mg/m^3 (925 ppm) SO_2, tungsten-treated animals died of seizures and

prostration, whereas the control group succumbed to respiratory insufficiency. The authors concluded that sulfite oxidase mainly alleviates acute systemic toxicity due to bisulfite and has little or no effect on subacute or chronic respiratory effects of SO_2. The sulfite oxidase pathway in the rat lung is capable of detoxifying bisulfite derived from inspired SO_2 at the rate of 600 μmole/day. The authors suggest that this is equivalent to 52.4 mg/m^3 (20 ppm) SO_2 in the atmosphere, assuming complete extraction of SO_2 by the rat lung. The capacity of the rat (200 g) to oxidize bisulfite amounts to 150,000 μmole of bisulfite/day, which is theoretically equivalent to continuous exposure to 13,100 mg/m^3 (5,000 ppm) SO_2. Since some rats exposed to 2,424 mg/m^3 (925 ppm) SO_2 died (25 to 38 percent mortality), factors other than oxidation by sulfite oxidase must be considered.[42]

Attempts to induce higher levels of sulfite oxidase through pretreatment of the animals with SO_2/bisulfite or phenobarbital failed.[42] Since sulfite oxidase is a mitochondrial enzyme with a long half-life, it is not likely that phenobarbital or chronic exposure to SO_2 would result in adaptation through induction of higher levels of sulfite oxidase.

12.2.1.4 Activation and Inhibition of Enzymes by Bisulfite--Both inhibition and activation of specific enzymes have been reported. This may be due to formation of S-thiosulfates since disulfide bonds often stabilize the tertiary structure of proteins. Sulfite ions activated several phosphatases including ATP-ase[46] and 2,3-diphosphoglyceric acid phosphatase.[47] The mechanism by which activation occurs is not known. Inhibition of several enzymes has been reported; these include aryl sulfatase,[47] choline sulfatase,[48] rhodanase,[38] and hydroxyl amine reductase.[49] Malic dehydrogenase was inhibited by micromolar concentrations of bisulfite (Ki = 5 μM).[50-51] Other dehydrogenases[52] and flavoprotein oxidases are inhibited by bisulfite.

Bisulfite effectively inhibits a number of other enzymes including potato and rabbit muscle phosphorylase.[53] Bisulfite inhibition was competitive with respect to glucose-1-phosphate and inorganic phosphate, suggesting that the bisulfite inhibition was caused by competition of bisulfite with the phosphate binding site of phosphorylase. Several important coenzymes, such as pyrodoxylphosphate, NAD^+, $NADP^+$, FMN, FAD, and folic acid, may react with sulfite to form addition products as discussed above. As a result, these coenzymes could theoretically aid in inhibition of a wide variety of critical enzymic reactions. Pyridine coenzyme-bisulfite adduct[8] and flavoenzyme-bisulfite adduct[10,54] have been studied in detail, and these adducts have been shown to be biologically inactive.

Despite all of the data obtained using in vitro systems on the inhibition of enzymes by bisulfite/SO_2, no inhibition or activation has been determined in vivo with SO_2 exposure. Such inhibition may occur, but there has been no concerted effort to search for inhibition of specific enzymes during SO_2 exposure.

12.2.2 Mortality

The acute lethal effects of SO_2 have been examined mostly in the older literature and have been reviewed in the previous Air Quality Criteria Document for Sulfur Oxides.[78] In early studies, a number of different animal species was examined for susceptibility to SO_2. These data show that mortality was not observed at exposures of 65.5 mg/m^3 (25 ppm) for up to 45 days in either rats or mice; this conclusion has been confirmed by subsequent studies.[68] Statistically significant mortality could be associated with long-term exposure to SO_2 at 134 mg/m^3 (51 ppm) or higher. The clinical signs of SO_2 intoxication appear to vary with the dose rate.[42] At concentrations

below approximately 1,310 mg/m^3 (500 ppm), mortality is associated with respiratory insufficiency; above this concentration, mortality is ascribed to central nervous disturbances producing seizures and paralysis of the extremities. These clinical signs depend upon the presence and activity of sulfite oxidase as discussed in Section 12.2.1.3.2 Injections of histamine or adrenalectomy can increase the lethality of SO$_2$.[230]

Matsumura[113,114] examined the effect of a 30-min exposure to several air pollutants on mortality consequent to the anaphylactic response of guinea pigs to protein antigens. Sensitization to the antigen administered by aerosol was augmented by pretreatment with 786 mg/m^3 (300 ppm) SO$_2$, but not with 472 mg/m^3 (180 ppm). The dyspneic attack of anaphylaxis was not affected by as much as 1,048 mg/m^3 (400 ppm) SO$_2$.

On the basis of mortality due to acute exposure, SO$_2$ is far less toxic than ozone and is similar in toxicity to nitrogen dioxide. Concentrations required to produce mortality from SO$_2$ are far in excess of those which occur in the atmosphere due to pollution (Table 12-2).

12.2.3 Tumorogenesis in Animals Exposed to SO$_2$ or SO$_2$ and Benzo(a)pyrene

Tumorogenesis after exposure to SO$_2$ alone or to SO$_2$ and an aerosol of benzo(a)pyrene has been examined. Mice were exposed over their lifetimes in a 180 liter chamber into which 500 ppm SO$_2$ was injected at a rate of 20 ml/min for 5 minutes, for 5 days/wk 5 days/wk for lifetimes[67] . Examinations for tumors of the lung and other organs were undertaken only in mice that survived longer than 300 days, since no primary lung tumors had been seen in younger mice. Primary pulmonary neoplasias increased in the males (n = 35) from 31 percent in the control group to 54 percent in the SO$_2$-exposed group and in the females (n = 30) from 17 to 43 percent. The incidence of the next most common tumors in this strain of mice, hepatomas and lymphomatoses, was not affected. The

TABLE 12-2. LETHAL EFFECTS OF SO_2 ON ANIMALS

SO_2 Concentration g/m³	ppm	Duration	Species	Remarks	Reference
26.2	10	6 hr/day x 5 day/wk x 113 day	Rat	No mortality in excess of control	Laskin et al.[68]
134	51	113 days		No mortality in excess of control	
275	105	22 day		64% mortality (treated-control)	
~~1,310~~ *see text*	~~500~~	5 min/day x 5 day/wk > x ~~300 days~~ *lifetime*	Mice	No increased mortality; tumor formation found	Peacock and Spence[67]
1,598	610	LT_{50} 285.6 min	Mice (Connaught Med. Res. Lab. Strain)	IP injection of 200 to 300 mg histamine/mouse increased toxicity	Leong et al[230]
2,392	913	74.5 min			
3,086	1,178	38.7 min			
5,175	1,975	LT_{50} 197.6 min	Rat (Sprague-Dawley)	IP injection of 200 to 300 mg histamine/rat or adrenalectomy increased toxicity	Leong, et al.[230]
9,165	3,498	71.7			
13,236	5,052	41.0			
5,782	2,207	LT_{50} 68.2 min	Guinea Pig		Leong, et al.[230]
6,571	2,508	28.7			
7,205	2,750	35.5			
786	300	30 min	Guinea Pig	Increased mortality due to anaphylaxis from antigen challenge to sensitized animals	Matsumura[113,114]

authors classified only tumors which invaded blood vessels as carcinoma. In males, SO_2 did not affect the incidence of malignant tumors (2/35, 6 percent in air group; 2/28, 7 percent in SO_2 group). However, in females, the incidence of primary lung carcinoma increased from 0/30 in the controls to 4/30 (18 percent) in the SO_2-exposed mice. These were early studies and the statistical analysis is vague. The significance of these increases,[67] therefore, is questionable. The investigators concluded that the increased incidence of primary lung tumors was due to the initial inflammatory reaction to SO_2, followed by tolerance, which accelerated spontaneous tumor development. They further state that this study does not "justify the classification of SO_2 as a chemical carcinogen as generally understood."

Lung tumors or other significant pathological effects were not observed in hamsters exposed for 98 wk to 26.2 mg/m^3 (10 ppm) SO_2 for 6 hr/day, 5 days/wk for 534 exposure days or to 9.17 mg/m^3 (3.5 ppm) SO_2 plus 10 mg/m^3 benzo(a)pyrene for 1 hr/day, 5 days/wk for 494 exposure days or to a combination of the 2 regimens.[68] When rats[68] were exposed to the same regimen, however, lung squamous cell carcinoma was found in 5/21 (23.8 percent) animals receiving the combined exposure of 26.2 mg/m^3 (10 ppm) SO_2 for 6 hr/day and 9.17 mg/m^3 (3.5 ppm) SO_2 plus 10 mg/m^3 benzo(a)pyrene for 1 hr/day and in 2/21 (9.5 percent) animals exposed to the benzo(a)pyrene plus SO_2 for 1 hr/day. Renal metastasis also occurred. Control rats exposed to air (n = 3) or to 26.2 mg/m^3 (10 ppm) SO_2 (n = 3) had no tumors.

This study was subsequently extended to lifetime (exact time not specified) exposures (5 days/wk) of rats.[194] Exposure to air alone (n = 15) or 26.2 mg/m^3 (10 ppm) SO_2 (n = 15) for 6 hr/day caused no cancers (squamous

cell carcinoma). A 1 hr/day exposure to 10 mg/m^3 benzo(a)pyrene caused cancer in 1/30 (3.3 percent) rats. A 6 hr/day exposure to 26.2 mg/m^3 (10 ppm) SO$_2$ plus a 1 hr/day exposure to 10 mg/m^3 benzo(a)pyrene resulted in a cancer incidence of 6.7 percent (2/30). When animals received a combination of 10 mg/m^3 benzo(a)pyrene and 10.48 mg/m^3 (4 ppm) SO$_2$, 4/45 (8.9 percent) of the rats had cancer. The highest incidence (19.6 percent, 9/46) was found in animals exposed for 6 hr/day to 26.2 mg/m^3 (10 ppm) SO$_2$ plus a combination of 10 mg/m^3 benzo(a)pyrene and 10.48 mg/m^3 (4 ppm) SO$_2$ for 1 hr/day.

The biological significance of these studies (Table 12-3) is complex and difficult to interpret, particularly since statistical analyses were not reported in the publications. Few SO$_2$ exposure experiments have been carried out for the near lifetime of the animal as in the early mouse study[67] and the subsequent rat study.[194] Most work has centered around short-term acute studies in which the experimental design and other aspects of the study would be inadequate to detect a low incidence of tumors. The incidence of lung tumors increases as the animals age; but no historical control data are available for the colony of rats used,[68,194] making the increased incidence by the combined SO$_2$-benzo(a)pyrene treatment difficult to interpret. Tumor formation may be a multistep process, requiring more than just the initiation for expression. Thus, the potential co-carcinogenic activity of SO$_2$ may be real and significant in terms of a human health hazard, but it is not definitely proven by these experiments.

12.2.4 Morphological Alterations

Because of the high solubility of SO$_2$ in water, morphological and physiological effects have been detected in the upper and lower airways (Table 12.4). At relatively high concentrations (used in most studies designed to

TABLE 12-3. TUMOROGENESIS IN ANIMALS EXPOSED TO SO_2 OR SO_2 AND BENZO(a)PYRENE

Concentration	Duration	Species	Results	Reference
~~1310 mg/m³ (500 ppm) SO₂~~ *(see text)*	5 min/days, 5 day/wk, lifetime	Mice	Primary pulmonary neoplasias increased in the males from 31 to 54% and in the females from 17 to 43%. Incidence of hepatomas and lymphomatoses were not affected. Carcinoma incidence increased in females from 0 to 18%; no change in carcinomas in males	Peacock and Spence[67]
26.2 mg/m³ (10 ppm) SO₂ for 534 exposure days, or 1 hr exposure (5 day/wk) to 9.17 mg/m³ (3.5 ppm) SO₂ + 10 mg/m³ benzo(a)-pyrene for 494 exposure days, or a combination of the 2 regimens	6 hr/days, 5 day/wk, 98 wk	Hamster	No lung tumors or other pathological effects	Laskin et al.[68]
26.2 mg/m³ (10 ppm) SO₂ for 534 exposure days, or 1 hr exposure (5 day/wk) to 9.17 mg/m³ (3.5 ppm) SO₂ + 10 mg/m³ benzo(a)pyrene for 494 exposure days, or a combination of the 2 regimens	6 hr/day, 5 days/wk, 98 wk	Rat	Lung squamous cell carcinoma: 5/21 (23.8%) animals exposed to combined regimen of 26.2 mg/m³ (10 ppm) SO₂ for 6 hr/day and 9.17 mg/m³ (3.5 ppm) SO₂ + 10 mg/m³ benzo(a)pyrene for 1 hr/day; 2/21 (9.5%) animals exposed to benzo(a)pyrene + SO₂ for 1 hr/day; 0/3 in animals exposed to 26.2 mg/m³ (10 ppm) SO₂; and 0/3 in animals exposed to air	Laskin et al.[68]
26.2 mg/m³ (10 ppm) SO₂, or 10.5 mg/m³ (4 ppm) SO₂ + 10 mg/m³ benzo(a)pyrene, or a combination of the 2 regimes	Lifetime (5 days/wk)	Rat	A 1 hr/day exposure to 10 mg/m³ benzo(a)pyrene caused cancer in 1/30 (3.3%). A 6 hr/day exposure to 26.2 mg/m³ (10 ppm) SO₂ + a 1 hr/day exposure to 10 mg/m³ benzo(a)pyrene resulted in squamous cell carcinoma incidence of 6.7% (2/30). A combination of 10 mg/m³ benzo(a)pyrene and 10.5 mg/m³ (4 ppm) caused cancer in 4/45 (8.9%). Highest incidence (19.6%, 9/46) found in exposure for 6 hr/day to 26.2 mg/m³ (10 ppm) SO₂ + 10 mg/m³ benzo(a)-pyrene and 10.5 mg/m³ (4 ppm) SO₂ for 1 hr/day. The air control had an incidence of 0/15 and the 26.2 mg/m³ (10 ppm) SO₂ exposure caused an incidence of 0/15.	Laskin et al.[194]

TABLE 12-4. EFFECTS OF SULFUR DIOXIDE ON LUNG MORPHOLOGY

Concentration	Duration	Species	Results	Reference
0.34, 2.65, or 15.0 mg/m³ (0.13, 1.01, or 5.72 ppm) SO₂	1 yr, continuous	Guinea pig	Lungs of 15.0 mg/m³ (5.72 ppm) group, killed after 13 or 52 wk of exposure, showed less spontaneous pulmonary disease than controls. Controls and 0.34 and 2.64 mg/m³ (0.13 and 1.01 ppm) animals had evidence of lung disease. Tracheitis present in all but 15.0 mg/m³ (5.72 ppm) group. Survival greater in the latter group	Alarie et al.[88]
0.37, 1.7 or 3.35 mg/m³ (0.14, 0.64 or 1.28 ppm)	78 wk, continuous	Cynomolgus monkey	No remarkable morphologic alterations in the lung	Alarie et al.[90,91]
12.3 mg/m³ (4.69 ppm) then between 524 and 2620 mg/m³ (200-1000 ppm) then 0mg/m³ *O mg/m³*	30 wk then 1 hr then 48 wk	Cynomolgus monkey	Persistent changes in lung morphomology including: alterations in the respiratory bronchioles, alveolar ducts, and alveolar sacs; proteinaceous material within the alveoli; thicker alveolar walls infiltrated with histocytes and leucocytes; moderate hyperplasia of the epithelium of the respiratory bronchioles; bronchiectasis and bronchiolectasis; vacuolation of hepatocytes	Alarie et al.[90,91]
13.4 mg/m³ (5.12 ppm)	18 mo, continuous	Cynomolgus monkey	No alterations in lung morphology	Alarie et al.[92]
13.4 mg/m³ (5.1 ppm)	21 hr/day, 620 days	Dog	No alterations in lung morphology	Lewis et al.[104]
26.2 mg/m³ (10 ppm)	72 hr, continuous	Mouse	Pathological changes in the nasal mucosa appeared after 24 hr of exposure and increased in severity after 72 hr. Mice free of upper respiratory pathogens were significantly less affected than the conventionally raised animals. Morphological alterations were qualitatively identical in both groups.	Giddens and Fairchild[80]
91.7 mg/m³ (35 ppm) [rose on occasion to 262 mg/m³(100 ppm)]	1 to 6 wk	Pig	Loss of cilia in nasal cavity, disappearance of goblet cells, metaplasia of the epithelium	Martin and Willoughby[81]
1048 mg/m³ (400 ppm)	3 hr/day, 5 day/wk, 6 wk	Rat	Tracheal goblet cells increased in number and size. Incorporation of ³⁵SO₄²⁻ into mucus increased. Sialidase resistant mucus secreting cells were found much more distally. Chemical composition of mucus altered	Reid[83]
1048 mg/m³ (400 ppm) SO₂	3 hr/day, 5 day/wk, 3 wk	Rat	Increased mitosis of goblet cells. Alteration not lost by 5 wk post-exposure	Lamb and Reid[82]

detect morphological alterations), most of the inhaled SO_2 is removed by the nasopharyngeal cavity. (See Chapter 11, Section 11.2.4 for an expanded discussion of SO_2 absorption.) In rabbits, the concentration of inspired SO_2 determines how much is removed in the nasopharyngeal cavity as opposed to the bronchial and alveolar regions of the lung.[79] At high SO_2 concentrations, greater than 26.2 mg/m^3 (10 ppm), 90 to 95 percent is removed in the nasopharyngeal cavity. A small part, 3 to 5 percent, is removed by the bronchiolar-alveolar region. So at concentrations in this range, most of the dose is delivered to the nasal turbinates with only a small percentage going to the lung parenchyma. At lower concentrations of inspired SO_2, such as 0.13 mg/m^3 (0.05 ppm), which is closer to ambient levels, only 40 percent of the dose is delivered to the nasopharyngeal cavity upon inspiration, while another 40 percent is removed by the respiratory tract upon expiration. Thus, at lower concentrations, the actual percentage of SO_2 removed in specific regions of the respiratory tract is not known precisely. In the dog, over 95 percent was removed by the upper airways and nose at concentrations between 2.62 and 131 mg/m^3 (1 to 50 ppm) SO_2.[77,101]

Giddens and Fairchild[80] pointed out that these differences in removal of inspired SO_2 could explain the apparent anomaly of little damage to the lower respiratory tract at high SO_2 concentrations. They undertook a study of the effects of inhaled SO_2 on the nasal mucosa of mice. Two groups of mice were used; one group that was free of specific upper respiratory pathogens, and an ordinary laboratory group that was presumed to be infected or to have a latent infection of upper respiratory pathogens. Mice were exposed continuously to 26.2 mg/m^3 (10 ppm) SO_2 for a maximum of 72 hr. Pathological changes in the nasal mucosa appeared after 24 hr of exposure and increased in severity after

72 hr of exposure. Mice free of upper respiratory pathogens were significantly less affected than the conventionally raised animals. Giddens and Fairchild[80] concluded that resident or acquired pathogens exacerbated the morphological changes they had observed. Morphological alterations were, however, qualitatively identical in both groups of animals. Cilia were lost from the nasal mucosa; vacuolization appeared; and the mucosa decreased to about one half the normal thickness, and a watery fluid accumulated. Desquamation of the respiratory and the olfactory epithelia was evident. Alveolar capillaries were slightly congested, but edema and inflammatory cells were absent. Martin and Willoughby[81] reported loss of cilia, disappearance of goblet cells, and metaplasia of the epithelium of the nasal cavity of pigs exposed to 91.7 mg/m^3 (35 ppm) SO_2 for 1 to 6 wk. This study, however, was marred by difficulties with the control of the SO_2, rising on occasion to 262 mg/m^3 (100 ppm), and with high relative humidity occurring during cleaning of the pig pens.

Lamb and Reid[82] and Reid[83] attempted to use SO_2-exposed rats in a model of human chronic bronchitis. They presented favorable arguments that SO_2-induced bronchial hyperplasia is analogous to human chronic bronchitis. Most of their studies have been carried out at high concentrations of SO_2 (1,048 mg/m^3 or 400 ppm SO_2 for 3 hr/day, 5 days/wk). Under these conditions, the tracheal glands clearly increased. The goblet cell density also increased in the proximal airways, main bronchi, trachea, and distal airways, with proximal airways and main bronchi showing the largest changes. The incorporation of ^{35}S-sulfate by goblet cells into mucus also increased with exposure, reaching a plateau at approximately 3 wk. Changes in the mitotic index were observed (Figure 12-2). The effects of SO_2 were concentrated in
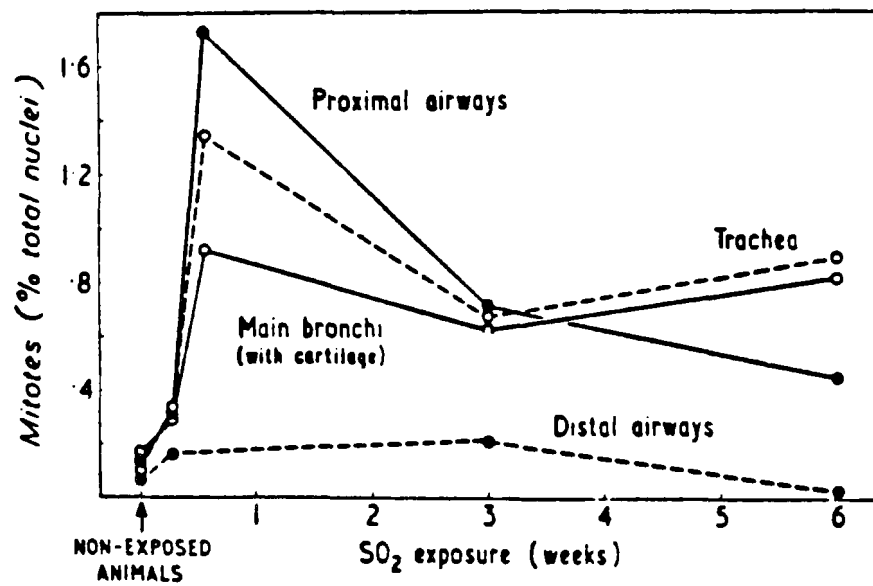
Figure 12-2. Mitotic count (four-hour period) after SO_2 exposure up to six weeks. Mitoses represented as percentage of total nuclei.[83]

the central airways, again suggesting that the solubility of SO_2 in water limits its accessibility to the periphery. Mitosis reached a maximum after 2 or 3 exposures and declined rapidly as injured cells were replaced. On repeated exposure for periods up to 6 wk, mitosis remained elevated in the proximal airways compared to the distal airway in which this value returned to the control level. The magnitude was proportional to the SO_2 concentration (Figure 12-3). An elevation of the mitotic index occurred at concentrations as low as 131 mg/m^3 (50 ppm) when given for 3 hr/day, 5 days/wk. Major changes in the goblet cell type or substance produced by the goblet cells were also detected. Goblet cells which produced mucous (Figure 12-4) resistant to digestion by sialidase increased in numbers, and their distribution extended distally from the upper bronchioles towards the respiratory bronchioles. Since each molecular type of mucin, sialidase resistant or susceptible, could be produced by one type of goblet cell, or each goblet cell could produce a different mucin, these results can be interpreted in two ways. The elaboration of a specific type of goblet cell could occur, or more goblet cells could be produced but with a change in their biochemical function towards sialidase resistant mucins.

Alarie et al.[88] examined the tissues of guinea pigs exposed continuously to 0, 0.34, 2.65, or 15.0 mg/m^3 (0, 0.13, 1.01, or 5.72 ppm) SO_2 for 1 yr. The lungs of the guinea pigs exposed to 15.0 mg/m^3 (5.72 ppm) and killed after 13 or 52 wk of exposure showed less spontaneous pulmonary disease than the control group. The prevalence of pulmonary disease in the control groups which was not observed prior to exposure suggests that they acquired pulmonary disease during the exposure period. In these[88] and other studies by Alarie
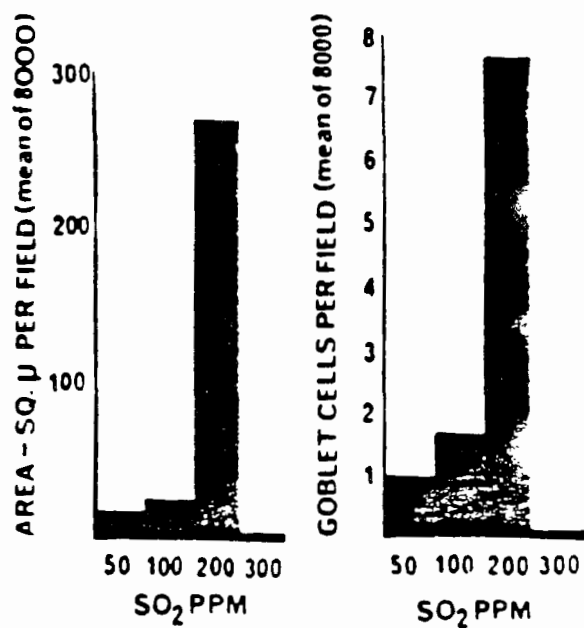
Figure 12-3. Histogram area covered by PAS sensitive material in tracheal epithelium of rats exposed to 50, 100, 200, and 300 ppm of SO_2 on eight rats at each concentration. 1,000 fields (x20) were evaluated. Counts made with an automated image analyzer.[83]

NORMAL

After RDE

SO$_2$ EXPOSED

After RDE
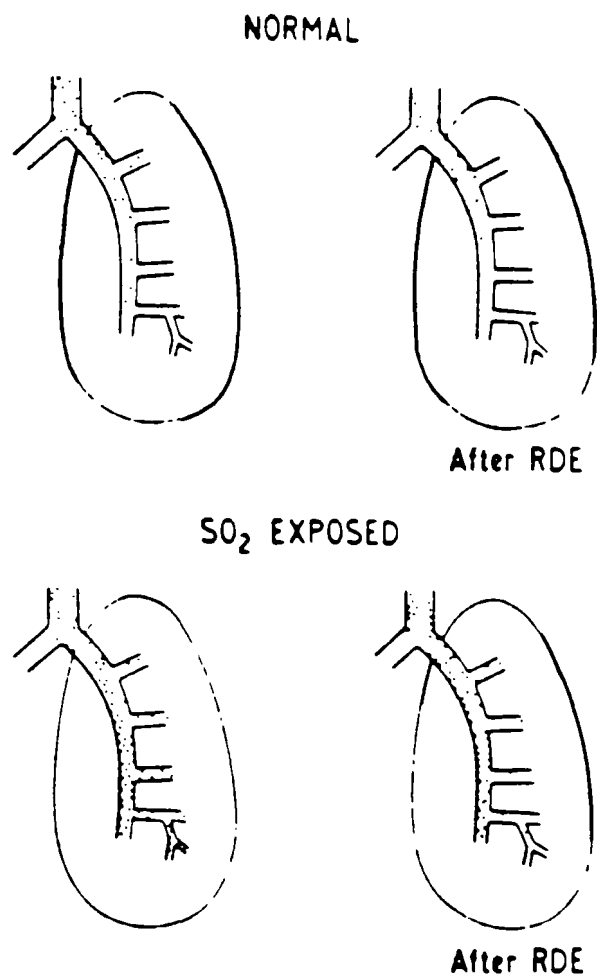
Figure 12-4. Increase in goblet cells after expos-
ure to SO$_2$. Increase in goblet cells assessed by
comparison of left-hand diagrams; increase and
extension of goblet cells resistant to sialidase
(RDE) in right-hand pair.[83]

and co-workers,[90-92] light microscopic observations were limited to
conventional hematoxylin-eosin stained paraffin sections. The control group,
as well as those exposed to 0.34 and 2.64 mg/m^3 (0.13 and 1.01 ppm), had
evidence of lung disease as shown by histocytic infiltration of the alveolar
walls. Tracheitis was also present in the above three groups, but not in the
15.0 mg/m^3 (5.72 ppm) group. Hepatocyte vacuolation was observed in the
latter group. The survival was greater (p <0.05) in the 15.0 mg/m^3 (5.72 ppm)
group than in the other groups including the air exposed control group. The
authors do not address the significance of the hepatocyte vacuolation. The
possible effects of SO_2 in this study cannot be accurately determined because
of the disease in the control animals.

Subsequently these researchers[90,91] exposed cynomolgus monkeys
continuously to 0.37, 1.7 or 3.35 mg/m^3 (0.14, 0.64 or 1.28 ppm) SO_2 for 78 wk
but found no remarkable morphological alterations. Another group exposed to
12.3 mg/m^3 (4.69 ppm) SO_2 for 30 wk was accidentally exposed to concentrations
of SO_2 not higher than 2,620 mg/m^3 (1,000 ppm) or lower than 524 mg/m^3 (200
ppm) for 1 hr, after which they were placed in a clean air chamber and held
for 48 more wk. Persistent changes were noted in this group. Alterations in
the respiratory bronchioles, alveolar ducts, and alveolar sacs were found.
Proteinaceous material was found within the alveoli. The distribution of such
lesions was focal, but was observed within all lobes of the lung. Alveoli
containing proteinaceous material were generally those which arose directly
from respiratory bronchioles. Alveolar walls were thicker and were
infiltrated with histocytes and leukocytes. Macrophages were present within
these foci. Moderate hyperplasia of the epithelia of the respiratory
bronchioles was found, and frequently the lumina of the respiratory

bronchioles were plugged with proteinaceous material, macrophages, and leukocytes. Bronchiectasis and bronchiolectasis were present in 8 of 9 animals. Vacuolation of hepatocytes was also observed, as with the guinea pig group exposed to 15.0 mg/m^3 (5.72 ppm) in the prior study.[88]

In a replication of this study, cynomolgus monkeys were exposed to 13.4 mg/m^3 (5.12 ppm) SO_2 continuously for 18 mo.[92] No alterations in lung morphology were reported to be due to SO_2. The morphological alterations reported in the control group included lung mite infections and associated "slight subacute bronchiolitis, alveolitis, and bronchitis." Pulmonary function measurements were made in the above mentioned studies[88,90-92] and are described in Section 12.2.5.

The absence of SO_2-induced morphological alterations as reported by Alarie et al.[88,90-92] and Lewis et al.[104] who exposed dogs for 620 days (21 hr/day) to 13.4 mg/m^3 (5.1 ppm) SO_2 is not in conflict with the broncho-constriction induced by acute SO_2 exposure reported by Amdur and her co-workers[93] at lower concentrations (see Section 12.2.5). Alarie et al.[88] pointed out, "As recent literature attests, there is also an obvious lack of knowledge about the correlation between subtle microscopic alterations in the lung and concomitant changes in this physiological parameter (lung function)." Further, the transient nature of the pulmonary function effects observed during short-term exposures would be difficult to detect morphologically unless the lungs were fixed during the time of exposure. Even then, if the cause of the increased pulmonary resistance were a simple alteration of smooth muscle tone as has been hypothesized, it might be morphologically undetectable.

Most of the studies in which the lungs of SO_2-exposed animals have been examined center around tracheitis, bronchitis, ulceration, and mucosal hyperplasia (Table 12.4). The lowest concentrations at which these alterations have been reported have been in the rat at 131 to 134 mg/m^3 (50 to 51 ppm) for 30 to 113 days. At higher concentrations (1,048 mg/m^3 or 400 ppm SO_2 for 3 hr/day, 5 days/wk for 3 wk), recovery to normal morphology did not occur after 5 wk post-exposure. The possibility of recovery from lower concentrations and shorter durations of exposure is not known.[82,83] The studies of Alarie et al.[88,90-92] are unfortunately flawed by the questionable health of the exposed animals and the accidental exposure to high concentrations.

12.2.5 Alterations in Pulmonary Function

Changes in pulmonary function have been among the most sensitive and fruitful areas of research in SO_2 toxicity. They have likewise been useful in studying the effects of aerosols alone or in combination with SO_2 (Sections 12.3.3.1 and 12.4.1.1). A variety of methods have been used, some of which have been applied to human exposures. A method for measuring increases in flow resistance in guinea pigs has been developed by Amdur.[94,95] Animals are not anesthetized and breathe spontaneously, which allows sensitive measurements of pulmonary function. (A complete description of this method appears in Appendix I, section 7.2.1.)

The respiratory rate of mice has been used as an indication of pulmonary irritation by Alarie et al.[85] Mice were exposed for 10 min to 0, 44.5, 83.8, 162, 233, 322, 519, or 781 mg/m^3 (0, 17, 32, 62, 89, 123, 198, or 298 ppm) SO_2. About a 12 percent decrease was observed at 44.5 mg/m^3 (17 ppm). The respiratory rate decreased inversely to the logarithm of the concentration of inspired SO_2. The decrease in respiratory rate, however, was transient,

returning to nearly control levels within 10 min even at continued exposure to 781 mg/m^3 (298 ppm) SO_2. Complete recovery to control values occurred within 30 min following all exposures to SO_2. The time for maximum response was inversely related to the logarithm of the concentration of SO_2, being shortest at highest concentrations. Mice exposed to 262 mg/m^3 (100 ppm) SO_2 for 10 min were allowed to recover in clean air prior to a subsequent 10 min exposure to the same concentration. As the length of the recovery period was decreased (from 12 min to 3 min), the effect of the subsequent SO_2 exposure on respiratory rate was lessened. "Desensitization" thus appeared to occur during the course of exposures. When another irritant, aerosols of chlorobenzilidene malononitrile (CBM), was used during the refractory period following SO_2 exposure, the respiratory rate decreased at a rate comparable to that following exposure to CBM alone. Thus, the refractory period associated with SO_2 exposures appeared specific to SO_2 and not to CBM. When 262 to 328 mg/m^3 (100 to 125 ppm) SO_2 was provided repeatedly for durations of 90 sec, with each exposure separated by a 60 sec recovery period, the refractory period was cumulative. Ten such exposures eventually abolished all respiratory rate responses to SO_2. Breathing clean air for 60 min resulted in a return of the response to initial levels. When mice were exposed to SO_2 by means of a tracheal cannula, no changes in the respiratory rate were observed, indicating that the decrease in respiratory rate was mediated by a reflex arc. This hypothesis has been developed in considerable detail in an extensive review by Alarie[86] who suggests that stimulation and desensitization occur via cholinergic nerve endings of the afferent trigeminal nerve. Alarie et al.[85] also suggest that SO_2 is hydrated to bisulfite and sulfite which react with a receptor protein to form an S-thiosulfate and a thiol, cleaving an existing

disulfide bond. The receptor protein slowly regenerates to its original disulfide configuration by the oxidation of S-thiosulfide and free thiol moieties of the receptor protein to disulfide. No direct evidence for this hypothesis has been presented.

Other investigators[87,98-100,251] found that bronchoconstriction resulted from both head-only and lung-only exposures in cats and dogs. When corrected for the amount of SO_2 hypothesized to reach the lung, Amdur's study[63] with guinea pigs has shown that SO_2 is highly effective in producing bronchoconstriction through direct exposure of the lung. Two sets of receptors are involved in the response of animals to SO_2. At high concentrations of SO_2 or following long durations of exposure, the nasopharyngeal receptors fatigue or become unresponsive, whereas the bronchial receptors do not. Nadel et al.[87,251] demonstrated the existence of a reflex arc by "cold blocking" the vagus nerve. Chilling the vagus nerve prevents conduction of nervous impulses and abolishes the bronchoconstriction produced by inhaled SO_2. Intravenous injection of atropine, which blocks some vagal responses, also prevents the SO_2-induced effect. Sulfur dioxide-induced bronchoconstriction probably involves smooth muscle contraction. By acting on the same smooth muscles, acetylcholine (which is the neurotransmitter of the vagus) aerosols evoke bronchoconstrictive responses similar to those of SO_2.[102] Since the bronchoconstriction is dependent upon smooth muscle, which is not likely to sustain constriction for long times, chronic exposures are not likely to evoke sustained bronchoconstriction. Hypersecretion of mucus and alteration of airway caliber are more likely chronic effects.

Exposure to SO_2 evokes an increase in resistance in guinea pigs which persists for several hr and exhibits none of the tachyphylaxis found with

other species.[98,99] However, different techniques were used for these different species. Amdur,[93] in a review of her data, reported that for a 1 hr exposure, a mean of 0.68 mg/m^3 or 0.26 ppm (range of 0.08 to 1.57 mg/m^3 or 0.03 to 0.6 ppm) was the lowest concentration of SO_2 that increased flow resistance in guinea pigs. The response, a 12.8 percent increase (p < .001) at these[93] low levels of SO_2, was the average of 71 guinea pigs; the individual data points were reported in other publications.[96,124,170] For a 1 hr exposure, the lowest concentration these researchers tested which caused an increase (p <0.01) in resistance was 0.42 mg/m^3 (0.16 ppm) SO_2.[124] In a more recent study, Amdur et al.[130] showed that a 1 hr exposure of guinea pigs to 0.84 mg/m^3 (0.32 ppm) SO_2 caused a 12 percent increase in resistance (p <0.02) and a non-statistically significant decrease in compliance. At concentrations of SO_2 below 2.62 mg/m^3 (1 ppm), the response of individual animals varied considerably.[93,170,250] Of 1,028 guinea pigs, 135 were "sensitive", responding to low concentrations of SO_2 with greater changes in resistance than the predicted mean. Amdur cites comparative data for other species, including man, to suggest that a certain fraction of all subjects may exhibit this phenomenon.[93,170,274] On the other hand, Amdur et al.[171] also point out that some batches of animals may by chance not have a "sensitive" individual. In this study, 3 groups of 10 animals each or a total of 30 guinea pigs exposed to 0.52, 1.05, or 2.1 mg/m^3 (0.2, 0.4, or 0.8 ppm) SO_2 had no significant increase in airway resistance above the control values. Based on data from earlier work,[96] she concluded that 10 to 13 percent of the guinea pig population is more responsive than the average.[170] In cats[98] and dogs,[99] on the other hand, few were found to be sensitive to short-term (< 1 hr) exposure to 52.4 mg/m^3 (20 ppm) SO_2 (cats) or 18.3 mg/m^3 (7 ppm) SO_2 (dogs).

Even with the relatively small sample sizes used, some cats and dogs responded and others did not.

Some of the problem of "sensitive" vs. "insensitive" members of the experimental population can be understood by considering a simple hypothesis. If one assumes that the response to a given toxicant, such as SO_2, is the result of a number of different genes within the population and not just a single gene, then a single individual could have a number of recessive or dominant genes which could contribute to either the "sensitivity" or "insensitivity" of that individual. Since experimental animals and human subjects are drawn on as random a basis as is possible (in most experimental designs), there will be a maximum chance of getting some "sensitive" responders in each experiment. The total number of "sensitive" responders will be small and variable because of the low incidence of "sensitive" responders in the general animal population. A small, but variable, number of "sensitive" responders will tend to shift the dose- or concentration-response curve toward lower concentrations and to decrease the slope of the curve (e.g., when the data are expressed as the log-probit transformation). Such phenomena have been studied in detail for "resistant" insects which have different genomes responsible for increased detoxification mechanisms. In the case of SO_2, the matter is further complicated by comparisons between batches of animals and between different strains or species. Even with guinea pigs, the total number of animals examined to date (about 1,000 to 2,000) is too small to give more than a crude estimate of those animals having a "sensitive" genome. The incidence of "sensitivity" in the guinea pigs (about 13 percent) is too low to have been detected clearly in the 100 or so cats and dogs used in SO_2 experiments. Here only 1 or 2 "sensitive" animals would have been

encountered. Further, the small number of animals has been studied in different laboratories and at different times, and the animals have come from different genetic stocks. It is fortuitous that Amdur's laboratory has persisted in these studies with the same animal; the guinea pig, using the same general methodology so this low incidence of "sensitivity" could be detected. While the mechanism(s) responsible for "sensitivity" is not known, the question of "sensitivity" is an important aspect deserving of further study. A similar incidence of some 10 percent "sensitive" individuals in man would have serious health policy implications.

Using Strandberg's[79] data from the rabbit to correct for the concentration of SO_2 hypothesized to reach the lung, Amdur[63] was able to normalize the concentration-response curve for SO_2-induced bronchoconstriction in the guinea pig resulting from nose-only exposures (Figure 12-5). A break occurs in the concentration-response curve at about 52.4 mg/m^3 (20 ppm) SO_2, perhaps due to the poorer extraction of gaseous SO_2 by the upper airways at low concentrations. However, it should be recognized that SO_2 extraction data for rabbits[79] and dogs[77,100,101] are in some conflict and that the data for rabbits are not clear with respect to the site of SO_2 removal. Thus, use of the rabbit data for guinea pig studies can be done only hypothetically. Sulfur dioxide introduced directly into the lung by a tracheal cannula was much more effective in producing bronchial constriction. Amdur[63] suggests that at concentrations of 1.05 to 1.31 mg/m^3 (0.4 to 0.5 ppm) very little removal of SO_2 occurs in the upper airways. These data contrast with the radiotracer studies in dogs.[77,100,101] Others have required concentrations greater than 18.3 mg/m^3 (7 ppm) to evoke increases in flow resistance in anesthetized cats[98] and dogs.[99] Differences in the sensitivity of the two
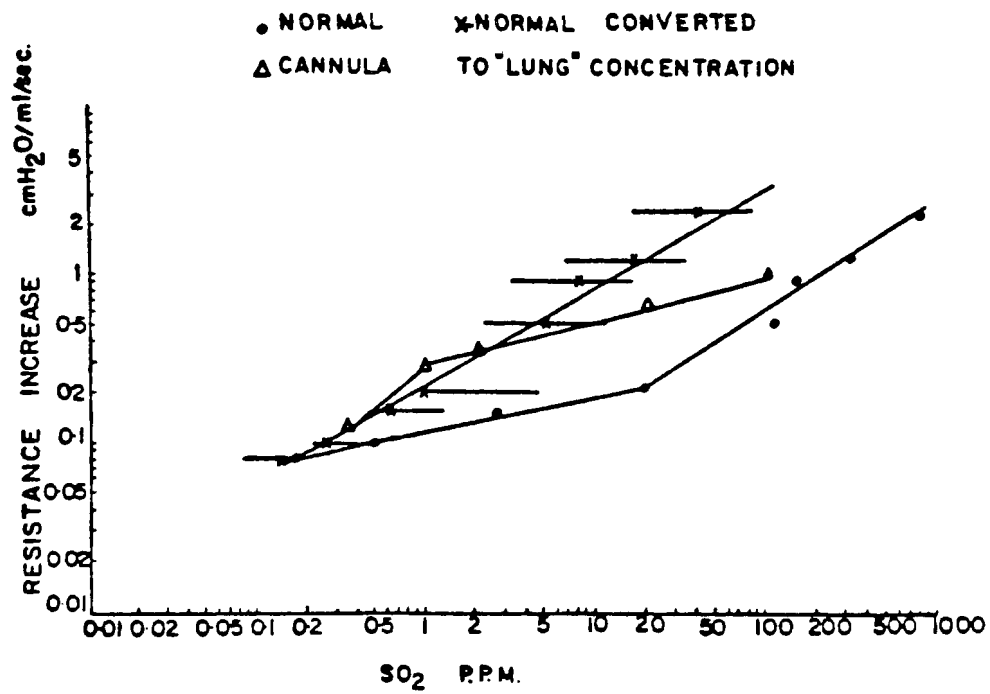
Figure 12-5. Dose-response curves.[63]

models may lie in the use of anesthesia, in the use of different species, or in a different incidence of "sensitive" individuals.

Using anesthetized, intubated, spontaneously breathing dogs exposed to 2.62, 5.24, 13.1, or 26.2 mg/m^3 (1, 2, 5, or 10 ppm) SO_2 for 1 hr, Islam et al.[102] found an increased bronchial reactivity to aerosols of acetylcholine, a potent bronchoconstrictive agent. Acetylcholine is also the endogenous neuromuscular transmitter which can cause bronchoconstriction. Bronchoconstriction was determined by esophageal pressure concomitant with tidal volume. Greatest response occurred at 5.24 mg/m^3 (2 ppm), although 2.62 mg/m^3 (1 ppm) also caused an effect. The effect of 26.2 mg/m^3 (10 ppm) was less than that at 2.62, 5.24, and 13.1 mg/m^3 (1, 2, and 5 ppm). These results suggest that SO_2 may modify bronchial reactivity and that bronchial reactivity is susceptible to other physiological modifications.

Lee and Danner[103] reported that exposure to SO_2 concentrations above 50 mg/m^3 (19 ppm) for 1 hr caused an increase in tidal volume and a decrease in respiratory rate in guinea pigs. When guinea pigs were exposed to 18 to 45 mg/m^3 (7 to 17 ppm) SO_2, a general decrease in tidal volume and an increase in respiratory rate were observed. The variability of these experiments was extreme. The hemoglobin concentration in the blood rose as much as 40 percent during the exposure, suggesting some extreme hemoconcentration phenomenon. Inorganic sulfate concentrations also increased by as much as 100 percent above pre-exposure values, but they were not corrected for hemoconcentration.

Animals chronically exposed to SO_2 have also been examined for alterations in pulmonary function. Guinea pigs exposed continuously to 0.34, 2.64, or 15 mg/m^3 (0.13, 1.01, or 5.72 ppm) SO_2 for up to 1 yr showed no changes in pulmonary function, however, spontaneous pulmonary disease was

present in all animals (including controls) except those exposed to the highest concentration.[88] Dogs exposed for 21 hr/day to 13.4 mg/m^3 (5.1 ppm) SO_2 for 225, but not 620, days demonstrated increased pulmonary flow resistance and decreased lung compliance,[89] after 620 days mean nitrogen washouts were increased. Alarie and co-workers[90-92] exposed cynomologus monkeys continuously to 0.37, 1.7, 3.4, or 13.4 mg/m^3 (0.14, 0.64, 1.28, or 5.12 ppm) SO_2. The latter concentration was used in an 18 mo study, whereas the others were used for 78 wk exposures. Pulmonary function was unchanged in all of these groups. After 30 wk of exposure to 12.3 mg/m^3 (4.69 ppm) SO_2, monkeys were inadvertently exposed to concentrations between 524 and 2,620 mg/m^3 (200 and 1000 ppm) for 1 hr. This treatment resulted in pulmonary function alterations which persisted for the remaining 48 wk of the study during which the animals were exposed to clean air. Morphological alterations were also seen in this group (see Section 12.2.4).

In summary, there are at least two sets of receptors responsible for changes in respiratory function in animals acutely exposed to SO_2. Decreases in respiratory rate or increased resistance to flow are reliable end points. Increased resistance to flow results from SO_2 concentrations as low as 0.42 mg/m^3 (0.16 ppm) using guinea pigs. Of the animals so far examined, guinea pigs are the most sensitive to SO_2. The reason for this is not known; potential factors include species, strains, and experimental technique used. Within the laboratory population, some individual animals are found to be more sensitive than the average, but the mechanism for their sensitivity is not known. While pulmonary function measurements in guinea pigs appear to be highly sensitive to acute SO_2 exposures, chronic SO_2 exposure has not been proven to have a similar effect, although chronic studies with guinea pigs are

unclear because of disease in the control group. In other chronic studies, pulmonary function of monkeys was unchanged at SO_2 concentrations up to 13.4 mg/m^3 (5.12 ppm), but dogs were affected by 225, but not 620, days of exposure to 13.4 mg/m^3 (5.1 ppm). High levels of SO_2 likely to initiate airway narrowing and hypersecretion of mucus do alter several parameters of pulmonary function. These results are not contradictory in view of the physiology of SO_2-initiated bronchoconstriction. Sulfur dioxide appears to cause bronchoconstriction through action on the smooth muscles surrounding the airways. Since smooth muscles fatigue or become adjusted to altered tone over time, chronic exposure to SO_2 is not likely to cause a permanent alteration in bronchial tone. Unfortunately, investigations of the reactivity of the airways after chronic exposure to SO_2 have not appeared. We do not know if chronic exposure to SO_2 causes an alteration in response to SO_2 itself, since only direct measurements of pulmonary function were made on the animals after chronic exposure. It would be very informative to learn if chronically exposed monkeys, for example, were more or less sensitive to SO_2. (Table 12-5)

12.2.6 Effects on Host Defenses

Because alterations in particle removal could lead to increased suscepti-bility to airborne microorganisms or increased residence times of other non-viable particles, the effects of SO_2 on particle removal and engulfment, as well as on integrated defenses against respiratory infection, have been studied. The function of the cilia does not appear to be affected by exposure. No changes were observed in the cilia beat frequency or the relative number of alveolar macrophages laden with particles in rats exposed to 2.62 or 7.86 mg/m^3 (1 or 3 ppm) SO_2 and graphite dust (mean diameter 1.5 µm, 1 mg/m^3) for up to 119 consecutive days.[106] Donkeys[256] were exposed by

TABLE 12-5. EFFECTS OF SULFUR DIOXIDE ON PULMONARY FUNCTION

Concentration	Duration	Species	Results	Reference
0.37, 1.7, 3.4, or 13.4 mg/m^3 (0.14, 0.64, 1.28, or 5.12 ppm) SO$_2$	72-78 wk, continuous	Cynomologus monkey	No change	Alarie et al.[90-92]
0.42 or 0.84 mg/m^3 (0.16 or 0.32 ppm) SO$_2$	1 hr	Guinea pig	Increase in resistance	Amdur et al.[124,130]
0.52, 1.04, or 2.1 mg/m^3 (0.2, 0.4, or 0.8 ppm) SO$_2$	1 hr	Guinea pig	No significant increase in airway resistance.	Amdur et al.[171]
2.62, 5.24, 13.1, or 26.2 mg/m^3 (1, 2, 5, or 10 ppm) SO$_2$	1 hr	Dog	Increased bronchial reactivity to aerosols of acetylcholine, a potent bronchoconstrictive agent	Islam et al.[102]
13.4 mg/m^3 (5.1 ppm) SO$_2$	21 hr/day, 225 and 620 days	Dog	Increased pulmonary flow resistance and decreased lung compliance at 225 days; increased nitrogen washout at 620 days	Lewis et al.[89]
18 to 45 mg/m^3 (7 to 17 ppm) SO$_2$	1 hr	Guinea pig	General decrease in tidal volume and an increase in respiratory rate	Lee and Danner[103]
0, 44.5, 83.8, 162, 233, 322, 519, or 781 mg/m^3 (0, 17, 32, 62, 89, 123, 198, or 298 ppm) SO$_2$	10 min	Mouse	Respiratory rate decreased proportionally to the log of the concentration; complete recovery within 30 min following all exposures. The time for maximum response was inversely related to the log of the concentration, being shortest at highest concentrations	Alarie et al.[85]
>50 mg/m^3 (>19 ppm) SO$_2$	1 hr	Guinea pig	Increase in tidal volume and a decrease in respiratory rate	Lee and Danner[103]

nasal catheters to 68.1 to 1,868 mg/m^3 (26 to 713 ppm) SO$_2$ for 30 min. Below 786 mg/m^3 (300 ppm) clearance was not affected, but at high concentrations (786 to 1,868 mg/m^3 or 376 to 713 ppm) clearance was depressed. Increased mucus flow and nasal irritation have been observed with as little as 26.2 mg/m^3 (10 ppm) SO$_2$ for 24 hr.

Ferin and Leach[110] exposed rats to 0.26, 2.62, and 52.4 mg/m^3 (0.1, 1, or 20 ppm) SO$_2$ for 7 hr/day, 5 days/wk, for a total of 10 to 15 days and then measured the clearance of an aerosol of titanium oxide (TiO$_2$). The aerosol was generated at about 15 mg/m^3 (1.5 μm MMAD, σ_g 3.3). These investigators took the amount of TiO$_2$ retained at 10 to 25 days as a measure of the "integrated alveolar clearance". Low concentrations of SO$_2$ (0.26 mg/m^3 or 0.1 ppm) accelerated clearance after 10 and 23 days, as did 2.62 mg/m^3 (1 ppm) at 10 days but not afterwards until 25 days when clearance was decreased. Hirsch et al.[111] found that the tracheal mucous flow was reduced in beagles exposed for 1 yr to 2.62 mg/m^3 (1 ppm) SO$_2$ for 1.5 hr/day, 5 days/wk. The dogs were examined by a broncho-fibroscope at the end of the exposures. No differences in pulmonary function were reported. Confirmation of this study and determination of the persistence of the decreased mucous flow at this low level of SO$_2$ would be important to confirm in light of other data available.

It appears that SO$_2$ may have more of an effect on anti-viral than on anti-bacterial defense mechanisms. Bacterial clearance was not depressed or altered in guinea pigs exposed to 13.1 or 26.2 mg/m^3 (5 or 10 ppm) SO$_2$ for 6 hr/day for 20 days.[107,192] Using the infectivity model (see Section 12.3.4.3), Ehrlich[178] found that short (3 hr/day for 1 to 15 days) or long (24 hr/day for 1 to 3 mo) exposures to 13.1 mg/m^3 (5 ppm) SO$_2$ did not increase mortality subsequent to a pulmonary streptococcal infection. Virus

infections, however, are augmented by simultaneous or subsequent SO_2 exposure. Mice were exposed to concentrations varying from 0 to 52.4 mg/m^3 (0 to 20 ppm) SO_2 continuously for 7 days.[108] Mice breathing 18.3 to 26.2 mg/m^3 (7 to 10 ppm) SO_2 began to experience an increase in pneumonia. The increase in lung consolidation was significant at 65.5 mg/m^3 (25 ppm), but not at 26.2 or 39.3 mg/m^3 (10 or 15 ppm). The rate of growth of the virus within the lung was unaffected by SO_2 exposure. When these results were reanalyzed,[109] SO_2 and virus exposure produced weight loss at concentrations as low as 9.43 mg/m^3 (3.6 ppm). Exposure to SO_2, whether alone or in combination with a viral agent, had more of an effect on weight reduction than on pneumonia. Since Giddens and Fairchild[80] showed that mice with apparent respiratory infection were more susceptible to the morphological effects of SO_2 (Section 12.2.4), a rebound effect may be possible in which SO_2 and microbes each potentiate the effect of the other.

Several studies of the effects of SO_2 on alveolar macrophages have been conducted, since these cells participate in clearance of viable and non-viable particles in the gaseous exchange regions of the lung. Alveolar macrophages from rats exposed for 24 hr to 2.62, 13.1, 26.2, and 52.4 mg/m^3 (1, 5, 10, and 20 ppm) SO_2 were investigated by Katz and Laskin.[195] Exposure to the 2 highest concentrations increased in vitro phagocytosis of latex spheres for up to 4 days in culture. At 13.1 mg/m^3 (5 ppm) SO_2, phagocytosis was increased after 3 or 4 days in culture, but not after 1 or 2 days. Histochemical studies of pulmonary macrophages from rats exposed to 786 mg/m^3 SO_2 (300 ppm) for 6 hr/day on 10 consecutive days showed no changes in the lysosomal enzymes, β-glucuronidase, β-galactosidase, and N-acetyl-β-glucosaminidase.[112] Acid phosphatase activity was markedly increased. This is in agreement with

Rylander's observation[107] which suggests that SO_2 exposure (26.2 mg/m^3 SO_2, 10 ppm, for 6 hr/day, 5 days/wk for 4 wk) does not affect the bactericidal activity of the lung. (Table 12.6)

12.3 EFFECTS OF PARTICULATE MATTER

Sulfur dioxide is oxidized to sulfuric acid in the atmosphere. Sulfuric acid can react with atmospheric ammonia to produce ammonium sulfate and bisulfate. Similar reactions can also occur in the animal exposure chamber and confound the cause-effect relationships investigated. Sulfur dioxide is often present in polluted atmospheres with complex mixtures of other compounds including heavy metals, which may be present as oxides or as sulfate or nitrate salts. In addition, organic compounds present in the atmosphere in the gaseous phase can be associated with the particulate fraction or become adsorbed on particles either in situ or during collection. The diversity of these organic compounds simply precludes any rational discussion of their toxicity at this time, since little or no inhalation data is available. The details of the composition of atmospheric aerosols are dealt with elsewhere (Chapter 5). The deposition and transport of particles are also discussed elsewhere (Chapter 11).

Since very few studies have appeared on the toxicity of complex atmospheric particles themselves, this section will deal primarily with the toxicity of the components of these particles and the toxicology of those compounds which have been identified as constituents of atmospheric particles. Therefore, these discussions, no matter how sophisticated for a single component, are inherently simplistic. The toxicities of the single components are likely to be less than the combination which exists in the atmosphere, although antagonistic interactions can also occur. For particles other than

TABLE 12-6. EFFECTS OF SULFUR DIOXIDE ON HOST DEFENSES

Concentration SO2	Duration	Species	Results	Reference
0.26, 2.62, or 52.4 mg/m³ (0.1, 1, or 20 ppm)	7 hr/day, 5 day wk	Rat	Low concentrations (0.26 mg/m³ or 0.1 ppm) accelerated clearance of TiO$_2$ aerosol after 10 and 23 days, as did 2.62 mg/m³ (1 ppm) at 10 days but not afterwards until 25 days when clearance was decreased.	Ferrin and Leach[110]
2.62, 13.1, 26.2, and 52.4 mg/m³ (1, 5, 10, and 20 ppm)	24 hr	Rat	Exposure to the 2 higher concentrations increased in vitro phagocytosis of latex spheres for up to 4 days in culture. At 13.1 mg/m³ (5 ppm) phagocytosis was increased after 3 or 4 days in culture, but not 1 or 2 days.	Katz and Laskin[195]
2.62 mg/m³ (1 ppm)	1.5 hr/day, 5 day/wk	Dog	Tracheal mucous flow was reduced.	Hirsch et al.[111]
2.62 or 7.86 mg/m³ (1 or 3 ppm) SO$_2$ + graphite dust (mean diameter 1.5 μm, 1 mg/m³)	Up to 119 days	Rat	No changes in the cilia beat frequency or the relative number of alveolar macrophages laden with particles.	Fraser et al.[106]
9.43 to 52.4 mg/m³ (3.6 to 20 ppm)	7 days continuous	Mouse	Exposure to SO$_2$ and a virus produced weight loss.	Lebowitz and Fairchild[109]
13.1 or 26.2 mg/m³ (5 or 10 ppm)	6 hr/day, 20 day	Guinea pig	Bacterial clearance was not altered.	Rylander[107,192]
13.1 mg/m³ (5 ppm)	3 hr/day, 1-15 days and 24 hr/day, 1-3 mo	Mouse	Did not increase mortality subsequent to a pulmonary streptococcal infection.	Ehrlich[178]
Varying from 0 to 52.4 mg/m³ (0 to 20 ppm)	7 days, continuous	Mouse	Increase in viral pneumonia at 18.3 to 26.2 mg/m³ (7 to 10 ppm). Rate of growth of virus unaffected.	Fairchild et al.[108]
26.2 mg/m³ (10 ppm)	6 hr/day for 20 days	Rat	Did not affect the bactericidal activity of the lung.	Rylander[107]
65.5 to 1868 mg/m³ (25 to 713 ppm)	30 min	Donkey	Below 786 mg/m³ (300 ppm) clearance was not affected, but at high concentrations (786 to 1868 mg/m³ or 376 to 713 ppm) clearance was depressed.	Spiegelman et al.[256]
786 mg/m³ (300 ppm)	6 hr/day, 10 days continuous	Rat	No changes in selected lysosomal enzymes.	Barry et al.[112]

H_2SO_4, $(NH_4)_2SO_4$, and NH_4HSO_4, no attempt will be made to be as inclusive as documents for some of the individual components. Rather, an attempt will be made in this section to integrate this information in the perspective of the potential biological effects of atmospheric particles.

As will be apparent from the discussion of the toxicity of sulfate aerosols in this section, the chemical composition of the atmospheric particulates will determine the toxicity of the aerosol. Atmospheric particles are likely to have direct toxic effects in themselves, indirect toxic effects through interactions with other pollutants, and chronic effects through cell transformation or chronic alteration in cell function. Direct toxic effects are best substantiated by studies of cytotoxicity. Those reviewed here are for some specific compounds which are known to occur in the particulate fraction. The studies cited are by no means complete and could be expanded by including a number of other investigations carried out in vitro or by exposures other than inhalation. The review was purposefully restricted to those most applicable to the inhalation route of exposure. Most of the indirect effects through interaction with other pollutants have previously been discussed for SO_2. Some additional data implicating interactions between SO_2 and particulate material, between SO_2 and ozone, and between H_2SO_4 and ozone are included here. One should recall that a large fraction of the mass of atmospheric particles is composed of sulfate and nitrate compounds.

12.3.1 Mortality

The susceptibility of laboratory animals to sulfuric acid aerosols varies considerably. Amdur[116] has reviewed the toxicity of sulfuric acid aerosols and pointed out that, of the commonly used experimental animals, guinea pigs are the most sensitive and most similar to man in their bronchoconstrictive

response to sulfuric acid. The lethal concentration (LC) of sulfuric acid depends upon the age of the animal (18 mg/m^3 for 1 to 2 mo-old versus 50 mg/m^3 for 18 mo-old animals), the particle size (those near 2 μm being more toxic), and the temperature (extreme cold increasing toxicity). In a recent study,[252] the LC50 (the concentration at which 50 percent of the animals die) in guinea pigs for an 0.8 μm (MMAD) aerosol was 30 mg/m^3, whereas for a 0.4 μm (MMAD) aerosol, the LC50 was above 109 mg/m^3. In determining acute toxicity, the concentration of the aerosol appears to be more important than the length of exposure.[117] The animals which died did so within 4 hr. Chronic studies have only recently been undertaken, and they support this conclusion that mortality rarely occurs at moderate concentrations of sulfuric acid.

Sulfuric acid aerosol appears to have two actions. Laryngeal and/or bronchial spasm are the predominant causes of death at high concentrations. When lower concentrations are used, bronchostenosis and laryngeal spasm can still occur. Pathological lesions in the latter case include capillary engorgement and hemorrhage. Such findings are in accord with anoxia as the prime cause of death.

12.3.2 Morphological Alterations

Alarie et al.[197] investigated the effects of chronic H_2SO_4 exposure. Guinea pigs were exposed continuously for 52 wk to 0.1 mg/m^3 H_2SO_4 (2.78 μm, MMD) or to 0.08 mg/m^3 H_2SO_4 (0.84 μm, MMD). Monkeys were exposed continuously for 78 wk to 4.79 mg/m^3 (0.73 μm, MMD), 2.43 mg/m^3 (3.6 μm, MMD), 0.48 mg/m^3 (0.54 μm, MMD). or 0.38 mg/m^3 (1.15 μm, MMD). Sulfuric acid had no significant hematological effects in either species. No microscopic lung

alterations resulting from H_2SO_4 exposure were observed in guinea pigs after 12 or 52 wk of exposure in this study [197] or in a later study.[92] Morphological changes were evident in the lungs of monkeys. At the two highest concentrations, there were changes (more prevalent in the 4.79 mg/m^3 H_2SO_4 group) regardless of the particle size. Major findings included bronchiolar epithelial hyperplasia and thickening of the walls of the respiratory bronchioles. Alveolar walls were thickened in monkeys exposed to 2.43 mg/m^3, but not to 4.79 mg/m^3 H_2SO_4. However, particle size had an impact at lower H_2SO_4 concentrations. No significant alterations were seen after exposure to 0.48 mg/m^3 of the smaller particle size (0.54 µm). However, bronchiolar epithelial hyperplasia and thickening of the walls of the respiratory bronchioles were seen after exposure to the larger size (1.15 µm, and lower concentration (0.38 mg/m^3). Pulmonary function changes followed a slightly different pattern (See Section 12.3.4.2). In these studies, the cynomolgus monkey was much more sensitive than the guinea pig. Dogs also appear to be relatively insensitive to morphological effects of H_2SO_4 alone. Lewis et al.[104] found no morphological changes after the dogs had been exposed for 21 hr/day for 620 days to 0.89 mg/m^3 H_2SO_4 (90 percent <0.5 µm in diameter).

Recently, Cockrell et al.[118] and Ketels et al.[120] studied the morphological changes resulting from sulfuric acid aerosols. Cockrell et al.[118] examined the effects of 25 mg/m^3 (1 µm, MMD, σ_g 1.6) for 6 hr/day for 2 days in guinea pigs. Segmented alveolar hemorrhage, type 1 pneumocyte hyperplasia, and proliferation of pulmonary macrophages were reported. Ketels et al.[120] examined the response of mice to 100 mg/m^3 sulfuric acid; these exposures produced injury to the top and middle of the trachea, but none to

the lower trachea and distal airways. In an attempt to investigate the dose-response relationship for sulfuric acid, mice received either 5 daily 3 hr exposures to 200 mg/m^3, 10 daily exposures to 100 mg/m^3, 20 daily exposures to 50 mg/m^3, or any one of these doses combined with 5 mg/m^3 carbon particles. The damage was judged to be proportional to the concentration (C), but not to the product of concentration and time (T) of exposure or to the time of exposure. (All of the exposures had the same C x T and therefore their equivalence might have been hypothesized.)

A number of other studies of the morphological effects of H_2SO_4 when combined with other pollutants have been conducted. (See Section 12.4.1.2. and Table 12-7)

12.3.3 Alterations in Pulmonary Function

12.3.3.1 Acute Exposure Effects--Generally, for short-term studies, respiratory mechanics have been much more sensitive to H_2SO_4 and some other compounds than other parameters tested. Amdur has cautioned[116] that her method for measuring resistance[94,95] should not be used as an indication of chronic toxicity and should be considered only for very short-term toxicity. As pointed out above, the Mead-Amdur method uses unanesthetized guinea pigs in which a transpleural catheter has been implanted. Amdur suggests[116] that, if anything, this procedure increases rather than decreases the sensitivity of the guinea pigs to inhaled irritants.

Using this method, Amdur and co-workers[96,97,121-125,130,171,172] have studied the effects of aerosols alone (see Table 12-8) or in combination with SO_2. The combination studies are described in Section 12.4.1.1. In all of their studies, exposures were for 1 hr. The method records resistance to air flow in and out of the lungs and airways, compliance (a measure of lung

TABLE 12-7. EFFECTS OF PARTICULATE MATTER ON LUNG MORPHOLOGY

Concentration	Duration	Species	Results	Reference
0.08 mg/m^3 H$_2$SO$_4$ (0.84 μm, MMD), or 0.1 mg/m^3 H$_2$SO$_4$ (2.78 μm, MMD)	52 wk, continuous	Guinea pig	No significant hematological effect. No microscopic lung alterations after 12 or 52 weeks exposure.	Alarie et al.[92,197]
0.38 mg/m^3 (1.15 μm, MMD), 0.48 mg/m^3 (0.54 μm, MMD), 2.43 mg/m^3 (3.6 μm, MMD), or 4.79 mg/m^3 (0.73 μm, MMD)	78 wk, continuous	Monkey	No significant hematological effect. Morphological changes in the lungs. At the two highest concentrations there were changes, regardless of the particle size. Major findings included bronchiolar epithelia hyperplasia and thickening of the respiratory bronchioles. Alveolar walls were thickened with 2.43 mg/m^3, but not 4.79 mg/m^3. No alterations with 0.48 mg/m^3 (0.54 μm), but with larger size (1.15 μm, 0.38 mg/m^3) hyperplasia and bronchiole thickening.	Alarie et al.[197]
0.89 mg/m^3 (90% <0.5 μm in diameter) H$_2$SO$_4$ aerosol	21 hr/day, 620 days	Dog	No morphological changes.	Lewis et al.[104]
25 mg/m^3 (1 μm, MMD, σ$_g$ 1.6) H$_2$SO$_4$ aerosol	6 hr/day, 2 days	Guinea pig	Segmented alveolar hemorrhage, type 1 pneumocyte hyperplasia, and proliferation of pulmonary macrophages.	Cockrell et al.[118]
50 mg/m^3 H$_2$SO$_4$, or 100 mg/m^3 H$_2$SO$_4$, or 200 mg/m^3 H$_2$SO$_4$, or any of of these doses combined with 5 mg/m^3 carbon particles (at all three duration schedules)	3 hr/day, 20 days; or 3 hr/day, 10 days; or 3 hr/day, 5 days	Mouse	Damage was proportional to the concentration.	Ketels et al.[120]

TABLE 12-8.   RESPIRATORY RESPONSE OF GUINEA PIGS EXPOSED FOR 1 HR TO PARTICLES
IN THE AMDUR et al. STUDIES

Compound	Concentration mg/m^3	Particle size, μm, MMD	Resistance cm H$_2$O/ml/sec % difference from control	Compliance ml/cm H$_2$O % difference from control	Reference
H$_2$SO$_4$	0.10	0.3	+41*	-27*	172,173
	0.51	0.3	+60*	-33*	172
	1.00	0.3	+78*	-40*	172
	1.90	0.8	+51*	-35*	64,125
	5.30	0.8	+54*	-40*	125
	15.40	0.8	+69*	-24*	125
	26.1	0.8	+89*	-38*	125
	42.00	0.8	+120*	-26*	125
	0.11	1.0	+14*	-13	172
	0.40	1.0	+30*	-8	172
	0.69	1.0	+47*	-25*	172
	0.85	1.0	+60*	-28*	172
	2.30	2.5	+39*	-16	125
	8.90	2.5	+61*	-26*	125
	15.40	2.5	+96*	-43*	125
	43.60	2.5	+317*	-76*	125
	30.50	7.0	+42*	-17	125
(NH$_4$)$_2$SO$_4$	0.50	0.13	+23*	-27*	130
	2.14	0.20	-4	-13*	130
	1.02	0.30	+29*	-23*	123,130,170
	9.54	0.81	0	-12*	130
NH$_4$HSO$_4$	0.93	0.13	+15*	-15*	130
	2.60	0.52	+28*	-30*	130
	10.98	0.77	+23*	-19*	130

TABLE 12-8 (continued).

Compound	Concentration mg/m^3	Particle size, μm, MMD**	Resistance cm H$_2$O/ml/sec % difference from control	Compliance ml/cm H$_2$O % difference from control	Reference
Na$_2$SO$_4$	0.90	0.11	+2	-7	130
ZnSO$_4$	0.91	1.4	+41*		123,170
ZnSO$_4$· (NH$_4$)$_2$SO$_4$	0.25	0.29	+22*		123,173
	0.50	0.29	+40*		123
	1.10	0.29	+81*		123,170
	1.80	0.29	+129*		64,123
	1.50	0.51	+43*		123,173
	2.48	0.51	+68*		123
	1.40	0.74	+29*		64,123,173
	1.10	1.4	+6		123,173
	3.60	1.4	+32*		123
CuSO$_4$	0.43	0.11	+9	-11*	130
	2.05	0.13	+25*	-15*	130
	2.41	0.33	+14*	-11*	130
NaVO$_4$	0.70		+7[a]		96
FeSO$_4$	1.00		+2[a]		96
Fe$_2$O$_3$ (2hr)	11.70	0.076 (GMD)	-9[a]		96,124
	21.00	0.076 (GMD)	0[a]		96,124
MnCl$_2$	1.00		+4[a]		96
MnO$_2$	9.70		-6[a]		96
MnSO$_4$	4.00		-1[a]		170

TABLE 12-1. POTENTIAL MUTAGENIC EFFECTS OF SO$_2$/BISULFITE

Concentration SO$_2$	Bisulfite	Organism	End Point	Response	Comments	Reference
	0.9 M HSO$_3^-$ pH 5.0	Phage T4-R11 System	GC→AT or deamination of cysocine	+		Summers and Drake[200]
	3 M HSO$_3^-$ pH 5-6	Phage T4-R11 System	deamination of cytocine	±	Poor dose response	Hayatsu and Miura[201] Iida et al.[202]
	1 M HSO$_3^-$ pH 5.2	E. coli K12 & K15	GC→AT or deamination of cytocine	+		Mukai et al.[203]
	5 x 10^{-3} M HSO$_3^-$ pH 3.6	S. cerevisiae	Point Mutation	+		Dorange and Dupuy[204]
	0.04 or 0.08 M	D. melanogaster	Point Mutation	-	May not be bioavailable	Valencia et al.[205]
1310 mg/m^3 (500 ppm)		Hela cells (Human)	Cytotoxicity	+		Thompson and Pace[207]
13.1 - 105 mg/m^3 (5 - 40 ppm x 3 min)		Mouse fibroblasts & Peritoneal macrophages				Nulsen et al.[208]

TABLE 12-8 (continued).

Compound	Concentration mg/m^3	Particle size, μm, MMD	Resistance cm H_2O/ml/sec % difference from control	Compliance ml/cm H_2O % difference from control	Reference
Na_2SO_4	0.90	0.11	+2	-7	130
$ZnSO_4$	0.91	1.4	+41*		123,170
$ZnSO_4 \cdot$ $(NH_4)_2SO_4$	0.25	0.29	+22*		123,173
	0.50	0.29	+40*		123
	1.10	0.29	+81*		123,170
	1.80	0.29	+129*		64,123
	1.50	0.51	+43*		123,173
	2.48	0.51	+68*		123
	1.40	0.74	+29*		64,123,173
	1.10	1.4	+6		123,173
	3.60	1.4	+32*		123
$CuSO_4$	0.43	0.11	+9	-11*	130
	2.05	0.13	+25*	-15*	130
	2.41	0.33	+14*	-11*	130
$NaVO_4$	0.70		+7[a]		96
$FeSO_4$	1.00		+2[a]		70,96
Fe_2O_3 (2hr)	11.70		-10[a]		96
	21.00		0		124
$MnCl_2$	1.00		+4[a]		96
MnO_2	9.70		-6[a]		96
$MnSO_4$	4.00		-1[a]		170

TABLE 12-8 (continued)

Compound	Concentration mg/m^3	Particle size, μm, MMD	Resistance cm H_2O/ml/sec % difference from control	Compliance ml/cm H_2O % difference from control	Reference
Open hearth dust	0.16		+11[a]		96,124
	7.00		+6[a]		96,124
Activated carbon	8.70		-3[a]		96
Spectographic carbon	2.00		+7[a]		96
	8.00		+17[a]		96

*$p < 0.05$

[a]Statistics not done

TABLE 12-8 (continued)

Compound	Concentration mg/m^3	Particle size, μm, MMD	Resistance cm $H_2O/ml/sec$ % difference from control	Compliance ml/cm H_2O % difference from control	Reference
Open hearth dust	0.16 7.00	0.037 (GMD) 0.037 (GMD)	+11[a] +6[a]	0 -16	96,124 96,124
Activated carbon	8.70		-3[a]		96
Spectographic carbon	2.00 8.00		+7[a] +17[a]		96 96

*$p < 0.05$

[a]Statistics not done

**Diameters are provided as mass median diameter (MMD) unless specified as geometric median diameter by count (GMD).

Additional References Recommended for Consideration in Chapter 12

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distensibility), tidal volume (the volume of air moved during normal breathing), respiratory frequency, and minute volume. While increased flow resistance is often the most striking feature of the response to aerosols, calculations of the elastic, resistive, and total work of breathing can also be made. The method is, therefore, nearly as elaborate and inclusive an evaluation of pulmonary mechanics as could be made in small laboratory animals until very recently. (See Appendix I for a more detailed discussion of methodology.)

The importance of particle size on the site of pulmonary deposition is described in Chapter 11. The health effects impact of these factors is clear from an early study.[125] Sulfuric acid aerosols of concentrations ranging from 1.9 to 43.6 mg/m^3 were generated in three particle sizes: 0.8 µm (σ_g, 1.32 µm), 2.5 µm (σ_g, 1.38 µm), or 7 µm (σ_g, 2.03 µm) MMD. Particles of the largest size (7 µm, at 30 mg/m^3) produced a significant increase in flow resistance but no other detectable changes in respiration. At the lowest concentration tested, 1.9 mg/m^3, the 0.8 µm particles produced an increase in resistance to flow and in elastic, resistive, and total work of breathing; but they produced a decrease in compliance. The 2.5 µm particles also increased the resistance to flow at concentrations from 2.3 to 43.6 mg/m^3. The relative efficacy of the 0.8 and 2.5 µm particles differed. At concentrations of 2 mg/m^3, the 0.8 µm particles were more effective than the 2.5 µm particles. The time course of the response also varied with the particle size, since the 2.5 µm particles did not evoke their major effects until the last 15 to 20 min of the 1 hr exposure. These differences in response were probably associated with the degree and site of obstruction within the bronchi. The 2.5 µm particles affected the larger bronchi producing obstruction, whereas the

0.8 μm particles caused narrowing of the smaller bronchi. While the results of the experiments are reported in a straightforward concentration-response curve, the physiological response producing the measurable effects is obviously highly complex. Detailed understanding is lacking.

In a more recent investigation, Amdur et al.[172] exposed guinea pigs for 1 hr to either 0.3 or 1 μm (MMD) H_2SO_4 in concentrations ranging from 0.1 to 1 mg/m^3. The concentration-response for percent change in resistance was linear for both particle sizes. However, the smaller particle caused a greater response, particularly at 0.1 mg/m^3 where a 26 percent increase in airway resistance was observed. Except for exposure to 0.11 mg/m^3 H_2SO_4 (1 μm), all increases in resistance were significant. The smaller particle size also decreased compliance at all concentrations tested. However, for the 1 μm particle the lowest effective concentration tested was 0.69 mg/m^3. For equivalent concentrations, the 0.3 μm particle decreased compliance more than the 1 μm particle. Animals were also examined for 30 min after exposure ceased. At this time, after exposure to 0.1 mg/m^3 H_2SO_4 (0.3 μm) resistance was still elevated above control in guinea pigs; but for the 1 μm particle, recovery had occurred. These exposures caused no alterations of tidal volume, respiratory frequency, or minute volume. In comparing these results to earlier work with SO_2,[155] Amdur et al. describe how the same amount of sulfur when given as H_2SO_4 produces 6 to 8 times the response observed when given as SO_2.

Silbaugh et al.[253] exposed Hartley guinea pigs for 1 hr to 1 μm (MMAD) sulfuric acid aerosols at concentrations and relative humidities of 0 mg/m^3 (control group) (40 or 80 percent RH), 1.2 mg/m^3 (40 percent RH), 1.3 mg/m^3 (80 percent RH), 14.6 mg/m^3 (80 percent RH), 24.3 mg/m^3 (80 percent RH), and

48.3 mg/m^3 (80 percent RH). Ten animals were exposed at each concentration except for the 24.3 and 48.3 mg/m^3 groups, which consisted of 9 and 8 animals, respectively. Measurements of tidal volume, breathing frequency, minute volume, peak inspiratory and expiratory flow, tidal transpulmonary pressure excursions, total pulmonary resistance and dynamic lung compliance were obtained every 15 min during (1) a 30 min baseline period, (2) the 60 min exposure period, and (3) a 30 min recovery period. Pulmonary function changes in sulfuric acid-exposed animals did not differ from controls, except for 1 animal exposed to 14.6 mg/m^3, 3 animals exposed to 24.3 mg/m^3, and 4 animals exposed to 48.3 mg/m^3. Pulmonary function changes in these 8 responsive animals included marked increases in total pulmonary resistance and marked decreases in dynamic compliance. Four of these 8 animals died during exposure. The proportion of responsive to non-responsive animals increased with exposure concentration, but the magnitude of pulmonary function change was similar for all responsive animals. Compared to non-responders, responsive animals tended to have higher pre-exposure values of total pulmonary resistance and lower pre-exposure values of dynamic compliance. These results suggest that the guinea pig reacts to acute sulfuric acid exposure with an essentially all-or-none airway constrictive response. The finding that resistance and compliance changes are important components of the guinea pig's airway response to sulfuric acid aerosols is consistent with results published by Amdur et al.[172] The presence of high pre-exposure pulmonary resistance values in responsive animals is similar to the finding by Amdur[254] that guinea pigs with high pre-exposure resistance values were those most severely affected during irritant aerosol exposure. However, the lack of effects at lower concentrations and the essentially all-or-none airway

constrictive response observed in these studies differs markedly from the graded response observed by Amdur et al.[125,172] during similar exposures. The reasons for these differences are unclear, but may be at least partially related to differences in animal strains used in these studies and the studies of Amdur and co-workers. These results indicate an absence of respiratory function responses to environmental concentrations of sulfuric acid, but suggest that sensitive subpopulations might exist.

Sackner et al.[221] evaluated pulmonary function in anesthetized dogs exposed either to approximately 18 mg/m^3 H_2SO_4 for 7.5 min or to 4 mg/m^3 H_2SO_4 for 4 hr immediately after exposure or 2 hr later. The MMAD was < 0.2 μm. There were no significant changes in respiratory resistance, specific respiratory conductance, specific lung compliance, or functional residual capacity. At the higher concentration, cardiovascular parameters (e.g., blood pressure, cardiac output, heart rate, and stroke volume) and arterial blood gas tensions were also studied, but no significant changes were observed. The pulmonary function (pulmonary resistance and dynamic compliance) of donkeys was not affected by H_2SO_4 exposure (1.51 mg/m^3, 0.3 to 0.6 MMAD, 1 hr).[222]

Studies of the irritant potential of sulfate salts have shown that these aerosols are not innocuous and evoke increased flow resistance similar to sulfuric acid aerosols. The influence of particle size on the effects of zinc ammonium sulfate has also been investigated by Amdur and Corn.[123] They showed, in guinea pigs exposed for 1 hr, that zinc sulfate had about half the potency of zinc ammonium sulfate, with ammonium sulfate being one-third to one-fourth as potent as zinc ammonium sulfate. Zinc ammonium sulfate was chosen for study because it had been reported as a major component of the aerosol from the Donora, PA episode of 1948.[184] Zinc ammonium sulfate is not

a common species found in urban air. Four sizes of aerosols were administered: 0.29, 0.51, 0.74, and 1.4 μm (particle mean size by weight). When the aerosol concentration was held constant at 1 mg/m^3, the smaller particles produced greater increased resistance to flow. This response was thought to be the result of the number of particles rather than of differential sites of deposition. The dose-response curve also became steeper with decreasing particle size. These data should be carefully compared with those from similar human exposures (Chapter 13, pp. 37-42) where no response occurred.

Amdur et al.[130] recently compared the effects of $(NH_4)_2SO_4$, NH_4HSO_4, $CuSO_4$, and Na_2SO_4. Although particle sizes and concentrations were not precisely matched throughout the study, statistical analyses for ranking were not applied, and the degree of response increased with decreased size (size range, 0.1 to 0.8 μm, MMD), the authors suggest that the order of irritant potency was $(NH_4)_2SO_4$ > NH_4HSO_4 > $CuSO_4$. Sodium sulfate (0.11 mg/m^3, 0.11 MMD) caused no significant effects on either resistance or compliance. At the lowest concentrations used, $(NH_4)_2SO_4$ (0.5 mg/m^3, 0.13 μm MMD), NH_4HSO_4 (9.93 mg/m^3, 0.13 μm MMD), and $CuSO_4$ (0.43 mg/m^3, 0.11 μm MMD) decreased compliance. These concentrations of $(NH_4)_2SO_4$ and NH_4HSO_4 also increased resistance. For $CuSO_4$, the lowest concentration tested which caused an increase in resistance was 2.05 mg/m^3 (0.13 μm MMD). All of these compounds are less potent than H_2SO_4 in the Amdur studies.

Comparisons between sulfuric acid and sulfate salt aerosols are difficult to make because of the marked dependence of the efficacy on the aerosol size. If the particles are of identical size, sulfuric acid is more efficacious than zinc ammonium sulfate; but if the zinc ammonium sulfate were present as a

submicron aerosol and the sulfuric acid as a large aerosol, then zinc ammonium sulfate would be more efficacious at the same concentration.[116] Regardless of the particle size, the equivalent amount of sulfur present as SO_2 is much less efficacious than if it were present as a sulfate salt or sulfuric acid. When present as SO_2, 2.62 mg/m^3 (1 ppm) SO_2 is equivalent to 1.3 mg/m^3 S and produces a 15 percent increase in flow resistance. If this amount of sulfur were present as 0.7 μm aerosol of sulfuric acid, it would evoke a 60 percent increase in flow resistance or be about 4 times more efficacious. If the sulfur were present as zinc ammonium sulfate as a 0.3 μm aerosol, the increase in flow resistance would be about 300 percent or a 20-fold increase in efficacy. Some sulfate salt aerosols are not irritating. For example, though ferrous sulfate and manganous sulfate do not cause an increase in flow resistance, ferric sulfate does cause this response. A summary or irritant potency is presented below.

Relative Irritant Potency of Sulfates In Guinea Pigs Exposed for One Hour.[a,130]	
Sulfuric acid	100
Zinc ammonium sulfate	33
Ferric sulfate	26
Zinc sulfate	19
Ammonium sulfate	10
Ammonium bisulfate	3
Cupric sulfate	2
Ferrous sulfate	0.7
Sodium sulfate (at 0.1 μm)	0.7
Manganous sulfate	-0.9

[a] Data are for 0.3 μm (MMD) particles. Increases in airway resistance were related to sulfuric acid (0.41% increase in resistance per μg of sulfate as sulfuric acid) which was assigned a value of 100.

Nadel et al.[126] found that zinc ammonium sulfate (no concentration given) and histamine aerosols produced similar increases in resistance to flow and decreases in pulmonary compliance in the cat. Histamine was more potent than zinc ammonium sulfate. The increase in flow resistance could not be blocked by intravenous administration of atropine sulfate, but was blocked by either intravenous or inhaled isoproterenol. The increased flow resistance was suggested to be due to an increase in bronchial smooth muscle tone. Histamine appears to be a likely mediator of the bronchoconstriction following inhalation of sulfate salt aerosols. Charles and Menzel[127] investigated the release of histamine from guinea pig lung fragments incubated with varying concentrations of sulfate salts. Almost complete release of tissue histamine occurred with 100 mM ammonium sulfate. Intratracheal injection of ammonium sulfate also released all of the histamine from perfused and ventilated rat lungs.[128] The potency ranking of different sulfate salts in the release of histamine from lung fragments[127,128] was equivalent to that for increased resistance to flow.[130] Bronchoconstriction of the perfused lung occurred on intratracheal injection of sulfate salts or histamine.[128] About 80 percent of the constriction could be blocked by prior treatment of the isolated lungs with an H-1 antihistamine. These experiments as well as the original observations of Nadel et al.[126] and Amdur,[130] support the concept that an intermediary release of histamine or some other vasoactive hormone is involved in the irritant response of sulfate aerosols. An ammonium sulfate particle is calculated to reach a concentration of about 275 mM at equilibration with the 99.5 percent relative humidity of the respiratory tract.[129] Thus, the concentration of the hydrated particle on striking the mucosa would be within the range found to cause release of histamine in guinea pig and rat lung

fragments.[127,128] A recently published estimate of the dose of inhaled ammonium sulfate needed to release histamine in the lung is in error.[129] Complete release of histamine (100 percent) occurred with 1 μmole of ammonium sulfate/lung and not 1 μM solution for the entire lung.[128] Further, total release of all histamine stores of a tissue rarely, if ever, occurs under physiological conditions. Only about 10 percent of the total histamine is released during degranulation reactions in vivo, producing anaphylactic shock. Therefore, even if the calculations were correct, only a small fraction of the ammonium sulfate dose would be required to produce the far less violent increases in flow resistance reported by Amdur et al.[130] for ammonium bisulfate and ammonium sulfate. Assuming the calculation of ammonium sulfate to be correct, a 4 hr, not a 2 day, inhalation would produce a marked increase in resistance to flow. Additionally, Charles et al.[131] found the rate of removal of $^{35}SO_4^{-2}$ from the rat lung both in vivo and in vitro to be a function of the cation associated with the salt and to follow the same order of potency as reported by Amdur and co-workers[130] in the guinea pig irritancy test. Especially noteworthy is the fact that manganous sulfate was removed at essentially the same rate as sodium sulfate, both of which did not produce increased resistance to flow in the guinea pig.

Hackney[196] has presented a preliminary summary of the effects of aerosols of H_2SO_4 and nitrate and sulfate salts on squirrel monkeys (Saimiri sciurens). Monkeys were exposed (head-only) to aerosols at 2.5 mg/m^3 of the respective salts or sulfuric acid, 40 or 85 percent RH at 25°C. The exposure system was designed to reduce stress on the unanesthetized monkey. A non-invasive method of pulmonary function measurement was used in which total respiratory resistance was measured by the forced pressure oscillation technique at sine

wave frequencies of either 10 or 20 Hz. The measurement of pulmonary resistance included the resistance of the chest wall which was assumed to be irrelevant to pollutant response and to be constant throughout the experiments. To correct for stress, control values were taken as those for a given monkey exposed on the previous day to an aerosol of distilled water (for aerosol experiments).

Hackney[196] reports that the measurement of resistance was frequency dependent with changes in resistance appearing greater in the 10 Hz than the 20 Hz measurements. The exposure period in the experiments was either 1 or 2 hr. Some aerosols were studied at only 40 percent RH. No attempt was made at a dose-response curve for aerosols and all exposures were at or near 2.5 mg/m^3. At low relative humidity (40 percent RH; MMAD 0.3 μm, σ_g 2.0), there were no differences between $(NH_4)_2SO_4$-exposed and control values, while at high relative humidity (85 percent RH, MMAD 0.6 μm, σ_g 2.3), 3 of 5 monkeys had increased airway resistance by 1 hr. Zinc ammonium sulfate aerosols produced increased resistance at low humidity (40 percent RH; MMAD 0.3 μm, σ_g 2.5) but no consistent increases over control values at high humidity (85 percent RH; MMAD 0.6 μm, σ_g 1.6). Ammonium bisulfate (40 percent RH; MMAD 0.4 μm, σ_g 1.8) also produced an effect at 2.7 mg/m^3.

Data[196] from exposures to sulfuric acid and NH_4NO_3 aerosols were analyzed by computer and differed quantitatively from the data reported above for those exposures which were reduced by hand. Differences were probably due to a systematic error in the hand reduced data which required a judgement in selection of raw data points. The biological interpretation does not appear to be altered by these two approaches, but it does point out the experimental difficulties in interpretation of pulmonary function data from experimental

animals. While H_2SO_4 aerosols (40 percent RH; MMAD 0.4 μm, σ_g 2.0) caused no statistically significant increases, there was a trend toward increased resistance after 60 min which then tended to decline. Ammonium nitrate exposures produced no changes.

Multiple contrast analysis of the above data[196] showed that no significant differences between baseline or control values could be found for any exposure using data collected at 20 Hz. At 10 Hz, the data was more variable, but significant differences indicative of increased airway resistance could be found for animals exposed to $ZnSO_4$, $(NH_4)_2SO_4$ and H_2SO_4 at 40 percent relative humidity. Several procedural aspects should be recognized. First, data were analyzed on a group mean basis, even though large differences between individual monkeys existed in both variability and absolute magnitude. Second, the time course of exposure to the aerosols illustrated a trend indicative of a transient response on the part of monkeys to sulfate, nitrate, or sulfuric acid aerosols. The use of group means tended to reduce the magnitude of the response and flatten the response-time curve. This is certainly true for the SO_2 exposures. Third, there were major differences in the response measured at either 10 or 20 Hz. Fourth, the response estimated by both manual and computer reduction differed by as much as 40 percent. However, compared to the data reported for guinea pigs, these experiments support the general trends originally proposed from the guinea pig data.

Sackner and co-workers[136-140] have noted a failure of ammonium sulfate aerosols to alter cardiovascular and pulmonary function in dogs or tracheal mucus velocity in sheep. Some of these reports are at variance with the previously cited published reports, and no detail is presently available to

evaluate this new evidence. No significant alterations in pulmonary

resistance and dynamic compliance were observed in donkeys exposed to 0.4 to

2.1 mg/m^3 (NH$_4$)$_2$SO$_4$ (0.3 to 0.6 µm MMAD) for 1 hr.[222]

Larson and co-workers[132] have proposed that breath ammonia is important

in neutralizing inhaled sulfuric acid. Ammonia is released in the breath from

blood ammonia and bacterial decay products in the buccal cavity. Ammonia in

the breath could react with sulfuric acid to produce ammonium bisulfate or

ammonium sulfate, depending upon the amount of ammonia and sulfuric acid

present in the aerosol droplet. Complete neutralization of sulfuric acid

would produce ammonium sulfate. This theory has been discussed at some

length.[129] Much of the data has not yet been published, so a critical review

of the model given for the neutralization of sulfuric acid aerosol droplets by

gaseous ammonia is not available. Calculation of the relation between inhaled

sulfuric acid aerosol and neutralization by breath ammonia is not simple, and

the model needs to be validated.

The biological effects of sulfuric acid aerosols could be due to a

combination of several factors. First, the pH of the particle could be very

important. Larson et al.[132] have calculated the neutralization capacity of

the breath ammonia. Once the neutralization capacity of the ammonia present

in the breath is exceeded, the pH of the aerosol reaching the lung may fall

rapidly. Under low pH, the physical properties of the mucous layer lining the

upper airways may be altered[219] or the permeability of the lung may be

increased.[134] Second, the chemical composition of the sulfate aerosol, if

other than sulfuric acid, may also alter the permeability of the lung to

sulfate.[131,134,135] Third, the cation associated with the sulfate compound

may have pharmacological properties in itself. The permeability of the lung

to sulfate ion presented as various sulfate salts[131] is in the same relative order as the irritant potential found for aerosols of the same sulfate salts.[130]

It is likely that ammonia functions within pulmonary tissue as a source of protons to increase the flux of sulfate to the site of action. Ammonia can diffuse readily across cell membranes as unionized ammonia to react with protons forming ammonium ion. Transport of sulfate would result in the accumulation of protons to preserve electrochemical neutrality. At physiological pH values, a significant fraction of ammonium salts is present as ammonia. Ammonium salts could augment the local ammonia concentration and thus increase the uptake of sulfate ions and result in release of histamine. Ammonia increased the uptake of sulfate by the lung,[128,134] possibly by this mechanism.

In relation to sulfuric acid, ammonium sulfate and bisulfate are less irritating to the lung because of their higher pH values once dissolved in the milieu of the lung. Thus, neutralization of sulfuric acid aerosols by breath ammonia could be an important detoxification step. The concept of breath ammonia does not negate the histamine release hypothesis since ammonium sulfate is active in the release of histamine in guinea pig lung fragments[127] and in rat lungs.[128]

An important problem is the relation of these observations to human effects. Unfortunately, histamine release by non-immune mediate reactions such as the apparent ion exchange process due to sulfate interaction with mast cell granules[134] is poorly understood. Metabolism of histamine by man and rodents could have important differences. Also, not all of the pharmacological action of ammonium sulfate instilled intratracheally in the

perfused rat lung could be blocked by an H-1 antihistamine.[128] A number of other inflammatory hormones, aside from histamine, mediate bronchial tone in man. Slow reacting substance of anaphylaxis (SRS-A), prostaglandins, and kinins would not be blocked by an H-1 antihistamine. Thus, species differences are not unanticipated, but should be clarified so the potential applicability of these data to man is understood.

One fact is clear from all of the studies so far reported. The biological effect of sulfate compounds is highly dependent upon the chemical composition of the compound. For example, for pulmonary function sulfuric acid is much more potent than any sulfate salt, but the sulfate salts also are of differing potency. The cationic species associated with the sulfate ion may promote the transport of the sulfate ion and, thereby, increase the biological response. The cation has biological effects by itself as discussed here. It is not possible, then, to predict the potential toxicity of a sulfate aerosol based solely on the sulfate content. Clearly, the acidity of the aerosol also plays an important role in the toxicity.

An important experimental problem is raised by the ammonia neutralization of sulfuric acid. Ammonia is produced in all animal experimental exposure systems through the accumulation of urine and feces. This is particularly so in whole-body chronic exposures. Few exposure systems provide a rapid turnover of the chamber air, e.g., 1 chamber volume/min, and given the technological problems in monitoring NH_3, even this rate of air flow may be insufficient. The usual turnover rate is 10 to 15 chamber volumes of air/hr or less. Under these conditions, animals exposed to sulfuric acid aerosols may, in fact, be inhaling ammonium sulfate and ammonium bisulfate aerosols as well. The high concentrations of sulfuric acid aerosols needed to produce

significant pathological effects on chronic exposure may be due to these chemical conversions. Since human exposure chambers would not be expected to have comparably high levels of ammonia, there could be difficulty in comparing results of human and animal studies of H_2SO_4. The level of ammonia in the breath of animals is also unknown and is sure to vary with the diet of the animals. Some commercial animal diets are low in protein, while others are high. The blood ammonia will depend, in part, on the total amount of protein and quality of the protein as well as on the kidney function of the animal. What effects, if any, the buccal flora have on the exhalation of ammonia in animals is totally unknown. Certainly, the propensity of SO_2^- and sulfuric acid-exposed animals to develop nasal infections raises disturbing questions. The buccal flora of animals may be very different from that of man in its ability to produce ammonia. This technical problem of ammonia in the exposure atmosphere should be addressed and solved before further reliance can be placed on these data for sulfuric acid. (Table 12-9)

12.3.3.2 <u>Chronic Exposure Effects</u>--The influence of chronic exposure to H_2SO_4 on pulmonary function was investigated by Alarie et al.[92,197] Guinea pigs exposed continuously to either 0.9 mg/m^3 (0.49 μm, MMD),[92] 0.1 mg/m^3 (2.78 μm, MMD),[197] or 0.08 mg/m^3 (0.84 μm, MMD)[197] for 52 wk had no significant changes of pulmonary mechanics (including measurements of flow resistance, respiratory rate, some lung volumes, and work of breathing) that could be attributed to H_2SO_4. However, cynomolgus monkeys exposed continuously and tested periodically during 78 wk were affected by some treatment regimens.[197] Monkeys exposed to 0.48 mg/m^3 (0.54 μm, MMD) experienced an altered distribution of ventilation (increased N_2 washout) early in the exposure period, but recovery occurred during exposure. Animals exposed to a similar

TABLE 12-9. EFFECTS OF ACUTE EXPOSURE TO PARTICULATE MATTER ON PULMONARY FUNCTION[a]

Concentration	Duration	Species	Results	Reference
0 mg/m^3 (40 or 80% RH) 1.2 mg/m^3 (40% RH), 1.3 mg/m^3 (80% RH), 14.6 mg/m^3 (80% RH), 24.3 mg/m^3 (80% RH), and 48.3 mg/m^3 (80% RH) 1 μm (MMAD) H$_2$SO$_4$ aerosol	1 hr	Guinea pig	Pulmonary function changes observed in one animal (out of 10) exposed to 14.6 mg/m^3, three animals (out of 9) exposed to 24.3 mg/m^3, and four animals (out of 8) exposed to 48.3 mg/m^3	Silbaugh et al.[253]
0.8 - 1.51 mg/m^3 H$_2$SO$_4$ (0.3 - 0.6 μm, MMAD) or 0.4 - 2.1 mg/m^3 (NH$_4$)$_2$SO$_4$ (0.3 - 0.6 μm, MMAD)	1 hr	Donkey	No significant alterations in pulmonary resistance and dynamic compliance	Schlesinger et al.[222]
2.5 mg/m^3 (NH$_4$)$_2$SO$_4$, ZnSO$_4$,(NH$_4$)$_2$SO$_4$, H$_2$SO$_4$, and NH$_4$NO$_3$; 2.7 mg/m^3 NH$_4$HSO$_4$	1 hr	Monkey	Increased airway resistance at high relative humidity for (NH$_4$)$_2$SO$_4$, and low relative humidity for ZnSO$_4$ (NH$_4$)$_2$SO$_4$. NH$_4$HSO$_4$ also increased resistance. No significant effects with H$_2$SO$_4$ or NH$_4$NO$_3$	Hackney[196]

[a]See Table 12-8 for the Amdur et al. studies on pulmonary function effects in guinea pigs.

concentration (0.38 mg/m^3) but a larger particle size (2.15 μm, MMD) had no change in this parameter. Higher concentrations altered distribution of ventilation, with the lesser concentration (2.43 mg/m^3) and larger particle size (3.6 μm, MMD) causing an onset sooner at 17 wk compared to 49 wk in monkeys exposed to 4.79 mg/m^3 H$_2$SO$_4$ (0.73 μm, MMD). Beginning at approximatey 8 to 12 wk of exposure, 0.38 mg/m^3 (2.15 μm, MMD), 2.43 mg/m^3 (3.6 μm, MMD) and 4.79 mg/m^3 (0.73 μm, MMD) H$_2$SO$_4$ increased respiratory rate. The only alteration in arterial partial pressure of O$_2$ was a decrease observed in monkeys exposed to 2.43 mg/m^3. Except for respiratory rate as described above, mechanical properties (including resistance, compliance, tidal volume, minute volume, and work of breathing) were not significantly altered by the chronic H$_2$SO$_4$ exposures. Morphological studies of these animals are described in Section 12.3.2.

Chronic studies of dogs were performed by Lewis et al.[89,104] The animals were exposed for 21 hr/day for 225 or 620 days to 0.89 mg/m^3 H$_2$SO$_4$ (90 percent < 0.5 μm in diameter) alone and in combination with SO$_2$ (see Section 12.4.1.2 for expanded discusion). After 225 days,[89] dogs receiving H$_2$SO$_4$ had a significantly lower diffusing capacity for CO than animals that did not receive H$_2$SO$_4$. After 620 days of exposure,[104] CO diffusiong capacity was still decreased (p < 0.05). In addition, residual volume and net lung volume (inflated) were decreased (p < 0.05), and total expiratory resistance was increased (p < 0.05). Total lung capacity, inspiratory capacity, and functional residual capacity were also decreased (p = 0.1). Other pulmonary function measurements were not significantly affected. (see Table 12-10)

TABLE 12-10. EFFECTS OF CHRONIC EXPOSURE TO PARTICULATE MATTER ON PULMONARY FUNCTION

Concentration	Duration	Species	Results	Reference
0.08 mg/m^3 H$_2$SO$_4$ (0.84 μm, MMD) or 0.1 mg/m^3 H$_2$SO$_4$ (2.78 μm, MMD)	52 wk, continuous	Guinea pig	No effects on pulmonary function.	Alarie et al.[92,197]
0.38 mg/m^3 (1.15 μm, MMD) 0.48 mg/m^3 (0.54 μm, MMD) 2.43 mg/m^3 (3.6 μm, MMD) 4.79 mg/m^3 (0.73 μm, MMD) H$_2$SO$_4$	78 wk, continuous	Monkey	Exposure to 0.48 mg/m^3 altered distribution of ventilation early in the exposure period, but not later. Exposure to 2.43 or 4.79 mg/m^3 altered distribution of ventilation. Exposure to 0.38, 2.43, or 4.79 mg/m^3 increased respiratory rate. Other pulmonary function parameters were not affected.	Alarie et al.[197]
0.89 mg/m^3 H$_2$SO$_4$ (90% <0.5 μm in diameter)	21 hr/day, 225 or 620 days	Dog	After 225 days lower CO diffusing capacity. After 620 days capacity was still decreased, residual volume and net lung volume were decreased, and total expiratory resistance was increased; total lung capacity, inspiratory capacity, and functional residual capacity were also decreased. Other pulmonary function parameters were not affected.	Lewis et al.[89,104]

12.3.4 Alteration in Host Defenses

To protect itself against inhaled viable or non-viable particles, the host has several mechanisms of defense. Particles which reach the gaseous exchange regions of the lung can be phagocytized and killed (in the case of microbes) by alveolar macrophages. Later these cells can be moved up to the ciliated airways where they are cleared from the lung, along with other particles that impact on the airways, by the mucociliary escalator. This very brief description of clearance is expanded in Chapter 11.

12.3.4.1 Mucociliary Clearance--Fairchild et al.[218] showed that 4 hr exposures to 15 mg/m^3 H$_2$SO$_4$ (3.2 μm, CMD) after exposure to a nonviable radio-labeled streptococcal aerosol reduced the rate of ciliary clearance of the bacteria from the lungs and noses of mice. When mice received a 90 min exposure to 15 mg/m^3 H$_2$SO$_4$ (3.2 μm, CMD) 4 days prior to the bacterial aerosol, clearance of nonviable bacteria was reduced in the nose but not in the lungs. Neither regimen affected clearance of viable streptococci. No significant effects were seen at concentrations of 1.5 mg/m^3 (0.6 μm, CMD).

Schlesinger et al.[222] demonstrated that 1 hr exposures to 0.3 to 0.6 μm H$_2$SO$_4$ mist at concentrations in the range of 0.19 to 1.36 mg/m^3 produced transient slowings of bronchial mucociliary particle clearance in 3 of 4 donkeys tested. In addition, 2 of the 4 animals developed persistently slowed clearance after about 6 exposures. Similar exposures had no effects on regional particle deposition or respiratory mechanics, and corresponding exposures to (NH$_4$)$_2$SO$_4$ up to 2 mg/m^3 had no measurable effects. In subsequent experiments,[223] the 2 animals showing only transient responses and 2 previously unexposed animals were given daily 1 hr exposures, 5 days/wk, to H$_2$SO$_4$ at 0.1 mg/m^3. Within the first few wk of exposure, all 4 animals

developed erratic clearance rates, i.e., rates which, on specific test days, were either significantly slower than or significantly faster than those in their pre-exposure period. However, the degree and the direction of change in rate differed to some extent in the different animals. The 2 previously unexposed animals developed persistently slowed bronchial clearance during the second 3 mo of exposure and during 4 mo of follow-up clearance measurements, while the 2 previously exposed animals adapted to the exposures in the sense that their clearance times consistently fell within the normal range after the first few wk of exposure. The sustained, progressive slowing of clearance observed in 2 initially healthy and previously unexposed animals is a significant observation, since any persistent alteration of normal mucociliary clearance can have important implications. Lippmann et al.[279] have conducted similar experiments in human subjects which are reviewed in Chapter 13.

Tracheal mucociliary transport rates have been measured in several other animal studies. Sackner et al.[221] failed to find significant changes in tracheal mucus velocity following short-term exposures to 14 mg/m^3 (0.12 μm) H_2SO_4 in sheep. Similarly, Schlesinger et al.[222] saw no effect on tracheal transport in donkeys after 1 hr exposures to concentrations up to 1.4 mg/m^3 (0.3 to 0.6 μm MMAD) H_2SO_4. On the other hand, Wolff et al.[224] reported a depression in tracheal transport rate in anesthesized dogs exposed for 1 hr to 1.0 mg/m^3 (0.9 μm, MMAD, σ_g 1.4) which persisted at 1 wk postexposure. Recovery had occurred when the animals were examined again at 5 wk post exposure. Following a 1 hr exposure to 0.5 mg/m^3 H_2SO_4, there were slight increases (p >0.05) in tracheal mucous velocities immediately and 1 day after exposure. However, 1 wk after exposure, clearance was significantly decreased. The latter results are quite similar to those observed in the

bronchi of individual humans in the Lippmann et al.[228] study (see Chapter 13), although they recorded no significant change in the mean tracheal mucociliary transport rates.

Clearly, the results of the donkey studies support the human experiments (Chapter 13) which indicate that H_2SO_4 aerosol affects mucociliary clearance in the distal conductive airways. Mucociliary clearance is dependent upon both the physicochemical properties of the mucus and the coordinated beat of the underlying cilia. Mucus is excreted into the airway lumen in an alkaline form which is then acidified by CO_2.[219] In vitro studies have shown that mucus is a sol in high pH solutions, while at lower pH it becomes viscous.[217] The H^+ supplied by the H_2SO_4 may stiffen the mucus and increase the efficiency of removal. This is consistent with the increase in bronchial clearance rate observed in humans following exposure to ~~100 µg/m³~~ 0.1 mg/m³. Other studies[181,182] have shown that exposures to 0.9 to 1.1 mg/m³ H_2SO_4 can cause a depression of tracheal ciliary beat frequency in hamsters which may lead to a depression in overall bronchial clearance. See Sections 12.4.1.1 and 12.4.2 for more details on these latter studies[181,182] which were conducted with pollutant mixtures.

Based on the results summarized above, it is possible that chronic H_2SO_4 exposures at concentrations of about 0.1 mg/m³ could produce persistent changes in mucociliary clearance and exacerbate preexisting respiratory disease. (see Table 12-11)

Cadmium and nickel chlorides also disrupt the activity of the ciliated epithelium.[156,157] Tracheal rings have been isolated from hamsters and the beat frequency and morphology of the ciliated epithelium have been observed. Concentrations of $CdCl_2$ as low as 6 µM in vitro resulted in decreased beat

TABLE 12-11. EFFECTS OF SULFURIC ACID ON MUCOCILIARY CLEARANCE

Concentration	Duration	Species	Results	Reference
0.1 mg/m^3 H$_2$SO$_4$	1 hr/day, 5 day wk, several mo	Donkey	Within the first few wk, all 4 animals developed erratic bronchial mucociliary clearance rates, either slower than or faster than those before exposure. Those animals never pre-exposed before the 0.1 mg/m^3 H$_2$SO$_4$ had slowed clearance during the second 3 mo of exposure.	Schlesinger et al.[223]
0.19 to 1.4 mg/m^3 H$_2$SO$_4$ (0.3 to 0.6 μm, MMAD)	1 hr	Donkey	Bronchial mucociliary clearance was slowed.	Schlesinger et al.[222]
0.5 mg/m^3 H$_2$SO$_4$	1 hr	Dog	Slight increases in tracheal mucociliary transport velocities immediately and 1 day after exposure. One wk later clearance was significantly decreased.	Wolff et al.[224]
1.0 mg/m^3 H$_2$SO$_4$ (0.9 μm, MMAD, σ$_g$ 1.4)	1 hr	Dog	Depression in tracheal mucociliary transport rate persisted at 1 wk post-exposure.	Wolff et al.[224]
1.4 mg/m^3 H$_2$SO$_4$ (0.3 to 0.6 μm, MMAD)	1 hr	Donkey	No effect on tracheal transport.	Schlesinger et al.[222]
1.5 mg/m^3 H$_2$SO$_4$ (0.6 μm, CMD)	90 min	Mouse	No significant effects.	Fairchild et al.[218]
14 mg/m^3 H$_2$SO$_4$ (0.12 μm MMAD)	Short-term	Sheep	No significant changes in tracheal mucociliary transport rate	Sackner et al.[221]
15 mg/m^3 H$_2$SO$_4$ (3.2 μm, CMD)	4 hr	Mouse	Exposure to H$_2$SO$_4$ after exposure to a nonviable streptococcal aerosol reduced the rate of ciliary clearance of the bacteria from the lungs and nose.	Fairchild et al.[218]
15 mg/m^3 H$_2$SO$_4$ (3.2 μm, CMD)	90 min	Mouse	Exposure to H$_2$SO$_4$ 4 days prior to bacterial aerosol. Clearance of nonviable bacteria reduced in nose, but not lungs.	Fairchild et al.[218]

frequency and degradation of the ciliated epithelium architecture.[157] A prior

2-hr exposure in vivo to 2 µm aerosols of $CdCl_2$ at 0.05 to 1.42 mg/m^3 caused a

significant decrease in cilia beat frequency proportional to the aerosol

concentration. When hamsters were exposed to 1.33 mg/m^3 Cd for 2 hr/day for 2

days, the beat frequency did not return to control values until 6 wk after

exposure. Nickel chloride aerosols or solutions had similar, but less marked,

effects.[156] The beat frequency decreased by 60 beats/min on exposure to 0.1

mg/m^3 Ni for 2 hr. The decrement in beat frequency was proportional to the

concentration of Ni aerosol or solution. A single 2 hr exposure to 0.1 mg/m^3

Ni depressed cilia beat frequency 24 hr after exposure, but the frequency

returned to near normal values after 72 hr. After exposure to 0.1 mg/m^3, Cd

was about 20 percent more effective than Ni in slowing cilia beat. (Table

12-12)

12.3.4.2 Alveolar Macrophages--Cytotoxicity of components of atmospheric

aerosols has been studied with alveolar macrophages (AM). The physiological

role of AM in the prevention of infection and in the defense of the lung

through removal of inhaled particles has been amply demonstrated.[148]

Allison and Morgan[225] have summarized the evidence that AM ingest both

toxic and non-toxic particles in the same manner. In the case of fibers,

ingestion appears more dependent upon the length of the fiber.[226] Short

fibers of >5 µm are almost always ingested, while fibers >30 µm are seldom

ingested completely and remain in contact with the plasma as well as with the

lysosomal surface. Intermediate sized particles (5 to 20 µm) are sometimes

completely ingested and sometimes not. Once ingested, particles have two

effects. An immediate cytotoxicity appears which is apparently due to the

interaction of the particle with the plasma membrane.[225] This interaction is

similar to the hemolytic effects described for silica particles. The second effect results in delayed cytotoxicity and occurs after the particle has been ingested into a primary phagocytic vacuole which then combines with a primary lysosome to yield a secondary lysosome containing the particle.[225] Here toxic particles exert an effect upon the permeability of the lysosomal membrane, resulting in the release of lysosomal enzymes into the cell and into the external medium. These proteolytic enzymes have the potential of causing tissue damage.

Hatch et al.[177] examined the influence of in vitro exposure to a variety of particles on AM oxidant production (O_2^- and H_2O_2) and found the response to be chemical specific. All the particles studied stimulated the chemiluminescence, with amphibole asbestos being the most active. Silica, chrysotile asbestos, and metal oxide (Pb, Ni, Mn)-coated fly ash had intermediate activity. Fugitive dusts and fly ash had the lowest activity.

Waters et al.[149] found that AM cultured with particulate forms of vanadium had decreased cell viability, indicating a direct cytotoxicity. Alveolar macrophages were cultured in medium containing vanadium pentoxide (V_2O_5), vanadium trixoide (V_2O_3), or vanadium dioxide (VO_2). Cytotoxicity was directly proportional to the solubility of the vanadium compound: $V_2O_5 > V_2O_3 > VO_2$. The concentration of V required to produce a 50 percent decrease in viability after 20 hr of culture was found to be: 13 µg V/ml as V_2O_5, 21 µg V/ml as V_2O_3, and 33 µg V/ml as VO_2. When V_2O_5 was dissolved in the medium prior to incubation with the AM, only about 9 µg V/ml were required to reduce viability by 50 percent, thus indicating that the soluble V was responsible for toxicity. Phagocytosis, an essential function for the defense of the lung, was decreased by 50 percent with 6 µg V/ml as dissolved V_2O_5. Acid

phosphatase, a lysosomal degradation enzyme necessary for digestion of phago-cytized bacteria, was inhibited by 1 µg V/ml as V_2O_5, while the lysosomal enzymes, lysozyme and β-glucuronidase, were not inhibited by concentrations as high as 50 µg V/ml.

Alveolar macrophages exposed <u>in</u> <u>vitro</u> for 20 hr to metallic salts were also studied by Graham et al.[175] using a technique to determine phagocytosis of viable cells only. The chlorides of Cd (2.2×10^{-5}M), Cr (3.1×10^{-3}M), Mn (1.8×10^{-3}M), and Ni (5.1×10^{-4}M) significantly inhibited phagocytosis. Ammonium vanadate (6.9×10^{-4}M) had no effect on phagocytosis, but did lyse and kill cells. Nickel, which caused the greatest reduction in phagocytosis, had very little effect on viability or cell lysis. Antibody-mediated rosette formation of AM was also inhibited <u>in</u> <u>vitro</u> by low concentrations of $CdCl_2$ (2.2×10^{-5}M) or $NiCl_2$ (10^{-4}M).[163] Inhibition was proportional to the Ni^{++} or Cd^{++} concentration and reached its maximum within 20 min. These studies showed that the antibody dependent recognition system of AM was inhibited by trace concentrations of Ni^{++} and Cd^{++} almost immediately after contact with the metal. Such an effect implies that these metals may affect receptors for phagocytosis of the opsonized bacteria. Depression of AM viability, phagocytosis, and receptors for phagocytosis may be a mechanism by which these heavy metal salts increase the susceptibility to airborne infections as discussed later (Section 12.3.4.3).

Aranyi et al.[150] reported cytotoxic effects to AM with fly ash particles coated with PbO, NiO, or MnO_2. The percentage of metal adsorbed on the fly ash was fairly similar across particle size for a given metal. The fly ash particles were of three size ranges: <2, 2 to 5, or 5 to 8 µm in diameter. All of the particles, regardless of the coating or particle size, decreased

cell viability and were phagocytized by the AM. Within a given chemical series of coated particles, the effects were both concentration and size related, with smaller particles and greater concentrations producing greater effects. The greater surface area of the smaller particles was suggested as being responsible for the greater toxicity of the small particles. Total cellular protein and lactic acid dehydrogenase also decreased after treatment, probably as a non-specific result of the death of the cultured AM. For each particle size, Pb-coated particles were most toxic, NiO- and MnO_2-coated particles had intermediate effects, and the untreated fly ash was least toxic. The toxicity did not appear related to the solubility of the metal oxide coating, since no soluble metal could be found using the AM themselves as a bioassay. The toxicity appeared to be associated with the uptake of the intact particle. No changes were observed in the total lysosomal enzyme content, but the latency or intactness of the lysosomal membrane was not examined. Toxicity could have resulted from the disruption of the intra-cellular lysosomal membrane, which in turn could have released intracellular lysosomal enzymes. Lysosomal enzyme release has been proposed as one potential mechanism for the toxicity of asbestos and silica particles.[151] These results support the concept that the surface activity of particles determines the toxicity of the particle.[225]

Bingham and co-workers[152,153] have examined the effects of Pb and Ni inhalation on the number and type of AM present in the lungs of rats. In a preliminary report, Bingham et al.[152] showed that a 3 mo exposure to 0.01 or 0.15 mg/m^3 Pb_2O_3 (0.18 µm, MMAD) decreased the number of AM/lung. The specificity of this response was investigated in a subsequent study[153] using

soluble $PbCl_2$ (0.1 mg/m^3, 0.17 μm MMD) and $NiCl_2$ (0.11 mg/m^3, 0.32 μm MMD) and insoluble Pb_2O_3 (0.15 mg/m^3, 0.15 μm MMD) and NiO (0.12 mg/m^3, 0.25 μm MMD) aerosols. Rats were exposed for 12 hr/day, 6 days/wk for 2 mo. The only exceptions were those exposed to Pb_2O_3 continuously. Exposure to Pb_2O_3, but not $PbCl_2$, aerosols resulted in a depression of the number of AM which persisted throughout the experiment (Figure 12-6). The number of AM was depressed on inhalation of 0.15 mg/m^3 Pb_2O_3 for up to 3 mo, but returned to control levels within 3 days after discontinuation of the exposure. The solubility of the Ni compound also had marked effects on the biological response. Nickel oxide produced a marked elevation in the number of AM/lung, while $NiCl_2$ did not. The most significant effects in $NiCl_2$-exposed rats were marked increases in mucus secretion and bronchial hyperplasia. No morphological alterations were observed in those rats exposed to $PbCl_2$ or Pb_2O_3. Isolated AM also varied in diameter with the exposure, but the biological significance of this size variation is not known at present. Perhaps different cell populations were recruited into the lung with the differing exposure conditions.

Cadmium chloride aerosols also altered the number and kind of cells recoverable by lavage following exposure.[154,176] The total number of AM isolated from exposed rats decreased following exposure to 1.5 mg/m^3 Cd (99 percent <3 μm in diameter) but returned to normal values within 24 hr. The viability of the isolated cells decreased by 11.2 percent immediately after exposure and was still depressed 24 hr later. There was an influx of polymorphonuclear leukocytes, especially 24 hr post-exposure, but no increase in lymphocytes.
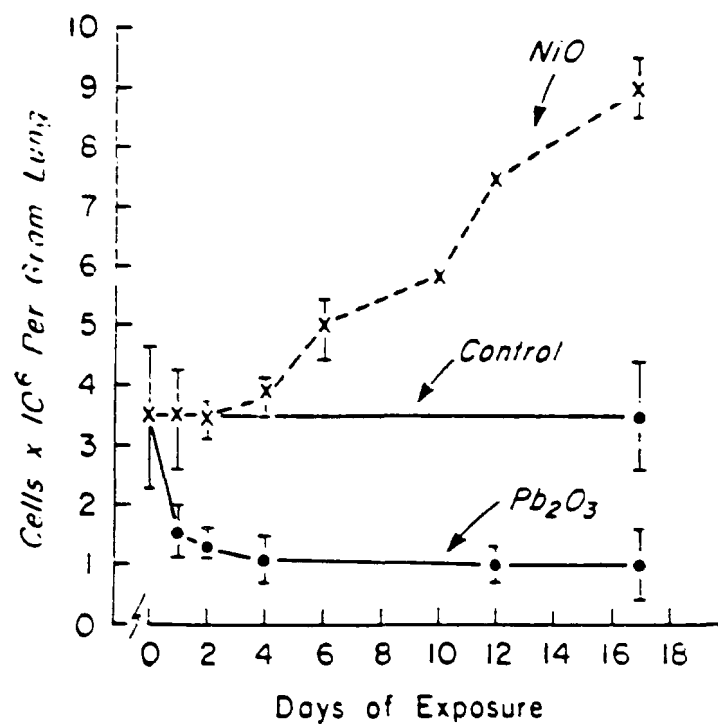
Figure 12-6. Mean number and standard error of alveolar cells washed from lungs of rats after inhalation of oxides of lead and nickel.

These effects were not observed at 0.5 mg/m^3 Cd, indicating that the minimum effective dose may lie somewhere between these two concentrations.

Nickel chloride aerosols[155,176] produced neither an effect on the number of AM isolated by lavage of rats the day following a 2 hr exposure to 0.65 mg/m^3 Ni nor an influx of polymorphonuclear leukocytes. The phagocytic capacity of the isolated AM was, however, depressed. A 2 hr exposure of mice to 0.9 mg/m^3 Mn$_3$O$_4$ reduced the number of AM which could be recovered by lavage, but did not result in an influx of other cell types.[188] The AM had a reduced concentration of ATP and total protein and acid phosphatase activity. Viability and phagocytic activity of AM were normal.

The number, function and kind of cells isolated from the lung by lavage are influenced by the prior exposure to heavy metal aerosols. Not all metals produced the same effect but Cd, Ni, and Mn also enhanced the susceptibility of mice to subsequent airborne infections.[176] The observations of two independent laboratories[152,153,155] on NiCl$_2$ aerosols are essentially in agreement. (Table 12-12)

12.3.4.3 <u>Interaction with Infectious Agents</u>--Gardner[176] and Ehrlich[179] have reviewed their groups' studies and presented new data on the effects of aerosols on host defense mechanisms against infectious pulmonary disease in mice. In all of the Gardner studies, 94 to 99 percent of the aerosols was less than 1.4 μm in diameter.[154,176] Animals were placed in a head-only exposure system for 2 hr and were given graded concentrations ranging from 0.075 to 1.94 mg/m^3 Cd,[154] from 0.1 to 0.67 mg/m^3 Ni,[155] or from 0.5 to 5 mg/m^3 Mn.[189] In mice, these exposures to Cd and Ni chlorides and Mn$_3$O$_4$ resulted in the deposition of 0.002 to 0.026 mg Cd,[154] 0.001 to 0.012 mg Ni,[155] or 0.005 to 0.042 mg Mn[190] per g dry weight of lung respectively.

Nickel clearance[160] from the lungs of mice had a half-life of 3.4 days; while Mn[190] clearance was rapid, with a half-life of only 4.6 hr. None of the exposures appeared to be edematogenic as judged by the ratio of dry weight to wet weight of the lung. After metal exposure, mice were challenged with an aerosol of <u>Streptococcus</u> <u>pyogenes</u> (<u>S. pyogenes</u>). The aerosols of $CdCl_2$,[154] $NiCl_2$,[155] or $MnCl_2$[176] increased the mortality from the subsequent standard airborne infection. Cadmium was more toxic than Ni, which was more toxic than Mn. Exposure to Cd and Mn resulted in a significant linear concentration response. The lowest concentration tested at which a significant increase in mortality was detected was 0.1 mg/m^3 Cd or 0.5 mg/m^3 Ni. Manganese, as Mn_3O_4,[189] was statistically estimated to produce a 10 percent increase in mortality at 1.55 mg/m^3 Mn, while $MnCl_2$[176] required a higher concentration to produce a measurable increase in mortality. Using a different infectivity model,[191] 3 or 4 days (3 hr/day) of exposure to 109 mg/m^3 MnO_2 (0.70 µm, mean diameter) were required to increase mortality consequent to <u>Klebsiella</u> <u>pneumoniae</u> infection when the mice received the bacterial aerosol immediately after exposure.

The toxicity of $NiCl_2$ was complex.[155] Nickel exposure had no effect on the <u>S. pyogenes</u> infection if the bacteria was given immediately after Ni aerosol exposure. When the bacterial exposure was delayed by 24 hr, Ni aerosols increased the mortality in a concentration-related fashion. In contrast, effects of $CdCl_2$[154] and Mn[176] were observed when the bacterial challenge immediately followed exposure. The concentration-response curve of Ni was very steep compared to Cd and Mn exposures.[176] No explanation has been offered for the delay in effect of Ni. Perhaps the delayed effects represent either redistribution of Ni to the site of action or some major change in the

lung such as death of a specific cell type. The delayed toxicity does raise the possibility of carry-over of effects from a single exposure to a second.

The influence of a variety of sulfate species on host defense mechanisms against infectious respiratory disease has been investigated by Ehrlich[178] and Ehrlich et al.[179] using the infectivity model with $\underline{S}$. $\underline{pyogenes}$. Mice were exposed for 3 hr. The estimated concentrations of the compounds which caused a 20 percent enhancement of bacterial-induced mortality over controls were 0.2 mg/m^3 $CdSO_4$, 0.6 mg/m^3 $CuSO_4$, 1.5 mg/m^3 $ZnSO_4$, 2.2 mg/m^3 $Al_2(SO_4)_3$, 2.5 mg/m^3 $Al(NH_4)_2(SO_4)_2$, and 3.6 mg/m^3 $MgSO_4$. Ammonium sulfate at 5.3 mg/m^3 SO_4, NH_4HSO_4 at 6.7 mg/m^3 SO_4, Na_2SO_4 at 4 mg/m^3 SO_4, $Fe_2(SO_4)_3$ at 2.9 mg/m^3 SO_4, and $Fe(NH_4)_2SO_4$ at 2.5 mg/m^3 SO_4 did not cause significant alterations. The nitrates of Pb, Ca, Na, K, and NH_4 did not cause an effect at concentrations of 2 mg/m^3 or higher. However, $ZnNO_3$ caused effects similar to $ZnSO_4$. From this body of work, it appears that the NH_4 ion rendered the compound less toxic, and that the toxicity is primarily due to the cation. With the infectivity model, $ZnSO_4$ and $Zn(NH_4)_2(SO_4)_2$ ranked differently than with airway resistance experiments.[130] This is not unexpected as airway resistance primarily detects alterations of the medium to large conducting airways, while the infectivity model[180] is hypothesized to reflect alveolar level changes.

The increased mortality of the infectivity model does seem to be a measure of toxicity. When mice were exposed for 2 hr to 5.0 mg/m^3 carbon black or 2.5 mg/m^3 iron oxide, no significant increases in mortality resulted on subsequent exposure to airborne infection.[176]

Death from $\underline{S}$. $\underline{pyogenes}$ exposure in this infectivity model is due to septicemia.[154] Septicemia occurs when the bacteria have grown to 10^5 organisms per lung. Removal and killing of the inhaled organisms will reduce

the growth of the bacteria within the host and prevent the occurrence of septicemia. For these reasons, the infectivity model is an integrative assessment of toxicity for host defense systems against infectious pulmonary disease. As reported above, the number, kind, function and viability of the cells isolated by lavage from the lungs of animals exposed to heavy metal aerosols are different from control animals. Studies of tracheal rings isolated from aerosol-exposed hamsters also indicate depression of mucociliary clearance. Both mucocilary and AM clearance of bacteria are depressed by aerosols of these heavy metals.[176] (Table 12-12)

12.3.4.4 Immune Suppression--Antibodies play a significant role in the ability of macrophages to recognize and engulf pathogenic bacteria. The functioning of the immune system interlocks with the macrophage system in other ways also. In mice, intramuscular injections of $NiCl_2$ depressed the number of antibody-producing cells in the spleen.[159] Using the Jerne plaque assay, a negative linear dose-response curve was found with injections ranging from 9.26 to 12.34 µg Ni/g body weight. No effect was observed with a dose of 3.09 µg Ni/g body weight. The inhalation of $NiCl_2$ aerosols (99 percent less than 3 µm in diameter) was more effective in suppressing the primary immune response. Graham et al.[160] calculated that exposure to an aerosol of 0.25 mg/m^3 Ni for 2 hr would result in a maximum deposition of 0.98 µg Ni, assuming complete retention and a minute volume of 1.45 ml/g body weight. This concentration was found to be the lowest tested which produced a significant depression in the immune response. The lowest dose found to produce a similar effect by injection was 208 µg Ni/mouse.[159] The inhalation dose was, therefore, approximately 200 times more potent. Ni was found to follow first order removal kinetics from the lung, but measurable elevations remained in

the lung up to 4 days after exposure. Similar kinetics of removal have been found using the isolated, ventilated, and perfused rat lung[230] and human, rat, and cat type II pneumocytes in culture.[231.]

Inhaled Cd also depresses the number of antibody producing cells and is more potent than intramuscularly injected Cd. The highest intramuscular dose of $CdCl_2$ examined by Graham et al.[160] was 11.81 µg Cd/g body weight (about 266 µg Cd/mouse), and it produced no immunosuppression. When mice were exposed to 0.19 mg/m^3 Cd for 2 hr, a significant suppression was observed. In both cases the Cd was administered as $CdCl_2$, a highly soluble salt. The inhalation dose can be calculated on the same basis as that given above for Ni to be at a maximum at 0.74 µg Cd/mouse. The inhaled dose was, therefore, at least 350-fold more potent. Inhalation also appeared to be more potent than ingestion or interperitoneal injection.[161,162] Koller et al.[162] found that 150 µg Cd given orally was required to produce immunosuppression.

For comparative purposes, the lowest inhalation exposure of $CdCl_2$ found to be immunosuppressive was 0.19 mg/m^3; 0.2 mg/m^3 was the 1971 Threshold Limit Value (TLV). The current TLV is 0.05 mg/m^3. The human intake from air has been estimated to be 7.4 µg/day and from water to be 160 µg/day.[229] $NiCl_2$ was found to be immunosuppressive at an inhalation exposure of 0.25 mg/m^3 while its TLV is 1 mg/m^3. The human exposure is estimated to be 2.36 µg/day from inhalation and 600 µg/day from ingestion.[229] Should the effectiveness of inhaled aerosols be equivalent in mice and men, then the inhaled doses are biologically almost equivalent to those ingested.

Inhaled Cd or Ni aerosols impair the bacterial defenses of the lung through direct cytotoxicity to AM, depression of antibody production, and

inhibition of antibody dependent aggregation reactions. All of these mechanisms can help to explain the increased susceptibility of mice to airborne pathogens following inhalation of Ni or Cd aerosols. The rapidity of clearance of Ni and Cd from the lung may allow rapid recovery. (see Table 12-12)

TABLE 12-12. EFFECTS OF METALS AND OTHER PARTICLES ON HOST DEFENSE MECHANISMS

12-86

Concentration	Duration	Species	Results	Reference
0.01 or 0.15 mg/m³ Pb_2O_3 (0.18 µm, MMAD)	3 mo	Rat	Decreased the number of alveolar macrophages/lung.	Bingham et al.[152]
0.01 mg/m³ (0.17 µm, MMAD) $PbCl_2$ or 0.11 mg/m³ (0.32 µm, MMAD) $NiCl_2$ or 0.15 mg/m³ (0.15 µm, MMAD) Pb_2O_3 or 0.12 mg/m³ (0.17 µm, MMAD) NiO	12 hr/day, 6 day/wk, 2 mo with $PbCl_2$, $NiCl_2$, or NiO; continuously for 2 mo with Pb_2O_3	Rat	Exposure to Pb_2O_3, but not $PbCl_2$, resulted in a depression of the number of alveolar macrophages (AM) for up to 3 mo but returned to control levels within 3 days after discontinuation. NiO produced a marked AM elevation, while $NiCl_2$ did not. $NiCl_2$ resulted in marked increases in mucus secretion and bronchial hyperplasia. No morphological alterations with $PbCl_2$ or Pb_2O_3.	Bingham et al.[153]
0.05 to 1.42 mg/m³ $CdCl_2$	2 hr	Hamster	Decreased ciliary beating frequency in trachea.	Adalis et al.[157]
0.1 mg/³ $NiCl_2$	2 hr	Hamster	Decreased ciliary beating frequency in trachea.	Adalis et al.[156]
Graded concentrations: 0.075 to 1.94 mg/m³ $CdCl_2$ 0.1 to 0.67 mg/m³ $NiCl_2$, or 0.5 to 5 mg/m³ Mn_3O_4; all aerosols (94-99%) <1.4 µm in diameter	2 hr	Mouse	The aerosols increased the mortality from the subsequent standard airborne streptococcal infection: $CdCl_2$ affect the response at 0.1 mg/m³ Cd, $NiCl_2$ at 0.5 mg/m³ Ni, and Mn_3O_4 at 1.55 mg/m³ Mn.	Gardner et al.[154] Adkins et al.[155,189]
109 mg/m³ MnO_2 (0.70 µm, mean diameter)	3 hr/day	Mouse	Increased mortality after 3 or 4 days exposure when mice received bacterial aerosol immediately after exposure. When the bacteria were administered 5 hr post pollutant exposure, a single 3 hr exposure increased mortality. In mice exposed to aerosols of virus 1 or 2 days prior to MnO_2, there were also increased mortality and pulmonary viral lesions.	Maigetter et al.[191]
0.2 mg/m³ $CdSO_4$, 0.6 mg/m³ $CuSO_4$, 1.5 mg/m³ $ZnSO_4$, 2.2 mg/m³ $Al_2(SO_4)_3$, or 3.6 mg/m³ $MgSO_4$	3 hr	Mouse	Estimated concentrations which caused a 20% enhancement of bacterial-induced mortality over controls.	Ehrlich et al.[178,179]
Ammonium sulfate at 5.3 mg/m³ SO_4, NH_4HSO_4, at 6.7 mg/m³ SO_4, NO_2SO_4 at 4 mg/m³ SO_4, $Fe_2(SO_4)_2$ at 2.9 mg/m³ SO_4, or $Fe(NH_4)_2SO_4$ at 2.5 mg/m³ SO_4	3 hr	Mouse	No significant alterations of host defense mechanisms.	Ehrlich et al.[178,179]

TABLE 12-12. (Continued)

Concentration	Duration	Species	Results	Reference
5.0 mg/m^3 carbon black or 2.5 mg/m^3 iron oxide	2 hr	Mouse	No significant increases in mortality resulted on subsequent exposure to airborne infection.	Gardner[176]
0.19 mg/m^3 CdCl$_2$ 0.25 mg/m^3 NiCl$_2$	2 hr	Mouse	Decreased number of antibody-producing spleen cells	Graham et al.[160]

12.4 INTERACTION OF SULFUR DIOXIDE AND OTHER POLLUTANTS

12.4.1 Sulfur Dioxide and Particulate Matter

Although man breathes a multitide of chemicals in various mixtures at various dose-rates, most animal toxicological and controlled human exposures are conducted with single chemicals. This simplifies the research and permits an improved estimate of cause-effect relationships, but it prohibits evaluation of the effects of pollutant mixtures which may be additive, synergistic, or antagonistic with respect to the individual pollutants.

However, some interaction studies which elucidate the complexity of toxicological interrelationships have been conducted. Some of this work utilized pollutant combinations that would favor the conversion of the primary pollutant to a secondary pollutant (i.e., SO_2 altered to H_2SO_4, etc.). Other research was directed at evaluating the influence of several pollutants when delivered in combination or in sequence.

12.4.1.1 Acute Exposure Effects--The question of the possible effect of aerosols on the response to SO_2 is a critical problem in air pollution toxicology.[173] The phenomenon has been investigated in simple model systems of SO_2 alone or in combination with an aerosol of a single chemical. The typical bioassay system has been the comparison of the increase in pulmonary flow resistance in guinea pigs produced by a given concentration of SO_2 alone with that produced in the presence of the aerosol. The aerosols used in many of these studies were "inert" in the sense that they did not produce an alteration in flow resistance when they were given alone.

The initial simple prototype aerosol used was sodium chloride (NaCl)at concentrations of 10 mg/m^3 and 4 mg/m^3.[97] These experiments with guinea pigs indicated that the response to a given concentration of SO_2 was potentiated by

10 mg/m^3 sodium chloride. For example, a concentration of 5.24 mg/m^3 (2 ppm) SO$_2$ alone produced an increase of 20 percent in pulmonary flow resistance; when the sodium chloride was present, the increase was 55 percent. The potentiation did not occur until the latter part of a 1 hr exposure. When the concentration of sodium chloride was reduced to 4 mg/m^3, the potentiation was greatly reduced. Examination of post-exposure data indicated that the response to the combination resembled the response to a more irritant aerosol. The length of recovery was related to the concentration of SO$_2$, and the presence of the aerosol delayed recovery to control values. The chamber relative humidities were below 70 percent, but on entering the high humidity of the respiratory tract, the sodium chloride would absorb water to become a droplet capable of dissolving SO$_2$ thus favoring the production of H$_2$SO$_4$. Sodium chloride does not catalyze the oxidation of SO$_2$ to sulfuric acid.

Experiments by McJilton et al.[141] indicate the importance of ambient relative humidity and the solubility of SO$_2$ in the sodium chloride droplet. They examined the effect of 1 mg/m^3 NaCl on the response to 2.62 mg/m^3 (1 ppm) SO$_2$ at low (<40 percent) and high (>80 percent) relative humidity. An increase in pulmonary flow resistance in guinea pigs was the criterion of response. As would have been predicted from the earlier work, no increase was observed with this sodium chloride concentration at low relative humidity. At high relative humidity, the potentiation was marked and was evident during both the early and late parts of the 1 hr exposure. The rapid onset indicates the formation of an irritant aerosol in the exposure chamber under conditions of high humidity. As would have been predicted, no conversion to sulfate was found, but the droplets were acid with an estimated pH of 4. Presumably, this was sulfurous acid. (See the discussion of the effect of relative humidity on

sulfate and nitrate aerosols above and on human exposure experiments in Chapter 13).

Amdur and Underhill[96] studied the effect of aerosols of soluble salts of metals shown to convert SO_2 to sulfuric acid. Manganous chloride, ferrous sulfate, and sodium orthovanadate caused a threefold increase in the response to SO_2 concentrations of 2.62 mg/m^3 (1 ppm). The potentiation was evident during the first 10 min as well as during the remainder of the 1 hr exposure. Chamber relative humidity was 50 percent, indicating that high humidity was not necessary for the formation of an irritant aerosol in the chamber when the catalyzing metals were present. Analysis of the collected aerosol indicated the presence of sulfate, presumably as sulfuric acid.[93] These analyses indicated that at an SO_2 concentration of 0.52 mg/m^3 (0.2 ppm) about 0.08 mg sulfuric acid was formed. When this amount of sulfuric acid was administered with 0.52 mg/m^3 (0.2 ppm) SO_2, the increase in flow resistance duplicated the increase observed with the iron and vanadium aerosols.[170] This suggests that sulfuric acid formation is the most likely mechanism of potentiation for the aerosols of these metals. Amdur et al.[130] have reported that a 1 hr exposure to 0.4 mg/m^3 copper sulfate also potentiated the response to 0.94 mg/m^3 (0.36 ppm) SO_2. At the moment, it is not certain whether this is mediated through the formation of sulfuric acid or through the formation of a sulfite complex. The response to 0.79 to 0.84 mg/m^3 (0.3 to 0.32 ppm) SO_2 with ammonium sulfate (0.9 mg/m^3), ammonium bisulfate (0.9 mg/m^3), or sodium sulfate (0.9 mg/m^3) was purely additive. It should be pointed out that these salts have not been tested under conditions of high relative humidity.

Amdur and Underhill[96] also examined the effect of a variety of solid aerosols (carbon, iron oxide, manganese dioxide, and fly ash) which do not

catalyze the conversion of SO_2 to H_2SO_4. None of these potentiated the response to SO_2. (Table 12-13)

12.4.1.2 Chronic Exposure Effects

Animals were exposed continuously to various combinations of SO_2, sulfuric acid (0.5 to 3.4 μm, MMD), and fly ash (3.5 to 5.9 μm, MMD) which were collected downstream from electrostatic precipitators of coal-burning electric generating plants).[92] Monkeys were exposed for 18 mo and guinea pigs for 12 mo. For monkeys, exposures were to SO_2, H_2SO_4 + fly ash, SO_2 + H_2SO_4, or SO_2 + H_2SO_4 + fly ash. Guinea pigs received either 0.9 mg/m^3 H_2SO_4 (0.49 μm MMD) or 0.08 mg/m^3 H_2SO_4 (0.54 or 2.23 μm MMD) + 0.45 mg/m^3 fly ash (3.5 or 5.31 μm MMD). In monkeys, a battery of hematological and pulmonary function (tidal volume, respiratory rate, minute volume, dynamic compliance, pulmonary flow resistance, work of breathing, distribution of ventilation, CO diffusing capacity, and arterial blood gases) tests were applied at various times during exposure, but no significant effects were attributed to the exposures. Similar methods (except for distribution of ventilation and CO diffusing capacity) were used with guinea pigs, but no significant effects were observed. At the end of the exposure to 2.59 mg/m^3 (0.99 ppm) SO_2 + 0.93 mg/m^3 H_2SO_4 (0.5 μm MMD, σ_g 1.5 to 3.8), the lungs of monkeys had morphological alterations in the bronchial mucosa (focal goblet cell hypertrophy and occasional hyperplasia and focal squamous metaplasia). Monkeys exposed to 2.65 mg/m^3 (1.01 ppm) SO_2 + 0.88 mg/m^3 H_2SO_4 (0.54 μm MMD, σ_g 1.5 to 3.8) + 0.41 mg/m^3 fly ash (4.1 μm MMD, σ_g 1.8 to 2.8) had similar alterations. Thus, fly ash did not enhance the effect. Monkeys which received 0.99 mg/m^3 H_2SO_4 (0.64 μm MMD, σ_g 1.5 to 3.0) + 0.55 mg/m^3 fly ash (5.34 μm MMD, σ_g 1.8 to 2.2) had slight alterations in the mucosa of the bronchi and

TABLE 12-13. EFFECTS OF ACUTE EXPOSURE TO SULFUR DIOXIDE IN COMBINATION WITH PARTICULATE MATTER

Concentration	Duration	Species	Results	Reference
5.24 mg/m^3 (2 ppm) SO$_2$, 10 mg/m^3 and 4 mg/m^3 NaCl	1 hr	Guinea pig	5.24 mg/m^3 (2 ppm) SO$_2$ alone produced an increase of 20% in pulmonary flow resistance; with NaCl at 10 mg/m^3 the increase was 55% and the potentiation did not occur until the latter part of the exposure. At 4 mg/m^3 NaCl, the potentiation was greatly reduced.	Amdur[97]
2.62 mg/m^3 (1 ppm) SO$_2$, 1 mg/m^3 NaCl at low (40 %) and high (80%) relative humidity (RH)	1 hr	Guinea pig	No increase in pulmonary flow resistance at low RH. At high RH, the potentiation was marked and evident during both early and late parts of the exposure.	McJilton et al.[141]
2.62 mg/m^3 (1 ppm) SO$_2$, an aerosol of soluble salts (manganous chloride, ferrous sulfate, and sodium orthovanadate) 50% RH	1 hr	Guinea pig	Presence of soluble salt increased pulmonary flow resistance about 3-fold. The potentiation was evident early in the exposure.	Amdur and Underhill[96]
0.94 mg/m^3 (0.36 ppm) SO$_2$, 0.4 mg/m^3 copper sulfate	1 hr	Guinea pig	Potentiated pulmonary flow resistance.	Amdur et al.[130]
0.79 to 0.84 mg/m^3 (0.3 to 0.32 ppm) SO$_2$ and 0.9 mg/m^3 ammonium bisulfate, or 0.9 mg/m^3 sodium sulfate	1 hr	Guinea pig	The effect on pulmonary flow resistance was additive.	Amdur et al.[130]

respiratory bronchioles. Focal areas of erosion and epithelial hypertrophy and hyperplasia were observed. The other groups of monkeys had no remarkable morphological changes. All monkeys exposed to fly ash displayed no morphological alterations, although presence of the fly ash was easily observed. Guinea pigs experienced no morphological effects which could be attributed to pollutant exposure.

In a previous study, Alarie et al.[199] found no effects on pulmonary function, hematology, or morphology of monkeys or guinea pigs exposed to approximately 0.56 mg/m^3 fly ash in combination with 3 concentrations of SO_2 (0.28, 2.62, or 13.1 mg/m^3; 0.11, 1, or 5 ppm). Monkeys were exposed continuously for 78 wk and guinea pigs for 52 wk.

Lewis et al.[89,104] investigated the effects of SO_2 and H_2SO_4 in normal dogs and in dogs which had been previously exposed for 191 days to 48.9 mg/m^3 (26 ppm) NO_2. Dogs identically treated with NO_2 had morphological changes in the lung, and one of the animals had striking bullous emphysema. Sulfur oxide exposures were for 21 hr/day for a maximum of 620 days to 13.4 mg/m^3 (5.1 ppm) SO_2, to 0.89 mg/m^3 H_2SO_4 (90 percent < 0.5 µm in diameter), or to a combination of the two. These concentrations were averaged over time, and when the animals were examined at 225 days, the concentration of H_2SO_4 was lower (0.76 mg/m^3 H_2SO_4 in the H_2SO_4 group and 0.84 mg/m^3 H_2SO_4 in the H_2SO_4 + SO_2 group). After 225 days of exposure,[89] dogs receiving H_2SO_4 had a significantly lower diffusing capacity for CO than those that did not receive H_2SO_4. In the SO_2-exposed animals, pulmonary compliance was reduced (p < 0.05), and pulmonary resistance was increased (p < 0.05) compared to animals that did not receive SO_2. Dogs not pre-exposed to NO_2 which received SO_2 + H_2SO_4 had a smaller residual volume (p < 0.01) than all other dogs.

These dogs were also examined after 620 days of exposure.[104] At 3, 7, 19 or 20.5 mo of exposure, sulfur oxides did not markedly affect hematological indices (number of erythrocytes and leukocytes, hemoglobin concentration, hematocrit, mean corpuscular hemoglobulin value, mean corpuscular volume, and mean corpuscular hemoglobin concentration). There were no morphological changes that could be clearly identified as resulting from sulfur oxide exposure. However, pulmonary function was altered. Generally, the animals pre-exposed to NO_2 were more resistant to the sulfur oxides. Sulfur dioxide did not produce any significant effects except for an increase in mean nitrogen washouts. Sulfuric acid caused a significant ($p < 0.05$) decrease in diffusing capacity for CO, residual volume, and net lung volume (inflated) with an increase in total expiratory resistance. There was also a significant ($p = 0.1$) decrease in total lung capacity, inspiratory capacity, and functional residual capacity. Total lung weight and heart weight were also decreased. Other measurements (other lung volumes, dynamic and static compliance, and N_2 washout) were not significantly affected. These alterations of diffusing capacity for CO and lung volumes are interpreted as a loss of functional parenchyma, and, along with the increase in total pulmonary resistance, are in the direction expected for animals that develop obstructive pulmonary effects. Although the standard histological techniques used did not detect morphological effects, it is conceivable that the pulmonary function effects preceeded measurable structural alterations.

Beagle dogs were exposed 16 hr/day for 68 mo to raw or photochemically reacted auto exhaust, oxides of sulfur or nitrogen, or their combinations. A description of the exposure groups is given in Table 12-14. They were examined after 18,[186] 36,[104] and 61[105] mo of exposure and 32 to 36 mo[185,187] after the 68 mo exposure ceased.

TABLE 12-14. POLLUTANT CONCENTRATIONS FOR CHRONIC EXPOSURE OF DOGS[185]

Atmosphere	Pollutant Concentration, mg/m^3						
	CO	HC (as CH$_4$)	NO$_2$	NO	OX (as O$_3$)	SO$_2$	H$_2$SO$_4$
Control Air (CA)[a]							
Nonirradiated auto exhaust (R)	112.1	18.0	0.09	1.78			
Irradiated auto exhaust (I)	108.6	15.6	1.77	0.23	0.39		
SO$_2$ + H$_2$SO$_4$(SO$_x$)[b]						1.10	0.09
Nonirradiated auto exhaust + SO$_2$ + H$_2$SO$_4$ (R + SO$_x$)	113.1	17.9	0.09	1.86		1.27	0.09
Irradiated auto exhaust + SO$_2$ + H$_2$SO$_4$ (I + SO$_x$)	109.0	15.6	1.68	0.23	0.39	1.10	0.11
Nitrogen oxides, 1 (NO$_2$ high)			1.21	0.31			
Nitrogen oxides, 2 (NO high)			0.27	2.05			

[a]Abbreviations in parentheses
[b]>90% of H$_2$SO$_4$ particles were < 0.5 μm in diameter (optical sizing)

After 18^{186} or 36 mo^{105} of exposure, no significant changes in pulmonary function were observed. A variety of alterations were found using analysis of variance after 61 mo^{105} of exposure, but only those significant results related to sulfur oxides will be discussed in detail here. Residual volumes were increased in dogs receiving R + SO$_x$ (see Table 12-14 for abbreviations) compared to those receiving I + SO$_x$, SO$_x$, and CA. Residual volumes of the SO$_x$ group were lower than those of the CA group. When x^2 analyses were applied to the data of the number of dogs/group having alterations as judged by clinical criteria, additional significant differences were found. More dogs of the I + SO$_x$ group had higher total expiratory resistance than their controls (CA and SO$_x$). The ratio of residual volume to total lung capacity was higher in animals exposed to R + SO$_x$, compared to those receiving air (CA). This change was interpreted as pulmonary hyperinflation. Although other lung volumes, compliance, resistance, diffusing capacity for CO, N_2 washout, peak expiratory flow, and maximum breathing capacity were also measured, sulfur oxides had no effects.

Thirty-two to 36 mo^{185} after exposure ceased, the lungs of the beagles were examined using morphologic (light, scanning electron and transmission electron microscopy) and morphometric techniques. Only the results for sulfur oxide combinations will be described in detail. In the SO$_x$ group, lung weight, total lung capacity and the displaced volume of the processed right lung were significantly increased over the controls (CA). In the most severely affected SO$_x$ dogs, the air spaces enlarged and the number and size of interalveolar pores increased. Only the NO$_2$ high dogs had a greater degree of air space enlargement. The SO$_x$ animals had a loss of cilia in the conducting airways without squamous cell metaplasia, nonciliated bronchiolar cell hyper-

plasia, and loss of interalveolar septa in alveolar ducts. When SO_x was combined with R, cilia were also lost, but squamous cell metaplasia occurred. Exposure to R + SO_x and I + SO_x produced nonciliated bronchiolar cell hyperplasia and an increase in interalveolar pores and alveolar air space enlargement. The enlargement of the distal air spaces was centered on respiratory bronchioles and alveolar ducts and was associated with an apparent loss of interalveolar septa in all animals receiving SO_2 and H_2SO_4. The authors consider these changes to be analogous to an incipient stage of human proximal acinar (centrilobular) emphysema.

Biochemical analyses were also performed on the lungs of these dogs at the time of sacrifice, 2.5 to 3 yr after exposure ceased.[187] Hydroxyproline concentration (used as an index of collagen content) and prolyl hydroxylase activity (the rate-limiting enzyme in collagen synthesis) were measured. No significant changes in hydroxyproline were found. The SO_x and I + SO_x groups had significantly elevated prolyl hydroxylase activity compared to the R, R + SO_x, and CA groups.

Zarkower[115] reported mixed effects on the immune system of mice exposed to 5.24 mg/m^3 (2 ppm) SO_2 and 0.56 mg/m^3 carbon (1.8 to 2.2 μm, MMD), alone and in combination for 100 hr/wk for up to 192 days. Animals were immunized with aerosols of bacteria (Escherichia coli) at various times during exposure. After 102 days of exposure, there were no statistically significant changes. Sulfur dioxide caused an increase ($p < 0.05$) in serum antibody titer at 135 days and a decrease ($p < 0.01$) at 192 days. Carbon and carbon + SO_2 produced an equivalent decrease ($p < 0.01$) in antibody titer at 192 days (but not at 135 days) which appeared to be a greater decrease than that found in the SO_2-exposed mice. In the spleen, SO_2 caused an increase ($p < 0.01$) in the

number of antibody-producing cells at 135 days and a decrease ($p < 0.01$) in number at 192 days. In the mediastinal lymph nodes (which drain the lung), SO_2 caused no such changes. Carbon + SO_2, but not carbon alone, caused an increase ($p < 0.01$) in the number of antibody-producing cells in the mediastinal lymph nodes and a decrease ($p > 0.05$) in the spleen at 135 days. After 192 days of exposure to carbon or carbon + SO_2, the number of antibody producing spleen cells decreased ($p < 0.01$). The immunosuppression in these 2 groups was roughly equivalent and appeared to be more severe than that in the SO_2 alone group. In the mediastinal lymph nodes, only carbon + SO_2 caused immunoenhancement ($p < 0.05$). Thus, for the pulmonary immune system, only exposure to the combination of SO_2 and carbon caused significant effects. After 192 days, the systemic immune system was affected in all 3 exposure groups. It appeared that carbon and carbon + SO_2 caused equivalent effects and that both regimens were more effective than SO_2.

Fenters et al.[183] showed that exposure for 3 hr/day, 5 days/wk for up to 20 wk to a mixture of 1.4 mg/m^3 H_2SO_4 plus 1.5 mg/m^3 carbon (0.4 µm, mean particle diameter) or to 1.5 mg/m^3 carbon only (0.3 µm, mean particle diameter) also altered the immune system of mice. Some classes of serum immunoglobulins (Ig) decreased, with the exception of IgM which was increased after 1 wk of exposure to either carbon or H_2SO_4 + carbon. After 1 wk, some Ig classes decreased in both exposure groups, but after 4 or 12 wk of exposure, alterations were observed only in the H_2SO_4 + carbon group. Results for Ig were mixed at 20 wk. In the carbon group, the number of specific antibody-producing spleen cells was increased at 4 wk, unchanged at 12 wk, and decreased at 20 wk. A similar trend was observed in the H_2SO_4 + carbon group, but only the immunosuppression at 20 wk was significant. In examining other

*host defense systems, no alterations of alveolar macrophage viability or cell
*numbers were observed. After 4 and 12 wk of exposure, pulmonary bactericidal
'activity was increased in both exposure groups. By 20 wk of exposure, values
were not significantly different from controls. Using the infectivity model
with influenza A_2/Taiwan virus, a 20-, but not a 4-, wk exposure to H_2SO_4 +
carbon increased mortality.

Morphological changes were observed in these mice[183] using scanning
electron microscopy after 12 wk of carbon exposure. In the external nares,
there was excess sloughing of squamous cells. In the trachea, the number of
mucous cells appeared to increase; dying cells were present, and microvilli
were lost. No alterations of the bronchi were seen. The alveoli had some
areas of congestion with thickening, loss of interalveolar septa, and enlarged
pores. After 20 wk of exposure, damage was similar, but to a lesser degree.
Mice exposed to the mixture of H_2SO_4 and carbon showed equivalent effects, but
the damage was somewhat more severe than that seen in the carbon only group.

The influence of H_2SO_4 and carbon on the trachea of hamsters was
investigated by Schiff et al.[182] Animals were exposed for 3 hr to 1.1 mg/m^3
H_2SO_4 (0.12 μm, mean size) and/or 1.5 mg/m^3 carbon (0.3 μm, mean size) and
were examined either immediately, or 24, 48, or 72 hr later. Carbon caused no
change in ciliary beat frequency. Sulfuric acid exposure, however, caused
depression in this frequency at all time periods. The combination of H_2SO_4
and carbon produced similar effects, but recovery had occurred by 48 hr
post-exposure. Using light microscopy, the percentage of normal tracheal
epithelium was determined. Up to 48 hr after exposure, the combination of
H_2SO_4 and carbon resulted in more tissue destruction than either pollutant
alone, although the single pollutants did cause some damage. Morphological

alterations of all pollutant exposure groups were observed using light and scanning electron microscopy. (see Table 12-15)

12.4.2 Interaction with Ozone

Cavender et al.[143] exposed rats and guinea pigs to sulfuric acid aerosols (10 mg/m^3, 1 μm MMD), 3.9 mg/m^3 (2 ppm) ozone, or a combination of the two for 6 hr/day for 2 or 7 days; they then measured the ratio of lung to body weight and examined the lungs histologically. No synergism was observed between the ozone and sulfuric acid treatments. The histological lesions were those ascribed to ozone alone. This same group[119] exposed rats and guinea pigs to sulfuric acid aerosols (10 mg/m^3, 50 percent equivalent aerodynamic diameter, 0.83 μm, σ_g = 1.66), 1.02 mg/m^3 (0.52 ppm) ozone, or a combination of the two for 6 hr/day, 5 days/wk for 6 mo. The histological alterations were those due to ozone alone.

Last and Cross[144] found synergistic effects of a continuous exposure of sulfuric acid aerosol (1 mg/m^3) and ozone (0.78 to 0.98 mg/m^3 or 0.4 to 0.5 ppm) when administered simultaneously to rats for 3 days. Glycoprotein synthesis was stimulated in tracheal ring explants measured ex vivo. Ozone alone caused a decreased glycoprotein secretion; sulfuric acid was relatively inactive, requiring concentrations in excess of 100 mg/m^3 to produce changes in glycoprotein secretion. The lung DNA, RNA, and protein content increased in the group exposed to ozone and sulfuric acid aerosols, while the ozone-exposed group had only a small increase and the sulfuric acid group had none.

Grose et al.[181] investigated the interaction of H_2SO_4 and O_3 on ciliary beat frequency in the trachea of hamsters. A 2 hr exposure to 0.88 mg/m^3 H_2SO_4 (0.23 μm, VMD) significantly depressed ciliary beat frequency. By 72 hr after exposure, recovery had occurred. Hamsters exposed to 0.196 mg/m^3 (0.1

Concentration	Duration	Species	Results	Reference
Various combinations of SO_2, H_2SO_4 (0.5 to 3.4 μm, MMD), and fly ash (3.5 to 5.9 μm, MMD): SO_2, H_2SO_4 + fly ash, SO_2 + H_2SO_4, SO_2 + H_2SO_4 + fly ash	18 mo, continuous	Monkey	No significant effects on hematology or pulmonary function tests during exposure. At end of exposure to 0.99 ppm SO_2 + 0.93 mg/m³ H_2SO_4 (0.5 μm, MMD) lungs had morphological alterations in the bronchial mucosa. Exposure to 1.01 ppm SO_2 + 0.88 mg/m³ H_2SO_4 (0.54 μm, MMD) + 0.41 mg/m³ fly ash (4,1 μm, MMD) had similar alterations, thus fly ash did not enhance effect. Exposure to 0.99 mg/m³ H_2SO_4 (0.64 μm, MMD) + 0.55 mg/m³ fly as (5.34 μm, MMD) had slight alterations.	Alarie et al.[92]
0.9 mg/m³ H_2SO_4 (0.49 μm, MMD); 0.08 mg/m³ H_2SO_4 (0.54 or 2.23 μm, MMD) + 0.45 mg/m³ fly ash (3.5 or 5.31 μm, MMD)	12 mo, continuous	Guinea pig	No significant effects on hematology, pulmonary function, or morphology.	Alarie et al.[92]
Approximately 0.56 mg/m³ fly ash in combination with SO_2 at 0.28, 2.62, or 13.1 mg/m³ (0.11, 1, or 5 ppm).	78 wk, continuous	Monkey	No effects on pulmonary function, hematology, or morphology.	Alarie et al.[199]
Approximately 0.56 mg/m³ fly ash in combination with SO_2 at 0.28, 2.62, or 13.1 mg/m³ (0.11, 1, or 5 ppm)	52 wk, continuous	Guinea pig	No effects on pulmonary function, hematology, or morphology.	Alarie et al.[199]
13.4 mg/m³ (5.1 ppm) SO_2, or 0.89 mg/m³ H_2SO_4 (90% <0.5 μm in diameter), or to a combination of the two	21 hr/day, 620 days	Dog	After 225 days, dogs receiving H_2SO_4 had a lower diffusing capacity for CO than those that did not receive H_2SO_4. In the SO_2-exposed group, pulmonary compliance was reduced and pulmonary resistance was increased compared to dogs that did not receive SO_2. Dogs not pre-exposed to NO_2 who received SO_2 + H_2SO_4 had a smaller residual volume than all other dogs. After 620 days, pulmonary function was altered from sulfur oxide exposure but no hematological or morphological changes occurred. SO_2 did not produce any effects except for an increase in mean nitrogen washout. H_2SO_4 decreased diffusing capacity for CO, residual volume, and net lung volume and increase in total expiratory resistance. Total lung capacity, inspiratory capacity functional residual capacity were decreased. Total lung weight and heart rate were also decreased.	Lewis et al.[89,104]

TABLE 12-15 (continued).

Concentration	Duration	Species	Results	Reference
(see Table 12-14)	16 hr/day, 68 mo	Dog	After 18 or 36 mo exposure no changes in pulmonary function. Residual volumes increased in dogs receiving R + SO_x compared to I + SO_x, SO_x, and CA. Residual volumes of the SO_x group were lower than of the CA group. More dogs of the I + SO_x had higher total expiratory resistance than their controls (CA and SO_x). The ratio of residual volume to total lung capacity was higher in R + SO_x than CA. 32 to 36 mo after exposure ceased, the SO_x group had lung weight, total lung capacity, and displaced volume of the processed right lung increased over controls (CA). SO_x dogs had loss of cilia in the conducting airways. SO_x + R had loss of cilia and squamous metaplasia. Exposure to R + SO_x and I + SO_x produced nonciliated bronchiolar cell hyperplasia and an increase in interalveolar pores and alveolar air space enlargement.	Lewis et al.[89,104]
5.24 mg/m³ (2 ppm) SO_2, or 0.56 mg/m³ carbon (1.8 to 2.2 µm, MMD), or in combination	100 hr/wk, 192 days	Mouse	For the pulmonary immune system, only exposure to the combination caused significant effects. After 192 days, the systemic immune system was affected in all 3 exposure groups; carbon and carbon + SO_2 were more effective than SO_2, although SO_2 did cause significant effects.	Zarkower[115]
1.4 mg/m³ H_2SO_4 plus 1.5 mg/m³ carbon (0.4 µm, mean particle diameter), or 1.5 mg/m³ carbon only (0.3 µm, mean particle diameter)	3 hr/day, 5 day/wk, 20 wk	Mouse	Altered the immune system. Morphological changes observed; more severe with carbon only exposure.	Fenters et al.[183]
1.1 mg/m³ H_2SO_4 (0.12 µm, mean size), or 1.5 mg/m³ carbon (0.3 µm, mean size), or in combination	3 hr	Hamster	Carbon caused no change in ciliary beat frequency. Ciliary beat frequency was depressed after H_2SO_4 exposure. The combination produced similar effects, but recovery had occurred by 48 hr post-exposure. Up to 48 hr after exposure H_2SO_4 + carbon resulted in more tissue destruction than either pollutant alone.	Schiff et al.[182]

ppm) O_3 for 3 hr were not significantly affected. However, when animals were exposed in sequence, first to O_3 and then to H_2SO_4, ciliary beat frequency was decreased significantly, but to a lesser extent than that caused by H_2SO_4 alone. Analysis showed that antagonism ($p < 0.05$) occurred in this sequential exposure.

Gardner et al.[145] found that the sequence of exposure to sulfuric acid aerosols and ozone altered the response of mice to airborne infections. Mice were exposed alone or in sequence to 0.196 mg/m^3 (0.1 ppm) ozone for 3 hr and to 0.9 mg/m^3 sulfuric acid aerosol (VMC 0.23 μm ± 2.4 SD, geometric) for 2 hr. When given alone, neither pollutant caused a statistically significant increase in the mortality to a subsequent infection with Streptococcus pyogenes. When the pollutants were given sequentially, a significant increase in mortality occurred only when ozone was given immediately before exposure to sulfuric acid, and the response was additive. The reverse procedure had no effect on mortality due to Streptococcus pyogenes infections. Because photo-chemical oxidants and sulfur oxides often co-exist in polluted air, these studies are of very practical importance. The question of the temporal sequence has been poorly investigated. Simple mechanisms to predict this additive response sequence are not apparent. Thus, the results are opposite those of the Grose et al.[181] study described above with the tracheal model which showed that sequential exposure to O_3 and H_2SO_4 had an antagonisitic effect. The reasons for this difference are not known. However, the infectivity model is thought to reflect alveolar level effects,[180] whereas the ciliary beat frequency model is a measure of effects at the level of the trachea. In addition different animal species were used. These findings also indicate the complexity of interaction effects and the need to exercise care

in extrapolating the effects of pollutants from one parameter to another. (see Table 12-16)

12.5 CARCINOGENESIS AND MUTAGENESIS

Attempts have been made for several decades to correlate various indices of particulate air pollution with the development of cancer in man. In many cases a positive association has been found between increased community air pollution and cancer of the lungs and/or gastrointestinal tract. This knowledge has led to suspicions concerning the chemical nature of that portion or portions of airborne particulate matter which may be contributing to an excess of human cancer. At least three classes of potential etiologic agents have been studied in this regard: organic matter (including polycyclic hydrocarbons) which is adsorbed to suspended particles; sulfur oxides; and trace metals.

Test systems for the bioassay of potential mutagens and carcinogens are diverse, ranging from the measurement of chemically-induced reverse mutations in bacteria to the frank production of carcinomas by administration to mammals. However, it is commonly believed that fundamental similarities exist between the molecular mechanisms of both mutagenesis and carcinogenesis. This assumption is based on the theory that chemical interaction with DNA and/or other critical cellular macromolecules initiates a mutagenic or carcinogenic transformation.

Because of the strong formal relationship between molecular events involved in mutagenesis and carcinogenesis (Miller, 1978)[323], the demonstration of mutagenic activity for a substance is generally taken as strong presumptive evidence for the existence of carcinogenic activity. Therefore, it is believed that an investigation of the mutagenicity of a

TABLE 12-16.   EFFECTS OF INTERACTION OF SULFUR OXIDES AND OZONE

Concentration	Duration	Species	Results	Reference
10 mg/m^3 (1 µm, MMD) H$_2$SO$_4$ aerosol, or 3.9 mg/m^3 (2 ppm) O$_3$, or combination of the two	6 hr/day, 2 or 7 days	Rat and Guinea pig	No synergism in effect on ratio of lung to body weight. Histological lesions were those ascribed to O$_3$ alone.	Cavender et al.[143]
10 mg/m^3 (50% equivalent aerodynamic diameter, 0.83 µm, σ$_g$ = 1.66) H$_2$SO$_4$ aerosol, or 1.02 mg/m^3 (0.52 ppm) O$_3$, or combination of the two	6 hr/day, 5 day/wk, 6 mo	Rat and Guinea pig	Morphological alterations due to O$_3$ alone.	Cavender et al.[119]
1 mg/m^3 H$_2$SO$_4$ aerosol and 0.78 to 0.98 mg/m^3 (0.4 to 0.5 ppm) O$_3$	3 days, continuous	Rat	Synergistic effects. Glycoprotein synthesis was stimulated in tracheal ring explants; lung DNA, RNA, and protein content increased.	Last and Cross[144]
0.196 mg/m^3 (0.1 ppm) O$_3$; 0.9 mg/m^3 H$_2$SO$_4$ aerosol (VMC 0.23 µm ± 2.4 SD, geometric) exposed alone or in sequence	3 hr, O$_3$; 2 hr, H$_2$SO$_4$	Mouse	In response to airborne infections a significant increase in mortality only when O$_3$ was given immediately before exposure to H$_2$SO$_4$, and the response was additive.	Gardner et al.[154]
0.196 mg/m^3 (0.1 ppm) O$_3$; 0.88 mg/m^3 H$_2$SO$_4$ aerosol (0.23 µm, VMD) exposed alone or in sequence	3 hr, O$_3$; 2 hr, H$_2$SO$_4$	Hamster	H$_2$SO$_4$ depressed ciliary beat frequency. By 72 hr after exposure, recovery had occurred. O$_3$ exposure had no effect. Sequential O$_3$ then H$_2$SO$_4$ exposure decreased ciliary beating frequency significantly but to a lesser extent than that caused by H$_2$SO$_4$ alone.	Grose et al.[181]

substance may be predictive of its carcinogenic potential, and may serve as an early warning of a possible threat to human health in cases where positive results are obtained.

12.5.1   Airborne Particulate Matter

12.5.1.1 In vitro studies--Organic material associated with airborne particles has been investigated to a limited extent for mutagenic and carcinogenic potential. In these studies, particulate material is experimentally limited to that which is retained by the filter medium used (glass fiber, paper...etc.). Organics associated with aqueous particles cannot effectively be trapped, and thus there is no information on the biological effect or nature of these compounds. The particles that have created most interest are those with a carbonaceous core. These particles, because of their large surface area, adsorb many organic compounds some of which are known to be mutagenic and carcinogenic, such as benzo(a)pyrene. Because of the small size (0.2-0.3 μm mean diameter) of many of the particles, they can be effectively drawn into the deep compartments of the lung where the adsorbed organic material can desorb into the alveolar fluid and enter the associated tissue. The ability of soluble proteins to leach mutagens off particulates has been demonstrated using horse serum and coal fly ash (Crisp et al. 1978).[290]

A number of studies were conducted with fractionated extracts of particulate matter from urban air in order to obtain information on the chemical nature of the mutagens present (Teranishi, 1978; Møller and Alfheim, 1980; Dehnen and Tomingas, 1977; Tokiwa et al., 1980).[346,354,296,355] Estimates have been made as to the relative mutagenicity of each extract; however, due to the possible interaction among the many compounds present in

any fraction of the extracts the only conclusion that can be drawn is that both the polar and neutral fraction contain significant portions of the total mutagenic activity. These studies also have confirmed in two ways that polycyclic aromatic hydrocarbon (PAH) compounds are not the sole mutagens present in particulate matter. First, the total mutagenic activity does not co-fractionate with the PAH as evidenced by appreciable activity remaining in the polar fraction. Second, the presence of mutagenic activity in the absence of metabolic activation implicates non-PAH compounds. At present the identity of compounds which are acting as direct mutagens is uncertain.

In a similar manner as in studies with airborne particulate matter, mutagens were extracted from particles emitted from a coal powered electric plant (Crisp et al., 1978; Kubitshek and Venta, 1979),[290,356] gasoline engines (Wang et al., 1978),[351] and light-duty and heavy-duty diesel engines (Huisingh et al., 1978).[305] The extracts obtained from all sources were mutagenic to bacteria susceptible to frame-shift mutation, and no obligatory requirement for metabolic activation was shown. Only in the heavy duty diesel engine study was fractionation carried out on the crude extract. An extensive review of diesel engine particulate matter is available (Santodonato et al., 1978).[332]

The Ames assay has been used in an attempt to define air quality by measuring the mutagenic potential of airborne particulates. Tokiwa et al. (1977)[347] compared the number of revertants per µg of particulate matter collected in the industrial area of Ohmata with that collected in the residential area of Fukuoka, Japan. In a similar manner Pitts et al. (1978)[328] compared eight urban samples in the California South Coast Basin with one collected in a rural area of the San Bernadino mountains. In both

cases the mutagenic activity was less in the residential and rural areas compared to that observed in the urban areas. Also, mutagenic potential was determined in a quantitative manner for a variety of air samples collected in Chicago (Commoner et al., 1978).[294] In order to rank samples, the inverse of the minimum quantity of particulate matter needed to obtain a significant Ames assay result was calculated. Wind direction was then correlated with mutagenic potential.

Caution must be exercised when comparing in a quantitative manner results of Ames assays on complex environmental mixtures. Indirect mutagenesis is extremely difficult to quantitate, since the detoxifying action of the microsomal preparation makes the response of direct- and indirect-acting mutagens non-additive. For any valid comparison there has to be nearly complete separation of these two types of mutagens (Commoner et al., 1978).[294] Also, the effects on mutagenesis of synergism and antagonism among compounds in complex mixtures has not been adequately investigated. In the case ot complex mixtures obtained from tar-sand, the mutagenic activity of the known mutagen, 2-aminoanthracene, was greatly inhibited by interaction with the mixture (Shahin and Fournier, 1978).[336] For the above reasons a quantitative assessment of air quality is not readily obtainable with the use of the Ames Salmonella mutagenicity assay.

The data obtained with mammalian cell transformation assays support the conclusions derived from the Ames Salmonella assays. There appears to be a variety of biologically active agents present in the extracts of airborne particulate matter, and these agents are of both a polar and nonpolar nature. The identity of these compounds is unknown, however the activity present is greater than that which could be accounted for by the polycyclic aromatic

hydrocarbons present in the samples. Even though the cells transformed by extracts of particulate matter formed tumors when injected into newborn mice, it is presently unclear as to how the process of transformation in virus-infected cells relates to the process of chemical carcinogenesis. Hence, cell transformation assays should be considered in the same way as Ames assays; that is, as only an indicator of the presence of biologically active compounds.

The dominant lethal assay of Epstein et al. (1972)[299] is the only short term in vivo assay performed on airborne particulate extracts. The water soluble and benzene soluble fractions produced no fetal deaths or preimplantation losses beyond control limits. On the other hand, the oxygenated fraction showed significant fetal deaths and decreased total implants. Conclusions from these experiments are difficult to draw due to the limited validation and sensitivity of this assay system.

12.5.1.2. In vivo studies--It was realized as early as the 1930's that increasing amounts of particulate matter in the air may correlate with the increasing rate of human lung cancer. Some of the earliest in vivo experiments dealt with the repeated exposure of mice to clouds of soot, followed by autopsy examination for tumors at the end of their natural lifespan. A number of different kinds of soot have been chosen for these studies due to their significant contribution to airborne particulate matter. Upon bioassay of soot from chimneys (Campbell, 1939; Seelig and Benignus, 1938)[288,335] motor exhaust (Campbell, 1939)[288] and airborne particulate matter collected in the vicinity of a factory and roadway (McDonald and Woodhouse, 1942),[322] a slight increase over control in the number of lung tumors was observed. Only in the case where road dust from a freshly tarred road was

used were there significant increases, with 57 percent of the experimental and 8 percent of the control group having lung tumors (Campbell, 1934).[287] However, when five years later dust from the same road, which had not been retarred, was again tested only 8 percent of the experimental group and 1.4 percent of the control group developed lung tumors (Campbell, 1942).[289] In a recent study with lifetime exposure of rats to automotive exhaust, there were no tumors detected in the lungs of the treated animals. Although these studies have all attempted to demonstrate the potential of airborne particulate matter to cause lung tumors, the results obtained are ambiguous due to the low tumor incidence and the small size of the animal groups.

Among the various compounds associated with airborne particles, PAH's have received the greatest attention with regard to carcinogenic potential (Santodonato et al., 1979)[331] PAH's were the first compounds ever shown to be associated with carcinogenesis. To this day, carcinogenic PAH's are still distinguished by several unique features: (a) several compounds of this class are among the most potent animal carcinogens known to exist, producing tumors by single exposures to microgram quantities; (b) they act both at the site of application and at organs distant to the site of absorption; and (c) their effects have been demonstrated in nearly every tissue and species tested, regardless of the route of administration. The most widely studied PAH, benzo(a)pyrene, is ubiquitous in the environment and produces tumors in animals which closely resemble human carcinomas.

The production of lung tumors with airborne particulates has been extremely difficult. However, organic extracts of airborne particulates readily cause tumors when injected subcutaneously into mice. As early as 1942 sarcomas were produced in mice using the benzene extracts of particulate

matter collected from an urban area (Leiter and Shear, 1942; Leiter and Shimkin, 1942).[319,320] In these initial studies the tumor incidence was low, with only 8 percent of the mice developing tumors by the end of the study; however, none of the control mice had sarcomas. In one later study, the tumor incidence was as high as 61 percent when particulates were collected in the vicinity of a petrochemical plant (Rigdon and Neal, 1971).[330] Even in this case of high tumor production, no increase in the incidence of tumors over the spontaneous rate was observed in any organ of the animal distant to the site of injection. Only when neonatal mice were injected subcutaneously with particulate extracts did tumors appear distant from the injection site (Epstein et al., 1966),[300] with a very high incidence of hepatomas (83 percent) and multiple pulmonary adenomas (67 percent). Remote tumor formation after subcutaneous injection of neonatal mice was confirmed with both the crude extract of particulates collected in New York City and subfractions of this extract; the predominant tumors were again hepatomas (Asahina, 1972).[284]

The carcinogenic nature of extracts of particulate matter has also been demonstrated by studies involving skin painting on the backs of mice. With repeated application (three times per week for the life of the animal) of the benzene extract of particulates collected in the Los Angeles area, papillomas were formed which subsequently progressed to carcinomas (Kotin et al., 1954).[315] Papillomas first appeared after 465 days, and at the time the data were presented 42 percent of the mice had developed tumors. Although papillomas and carcinomas of the skin were the most commonly observed tumors, lung tumors have also been noted after skin application (Clemo et al., 1955).[291] Among the different methods of administering particulate extracts to the mouse for bioassay, skin painting yields the highest tumor incidence, with greater than 90 percent of the surviving animals in some cases developing tumors.

In subsequent studies, the phenomenon of two-stage tumorigenesis was used to further characterize the biological activity in airborne particulates. In two-stage tumorigenesis an initiator is an agent (usually a carcinogen) applied in a single dose to the skin of a mouse which does not produce tumors at the applied concentration but predisposes the skin so that later repeated application of a promoter (an agent that by itself will not produce tumors) will cause the formation of tumors. A complete carcinogen is one which, if applied in sufficient concentration, can produce tumors by itself. Extracts of airborne particulates from Detroit were fractionated, and the fractions examined for complete carcinogenicity and tumor initiating and promoting activity (Stern, 1968; Wynder and Hoffman, 1965).[342,352] Only the whole extract and the aromatic fraction proved to be a complete carcinogen, while the insoluble, acidic, aliphatic and oxygenated fractions produced no tumors (there was insufficient basic fraction to perform the assay).

In order to examine the aromatic fraction for initiating activity, this fraction was applied to the backs of mice in a sub-tumorigenic dose followed by repeated application of the known promoter croton oil. Tumor initiating activity corresponded in a general way to the benzo(a)pyrene content of the fraction. The other fractions of the particulate extract were not tested for initiating activity. It should be noted that an initiator does not necessarily have to be a complete carcinogen, although most if not all complete carcinogens will initiate if applied at a low dose where their complete carcinogenic action is not apparent. For this reason it is possible that some of the fractions could have initiating activity even though they did not act as complete carcinogens when first tested. However, the relevance of two-stage carcinogenesis to environmentally-caused cancer is not known.

Several contributing sources of airborne particulate matter, gasoline and diesel engines and the soot from coal and oil burning furnaces, have been examined individually and shown to produce tumors in vivo. Extracts of particulates from gasoline engines show carcinogenic activity when painted on the backs of mice (Brune, 1977; Wynder and Hoffman, 1962)[286,353] and when injected subcutaneously (Pott et al., 1977).[329] Extracts from diesel engines have shown tumorigenic activity in some studies but not in others; the same holds true for extracts of chimney soot where activity was shown in some instances (Campbell, 1939)[288] while not in others (Mittler and Nicholson, 1957).[324] The discrepancies among these results could be due to qualitative and/or quantitative differences in the nature of the organic compounds adsorbed to the particulates. These differences may be a reflection of the operating parameters of the generating source, or variations in particulate collection procedures. With diesel engines the mode of operation (the load under which the engine was run), the type of fuel and the temperature at which the particles were collected all affect the biological activity of the sample. (A complete review of diesel particulate matter is provided by Santodonato et al. 1978.)[332] With soot collected from chimneys, an important consideration is the temperature at which the particulate matter is collected. The organic material on particulates is generated in the gaseous phase and only after cooling are they adsorbed onto the inert core. Unless particulates are collected under similar conditions, disparities will exist in their chemical composition and biological activity. Taken together it is nevertheless apparent that all the major types of airborne particulate matter contain adsorbed compounds which are carcinogenic to animals and may contribute in some degree to the incidence of human cancer associated with exposure to urban particulate matter.

12.5.2   Sulfur Oxides

Sulfur dioxide hydrates rapidly in the moist upper airways, to form several ions. One of these, a bisulfite ion, effects the conversion reactions of nucleic acids. In 1970 and 1974 Shapiro et al. (1970,1974)[337,338] reported that bisulfite ions mediated the conversion of one nucleic acid cycle to another cycle. Compared with optimal conditions, 1 M bisulfite solution at pH 5 to 6, Shapiro (1977)[337] noted that the same solution at the physiological pH of 7 was only 1 percent as effective. In living cells the reaction could change the nucleotide sequence of DNA possibly resulting in mutations.

Uncharacterized free radical reactions may also occur under physiological conditions (Shapiro, 1977).[337] Since free radical reactions do not depend on high concentrations of bisulfite to obtain favorable equilibrium, they may be of greater significance in biological systems. The evidence that bisulfite reacts with model compounds (polycytidylic acid) and single- and possibly double-stranded DNA has lead to the investigation of its genotoxic, mutagenic and carcinogenic effects. This compound, however, has been considered innocuous, and has a GRAS (generally recognized as safe) designation as a food additive.

Mammalian in vitro and in vivo systems were used to determine the ability of bisulfite to cause chromosomal aberrations. Cultures of human lymphocytes treated by bubbling SO_2 gas through the media (Schneider and Calkins, 1970)[333] and cultures of human embryonic lung (Newell and Maxwell, 1974)[326] and mouse, cow, and ewe oocytes treated with bisulfite (Jagiello et al., 1975)[314] showed extensive chromosomal clumping after treatment. In severe cases of chromosomal damage, the cell will not survive and hence a mutagenic or carcinogenic transformation cannot occur. However, some cells showed only

moderate damage, with inhibition of DNA synthesis, fragmentation of chromosomes and inhibition of mitosis with damage to cells in anaphase. The possibility exists that sublethal changes in chromosomes may produce adverse effects on the cell which, particularly in the case of germ cells, may be transmitted to future offspring. Although cells in culture are sensitive to low concentrations of bisulfite, it has not been determined to what extent bisulfite exists in the intact animal. Also, the ability of the dominant lethal assay to detect mutagens has received only limited validation, and hence the sensitivity of this assay is not known.

Peacock and Spence (1967)[327] exposed LX strain mice, ~~to an atmosphere of 500 ppm SO₂, five days per week, for two years.~~ *over their lifetimes, in a 180 liter chamber into which SO₂ at a concentration of 500 ppm (1310 µg/m³) was injected at a rate of 20 ml/min for 5 minutes, 5 days/week.* The LX mice have a high incidence of spontaneous tumors, with 31 percent of the males and 17 percent of the females in the control group developing tumors of the lung by the end of the experiment. The SO_2 treated group had a greater number of tumors, with 54 percent of the males and 43 percent of the females developing adenomas and/or carcinomas. Due to the high spontaneous tumor incidence in these mice, it was concluded that SO_2 elicited an inflammatory response, which accelerated the development of spontaneous tumors.

A co-carcinogenic action has been ascribed to bisulfite because of the enhancement of the carcinogenic potential of benzo(a)pyrene. Kuschner (1968)[316] allowed rats to inhale a mixture of SO_2 and benzo(a)pyrene for one hour followed by six hours of exposure to either air or an SO_2 atmosphere. With this regimen, 18 percent and 50 percent , respectively, of the animals developed tumors. Control animals receiving air or SO_2 alone were tumor free. In a similar experiment von Nieding (1978)[303] noted also that SO_2 appeared to function as a cocarcinogen.

The lack of evidence for mutagenicity/carcinogenicity of bisulfite in mammalian in vivo systems may be due to the ability of mammals to rapidly bind bisulfite followed by enzymatic oxidation to sulfate. In mammals bisulfite can be regenerated by the reverse of the formation of S-sulfonates and the resulting free bisulfite oxidized enzymatically to sulfate by sulfite oxidase. Sulfite oxidase isolated from bovine liver has been extensively characterized (Cohen and Fridovich, 1971).[293] Approximately 80 percent of the reaction proceeds without the formation of free radicals. However, a portion of the reaction was inhibited by free radical scavengers, and the formation of the free radicals was shown to be dependent on the enzyme and the bisulfite concentration. From what is known, mammals have a high capacity of detoxifying bisulfite, but there is no assurance that reactions with plasma constituents and sulfite oxidase are sufficiently complete to prevent reactions with DNA and possible mutations. At present there has been no demonstration of genetic damage attributable to in vivo exposure to SO_2 or bisulfite. Sulfates have not been shown to be carcinogenic, but there is some evidence that they can augment the carcinogenic action of other compounds. Preliminary reports indicate an increased tumor incidence when sulfuric acid aerosols are administered along with benzo(a)pyrene (Lee and Duffield, 1977; Sellakumar, 1977).[318,334] In a novel theory of carcinogenesis, Hadler and Cook (1979)[304] showed that Tris salts of sulfates induced transitory uncoupling of mitochondria, with the speculated release of oncogenic mitochondrial genetic material. The cocarcinogenic action of sulfate was not fully confirmed in these laboratory studies, and at present only the inflammatory response, with its implications for carcinogenesis, has been demonstrated with ambient air.

In summary, sulfur dioxide, its oxidation products and their salts have been shown to react with DNA and other biological molecules, and in some instances to induce mutations in lower organisms. Although the potential for similar mutagenic/carcinogenic interactions to occur in mammals cannot be ruled out, it is apparent from the lack of genetic damage observed after in vivo administration that the risk of direct carcinogenic action by these compounds is small. The cocarcinogenic action, particularly by the inflammatory induction of a proliferative response, may be of greater significance. However, the work in this area is in its infancy and hence only highly speculative conclusions could be drawn.

12.5.3 Metals

Among the numerous trace metals found in the atmosphere, evidence of carcinogenicity in experimental animals has been shown for at least nine (beryllium, cadmium, cobalt, chromium, iron, nickel, lead, zinc, titanium). Limited evidence also points to compounds of molybdenum and manganese as possible tumorigens (Clemo and Miller, 1960; Cohen and Fridovich, 1971).[292,293] Moreover, three of these metals (cadmium, chromium, nickel), in addition to arsenic, are implicated as human carcinogens.

Although trace metals are ubiquitous in the environment, their levels are generally so low that it is difficult to predict the magnitude of carcinogenic risk in community settings. This problem is compounded by the fact that clear dose-response relationships have not been well-defined for most carcinogenic metals. For the present it is likely that the possible role of trace metals in the production of cancer due to particulate air pollution will be limited to qualitative judgements.

The topic of metal carcinogenesis has been extensively reviewed in recent years from various perspectives (Furst, 1977; Furst and Haro, 1969; Sunderman, 1978; Sunderman, 1979).[301,302,344,345] These surveys generally conclude that with certain compounds tumors can be induced via a mechanism which is apparently distinct from the phenomenon of so-called solid-state or foreign-body carcinogenesis. However, it is still debatable in many cases whether metal-induced tumors which are associated with a particular route of administration (e.g., local sarcoma by subcutaneous implantation) are indicative of of true chemical carcinogenesis. While most carcinogenic metals are active only in the form of organic and inorganic salts, for nickel and cadmium it appears that both the pure elemental form as well as several of their salts are carcinogenic.

One of the most widely recognized and well-studied carcinogenic metals is nickel (IARC, 1973; IARC, 1976).[306,307] Sunderman (1978, 1979)[344,345] indicated that nickel subsulfide (Ni_3S_2) is probably the most potent carcinogenic metal studied to date. Single intramuscular injections of 5 μmol (1.2 mg) or 10 μmol (2.5 mg) to Fischer rats produced rhabdomyosarcomas in 77 percent and 93 percent of the treated animals, respectively. Numerous investigators have confirmed that Ni_3S_2 produces local sarcomas following injection, and one group has indicated that chronic inhalation of Ni_3S_2 in rats caused lung cancer (IARC, 1973; IARC, 1976).[306,307] Several other forms of nickel have shown both positive and negative carcinogenic activity. The chronic inhalation of nickel carbonyl ($Ni(CO)_4$) by rats at levels as low as 0.03 mg/l has produced pulmonary carcinomas which were believed to be treatment-related (IARC, 1976).[307] In addition, Lau et al. (1972)[317] induced carcinomas and sarcomas in various organs, including liver and kidney, by

multiple intravenous injections of Ni(CO)$_4$ to rats. Inhalation of elemental nickel powder has produced equivocal results in mice, rats, and guinea pigs, and negative results in hamsters (IARC, 1976).[307] Single and repeated intramuscular injections of nickel powder induced local tumors in rats and hamsters, although intravenous injections were either marginally effective (rat) or ineffective (mouse, rabbit) (IARC, 1976).[307] A single intrapleural injection of nickel powder (0.02 ml of a 0.06 percent suspension) did not produce neoplasms in mice; multiple intrapleural injections at high doses in rats were effective in the induction of local tumors (IARC, 1976).[307]

The toxicology and carcinogenic potential of cadmium have been the subject of extensive reviews in the past several years (IARC, 1976; USEPA, 1979; Towill et al., 1978).[308,349,348] Cadmium is similar to nickel in that both the elemental form and several salts are carcinogenic, and that oral administration is ineffective in producing tumors. The ability of cadmium to induce tumors by inhalation exposure has not been adequately studied. However, single or repeated injections (intramuscular, subcutaneous) of cadmium powder, cadmium chloride (CdCl$_2$), cadmium oxide (CdO), cadmium sulfate (CdSO$_4$), or cadmium sulfide (CdS) to rodents frequently produces local sarcomas (Furst and Haro, 1969; IARC, 1976; Sunderman, 1979).[302,308,344] A unique feature of the action of cadmium is that single subcutaneous injections of CdCl$_2$ to rodents (3.7 - 5.5 mg/kg body weight) leads to a high incidence of interstitial cell (Leydig cell) tumors of the testis. Stoner et al. (1976)[343] recently reported that cadmium acetate did not cause a significant increase in pulmonary tumor response in the strain A mouse bioassay system.

Chromium in the hexavalent (but not trivalent) state has produced tumors following inhalation, implantation, and injection (IARC, 1973; Towill,

1978).[309,348] The inhalation of mixed chromate dust failed to induce lung tumors in mice, rats, and rabbits, although pulmonary adenomas developed in mice exposed by inhalation to calcium chromate ($CaCrO_4$) dust (IARC, 1973).[309] Local sarcomas in rats, mice, and rabbits have resulted from the intramuscular, subcutaneous, intrapleural, intraosseous, and intraperitoneal injection of chromium powder and hexavalent chromium compounds (IARC, 1973; Sunderman, 1979).[309,344] Several groups of investigators, however, have failed to induce tumors by the paren teral administration of chromium compounds.

Although arsenic is recognized as a human carcinogen based upon epidemiological data, there is little evidence to indicate carcinogenic activity in experimental animals (Furst and Haro, 1969; Sunderman, 1979).[302,344] In particular, the chromic administration of arsenous trioxide (As_2O_3) in drinking water (34 mg/l) to rats failed to induce tumors (Furst and Haro, 1969).[302] However, others have reported that the subcutaneous injection of a sodium arsenite compound led to an increase in the incidence of lymphocytic leukemias and malignant lymphomas in pregnant Swiss mice and their offspring (Sunderman, 1979).[344]

Although not generally recognized as a human carcinogen, lead compounds have shown considerable carcinogenic activity in rodents (IARC, 1972; Sunderman, 1979; USEPA, 1977).[310,350] Several studies confirmed that renal carcinomas result from the oral and parenteral administration of lead phosphate, lead acetate, or basic lead acetate to rats and mice, but not to hamsters. In addition, tumors of the testis (Leydig cell), adrenals, thyroid, pituitary and prostate have been found among rats fed lead acetate (3-4 mg/day for 18 months) (USEPA, 1977).[350] In a recent study using the strain A mouse

pulmonary tumor bioassay system, Stoner et al. (1976)[343] reported that lead subacetate caused a statistically significant increase in tumor formation. However, a dose-response relationship could not be demonstrated.

Beryllium salts have induced pulmonary cancers upon inhalation and osteo-sarcomas upon intravenous injection in a variety of animal species (IARC, 1972).[310] Aerosols of beryllium sulfate ($BeSO_4$) induced pulmonary carcinomas in all of a group of 43 rats (34 mg/m^3 for 56 weeks), and in two of ten Rhesus monkeys inhaling the compound at 35 mg/m^3 for eight years (IARC, 1972).[310] In addition, three of 20 monkeys developed pulmonary cancers after the intra-bronchial and/or bronchomural implantation of pure beryllium oxide (5 percent suspension in saline). Numerous investigators found that the intravenous injection of zinc beryllium silicate or beryllium oxide caused malignant bone tumors (osteosarcoma) in rabbits (IARC, 1972; Sunderman, 1979).[310,344]

Evidence to support the carcinogenic potential of zinc and iron is limited. Zinc compounds ($ZnCl_2$, $ZnSO_4$, $ZnNO_3$) are carcinogenic only by intratesticular injection (Furst and Haro, 1969; Sunderman, 1979).[302,344] When evaluated in the strain A mouse pulmonary tumor bioassay system, zinc acetate was found to be negative (Stoner et al., 1976).[343] Iron-polysaccharide complexes (e.g., iron-dextran) have commonly produced local sarcomas upon injection in mice, rats, and rabbits (Furst and Haro, 1969; IARC, 1973).[302,312] It is not clear whether this effect may have been due to solid state carcinogenesis. In contrast to the sarcomagenic properties of iron-dextran, ferric oxide (Fe_2O_3, hematite) produced no tumors in hamsters (intratracheal instillation), guinea pigs (inhalation) or rats (subcutaneous implantation).

The carcinogenicity of titanium has not been fully investigated. Chronic studies with mice involving the ingestion of a titanium salt in the drinking water gave negative results (Furst and Haro, 1969).[302] However, Furst and Haro (1969)[302] succeeded in producing local sarcomas and neoplasms in distant organs by the intramuscular injection of titanocene to rats and mice. In addition, local fibrosarcomas developed in three out of 50 rats injected with titanium dioxide.

Several groups of investigators have indicated that sarcomas can be produced by the subcutaneous, intramuscular, or intraosseous injection of cobalt powder, to rabbits and rats (Sunderman, 1979).[344] However, little additional data are available regarding the carcinogenic potential of cobalt. Stoner et al. (1976)[343] recently found that cobalt acetate had no effect on tumor incidence in the strain A mouse pulmonary tumor bioassay system.

Although selenium is not a metal, it has recently received considerable attention as a potential carcinogen, and is found in ambient air (IARC, 1975).[313] Oral administration of sodium selenite and sodium selenate to mice and rats has resulted in a wide range of neoplasmas including sarcomas, "lymphoma-leukemias," mammary carcinomas, lung adenocarcinomas, and hepatic tumors (IARC, 1975).[313] Because selenium is an essential trace element, its role in the etiology of environmentally-induced cancers remains unclear.

In an attempt to understand the fundamental biological activity of metals and its relationship to carcinogenesis, numerous in vitro experiments have been conducted. Many of these studies attempt to exploit the strong formal relationships between molecular events involved in mutagenesis and carcinogenesis. In particular, the interaction of xenobiotics with nucleic acids is believed to be a critical event in mutagenesis and/or cell transformation.

Cultures of mammalian cells and bacteria, as well as cell-free systems have been used to explore the potential mutagenicity/carcinogenicity of various metals.

Several biochemical studies have been completed which point to a possible direct action on nucleic acids by metal cations as the basis for metal carcinogenesis. Murray and Feisel (1976)[325] prepared mixtures of synthetic polynucleotides and measured the changes in the mixing curves induced by the addition of carcinogenic and non-carcinogenic metal salts at a 10^{-3}M concentration. Both cadmium chloride ($CdCl_2$) and manganese chloride ($MnCl_2$) induced alterations in spectrophotometric measurements which were indicative of mispairing of nucleotide bases.

More extensive studies have been conducted on the ability of metal salts to affect the fidelity of DNA synthesis in a cell-free system (Loeb et al., 1977; Sirover and Loeb, 1976).[321,340] These investigators found a high correlation between metals which were mutagenic/carcinogenic and the ability to increase the error frequency of deoxynucleotide incorporation. Nine metals were scored as positive in this system at concentrations between 20 mM and 150 mM; silver, beryllium, copper, cadmium, cobalt, chromium, manganese, nickel, and lead. Negative results were obtained with barium, calcium, aluminum, iron, potassium, magnesium, sodium, rubidium, strontium, and zinc. The authors concluded that the fidelity of DNA synthesis may have potential application as a screening technique for mutagenic/carcinogenic metals.

The recent proliferation of in vitro cell transformation assays has resulted in further confirmation of the carcinogenic/mutagenic action of several metals. The most noteworthy cell transformation studies thus far with metals have been those employing primary cultures of Syrian hamster embryo

cells (Costa, 1979; DiPaolo and Casto, 1979; DiPaolo et al., 1978).[295,297,298]
Morphological transformation has been obtained with salts of nickel, lead,
cadmium, chromium, beryllium, and arsenic. Salts of iron, titanium,
tungstate, zinc, and aluminum displayed no transforming properties.
Unfortunately there has not yet been an extensive validation of any single
test system for screening of potential metal carcinogens. Moreover,
techniques are not yet available to elucidate the molecular mechanism of
metal-induced transformation, or to explain how the physicochemical state of
the metal affects its carcinogenic potential.

12.6 CONCLUSIONS

12.6.1 Sulfur Dioxide

Once inhaled, SO_2 appears to be converted to its hydrated forms,
sulfurous acid, bisulfite, and sulfite. The rate of ~~absorption and~~ removal of
inhaled SO_2 varies with species, but ~~is~~ at least 80 percent of the inhaled
amount *is retained somewhere in the respiratory system* (see Chapter 11 for an expanded discussion on absorption).

The metabolism of SO_2 is predominantly to sulfate and is mediated by the
enzyme sulfite oxidase. Since sulfite oxidase is a molybdenum containing
enzyme, dietary factors could influence the function of the enzyme. No
conclusive evidence has yet been reported. The reaction of bisulfite with
serum proteins to form S-thiosulfates is rapid. The S-thiosulfates are
remarkably long-lived, supplying a circulating pool of bisulfite which can
reach all tissues. Since some circulating S-thiosulfates decompose to SO_2
which is exhaled, S-thiosulfates can donate their bisulfite content to distal
tissues. Sulfur dioxide and bisulfite are clearly mutagenic in microbial test
systems (Ames Salmonella and Yeast Systems). The mechanism for the
mutagenesis could be the deamination of cytosine at high concentrations. Free
radical reactions breaking glycosidic bonds in DNA may be responsible at low

concentrations. The potency of bisulfite in these _in vitro_ systems is moderate to weak when compared to agents such as nitrosamines or polycyclic aromatic compounds; but it is nonetheless positive. To date, experiments testing for mutagenicity or carcinogenicity by bisulfite in mammals have been equivocal. On the basis of present evidence, one can not decide whether or not bisulfite, and hence SO_2, is a mutagen in mammals.

The influence of SO_2 on tumorogenesis has also been examined. Rats exposed (5 days/wk for 98 wk to a lifetime) to 26.2 mg/m^3 (10 ppm) SO_2 for 6 hr/day in combination with 9.2 or 10.5 mg/m^3 (3.5 or 4 ppm) SO_2 plus 10 mg/m^3 benzo(a)pyrene had an increased incidence of lung squamous cell carcinoma. Hamsters were not affected. Statistical analyses were not performed, preventing definite interpretation of the data. However, from these studies, the possibility exists that SO_2 may be a co-carcinogen in rats. The question of carcinogenicity of SO_2 alone cannot be resolved at present. For the rat studies described above, a total of 15 rats were exposed to 26.2 mg/m^3 (10 ppm) SO_2 for 6 hr/day, 5 days/wk for lifetimes, and none developed cancer. However, this sample size is small and would have a small probability of detecting a low cancer incidence. In a different study, mice were exposed ~~for lifetimes in a 180 liter chamber into which SO_2 at a concentration of 500 ppm,~~ ~~5 min/day, 5 days/wk for a lifetime to 1310 mg/m^3 (500 ppm) SO_2.~~ This _(1310 µg/m³) was injected at a rate of 20 ml/min for 5 minutes, 5 days/week._ exposure increased the incidence of carcinoma in female, but not male, mice. The incidence of primary pulmonary neoplasias increased in both sexes. No statistical analyses were described, and thus, definitive interpretation is not possible. The investigators for this mouse study state that although SO_2 increased lung tumors, the results do "not justify the classification of SO_2 as a chemical carcinogen as generally understood." Other chronic SO_2 experiments have been conducted with several other animal species which

included lung morphology as an endpoint, but no lung tumors were reported. This does not negate the positive studies since they showed a species sensitivity to tumor development and were conducted either at very high concentrations or in the presence of benzo(a)pyrene. Without statistical analyses of the cancer incidence data, the general conclusion to be drawn from these studies is that SO_2 has an unproven potential to act as a carcinogen or a co-carcinogen in some animal species.

In rats, histopathological effects of SO_2 alone are confined to the bronchial epithelium, with most of the effects occurring on the mucus secreting goblet cells. Goblet cell hypertrophy occurs on chronic exposure of rats, leading some to suggest that SO_2 produces a chronic bronchitis similar in many respects to that in man. Repeated exposure to a critical concentration of SO_2 (not less than 131 mg/m^3 or 50 ppm) may be needed to produce the chronic bronchitis. The nasal mucosa of mice (particularly those with upper respiratory pathogens) was altered by 72 hr exposure to 26.2 mg/m^3 (10 ppm) SO_2. Continous exposure to 0.37 to 3.35 mg/m^3 (0.14 to 1.28 ppm) SO_2 for 78 wk did not cause any significant lung morphological alterations in monkeys.

An immediate effect of acute ($\leq$ 1 hr) SO_2 inhalation is either a decrease in respiratory rate or an increase in resistance to flow within the lung. The decrease in respiratory rate is mediated by a vagal reflex through receptors in the nose and upper airways. The response is transient in nature and occurs at 44.5 mg/m^3 (17 ppm). Lower concentrations were not tested. The increased resistance to flow is mediated through receptors in the bronchial tree and persists during continued exposure. With this physiological parameter, lower concentrations of SO_2 have been observed to cause reproducible changes in

respiration. The guinea pig is the most sensitive animal, having significant changes at concentrations as low as 0.42 mg/m^3 (0.16 ppm) SO$_2$ for 1 hr. Chronic exposures have produced alterations in pulmonary function in cynomolgus monkeys, but only at concentrations greater than 13.1 mg/m^3 (5 ppm). Dogs exposed to 13.4 mg/m^3 (5.1 ppm) SO$_2$ for 21 hr/day for 225 days had increased pulmonary flow resistance and decreased compliance. Lower concentrations were not examined. It should be remembered that SO$_2$ appears to cause its immediate bronchoconstrictive effect through action on airway smooth muscles. Since smooth muscles adapt or fatigue during long-term stimulation, chronic exposure to SO$_2$ is not likely to evidence bronchoconstriction equivalent to that occurring on short-term exposure. Alterations in pulmonary function after chronic exposure to SO$_2$ are likely to occur through other mechanisms, such as morphological changes in the airways or hypersecretion of mucus, which will result in narrowing the airway. Concentration, rather than duration of exposure, seems to be the most important parameter in determining responses to SO$_2$, whether the response is measured as a histopathological lesion or as a permanent alteration in respiration. There is no theoretical hypothesis available at present to integrate the short-term effects observed with 1 hr exposures and the effects of long-term exposures of several mo.

Some pulmonary host defense mechanisms are also affected by SO$_2$ exposure. After 10 and 23 days of exposure (7 hr/day, 5 days/wk) to 0.26 mg/m^3 (0.1 ppm), clearance of particles from the lower respiratory tract was accelerated in rats. At a higher concentration (2.62 mg/m^3, 1 ppm) there was an initial acceleration (at 10 days), followed by a slowing at 25 days. A 5 day (1.5 hr/day) exposure to 2.62 mg/m^3 (1 ppm) reduced tracheal mucous flow in dogs, but a longer exposure to this concentration caused no changes in ciliary beat

frequency of rats. Antiviral defenses were altered by a 7 day continous exposure to 18.3 to 26.2 mg/m^3 (7 to 10 ppm) SO_2 as evidenced by an increase in viral pneumonia. In this study, the combined exposure to SO_2 and virus produced weight loss at concentrations as low as 9.43 mg/m^3 (3.6 ppm) SO_2. Mice exposed to 13.1 mg/m^3 (5 ppm) SO_2 for 3 hr/day for 1 to 15 days or for 24 hr/day for 1 to 3 mo did not have increased susceptibility to bacterial lung disease. A variety of changes in the humoral immune response of mice exposed for up to 196 days to 5.24 mg/m^3 (2 ppm) have been reported.

12.6.2 Particulate Matter

The dissolution of SO_2 into liquid aerosols or the sorption onto solid aerosols tends to increase the potency of SO_2. The exact mechanism by which potentiation occurs is still controversial.

Reports disagree as to the potency of acute exposure to sulfate aerosols. Some investigators contend that sulfuric acid is highly irritating, producing increases in pulmonary flow resistance at low concentrations and linear concentration responses. The lowest effective concentration so far reported was 0.1 mg/m^3 (1 hr) in the guinea pig. Particle size influenced the results in several ways but the smaller sizes were generally more effective. Others have observed an "all or none" response (increased airway resistance) in guinea pigs exposed for 1 hr to 14.6, 24.3, or 48.3 mg/m^3 H_2SO_4. Exposure to lower concentrations (1.2 or 1.3 mg/m^3) caused no effects. Some of these conflicts may be due to differences in technique, strain of animal, or species of animal. Discrepancies are particularly marked in the potency of sulfate salt aerosols, with older reports presenting significant alterations in resistance to flow at low concentrations. The largest data base for the effects of 1 hr exposure of guinea pigs to sulfur oxides comes from 1

laboratory. This research has resulted in an apparent ranking of potency (for increased flow resistence): $H_2SO_4 > ZnSO_4(NH_4)_2SO_4 > Fe_2(SO_4)_3 > ZnSO_4 > (NH_4)SO_4 > NH_4HSO_4$, $CuSO_4 > FeSO_4$, Na_2SO_4, $MnSO_4$. The latter three caused no effects.

The toxicology of H_2SO_4 is complicated by its partial concentration-dependent conversion to $(NH_4)_2SO_4$ and NH_4HSO_4 by ammonia in the breath or in the air of animal exposure chambers. While there is a stoichiometry of this chemical reaction, the actual concentrations have not been measured definitively. Thus, comparing results of H_2SO_4 studies using animals to those using humans is confounded, particularly since extensive neutralization would not be expected in the atmosphere of human exposure chambers. One theory for the ~~initiating~~ _irritating_ action of sulfuric acid contends that sulfate salts can act to promote release of histamine or other mediators of bronchoconstriction and is supported by biochemical and pharmacological evidence in 2 species. Anionic release of histamine may play a role in the bronchial constriction as evidenced by the blockade with antihistamines and adrenergic drugs. Certainly, the clearance of sulfurous acid, bisulfite, sulfite, and sulfate from the lung is influenced by the cations present in the aerosols inhaled simultaneously. Since polluted air is such a complex mixture of these aerosols, the question of the toxicity of ambient aerosols can not be approached on a simplistic basis by estimating toxicity from the acidity alone.

Chronic exposure to H_2SO_4 also produces changes in pulmonary function. Monkeys exposed to 0.48 mg/m^3 H_2SO_4 continously for 78 wk had altered distribution of ventilation early in the exposure period. Higher concentrations (2.43 and 4.79 mg/m^3) changed the distribution of ventilation

and increased respiratory rate but caused no effects on other pulmonary function measurements. A lower concentration (0.38 mg/m^3) caused no effects. Morphological changes occurred at the lowest concentration tested (0.38 mg/m^3). The effects appeared to be related to size of the particle as well as to concentration. Major findings at 2.43 mg/m^3 H$_2$SO$_4$ included bronchiolar epithelial hyperplasia and thickening of the respiratory bronchioles and alveolar walls. Guinea pigs exposed continously for 52 wk to 0.08 or 0.1 mg/m^3 H$_2$SO$_4$ had no effects on pulmonary function or morphology. Dogs which inhaled 0.89 mg/m^3 H$_2$SO$_4$ for 620 days (21 hr/day) also had no morphological alterations. However, CO diffusing capacity, residual volume, and net lung volume were decreased. Several other changes were noted, including an increase in total expiratory resistance.

Sulfuric acid also alters mucociliary clearance which is responsible for clearing the lung of viable or non-viable particles. These particles impact on the ciliated airways during inhalation or reach this region as a result of alveolar clearance. A 1 hr exposure of dogs to 0.5 mg/m^3 H$_2$SO$_4$ increased tracheal mucocilary transport, whereas 1 mg/m^3 H$_2$SO$_4$ depressed this rate. A 2 to 3 hr exposure to 0.9 to 1 mg/m^3 H$_2$SO$_4$ also decreased tracheal ciliary beat frequency in hamsters. Lower concentrations (0.1 mg/m^3 H$_2$SO$_4$, 1 hr/day, 5 days/wk) caused erratic bronchial mucociliary clearance rates in donkeys after several wk of exposure. Continued exposure of the donkeys which had not received pre-exposures caused a persistent slowing of bronchial clearance after about 3 mo of exposure. From these and other studies, it appears that low concentrations of H$_2$SO$_4$ can slow mucociliary clearance. This might imply increased lung residence times of materials that would ordinarily be cleared.

Other host defense parameters, e.g., resistance to bacterial infection, are not altered by low concentrations of H_2SO_4, but are affected by metal sulfates. The apparent relative potency of various particles for increasing susceptibility to infectious (bacterial) respiratory disease has been determined in mice exposed for 3 hr: $CdSO_4 > CuSO_4 > ZnNO_3$, $ZnSO_4 > Al_2(SO_4)_3 > Al(NH_4)_2(SO_4)_2$. At concentrations > 2.5 mg/m^3 the following particles had no significant effects in this model system: H_2SO_4, $(NH_4)SO_4$, NH_4HSO_4, Na_2SO_4, $Fe_2(SO_4)_3$, $Fe(NH_4)_2SO_4$, $NaNO_3$, KNO_3, and NH_4NO_3.

It is evident that accurate estimates of the toxicity of complex aerosols occurring in urban air based solely on their sulfate contents are inappropriate. The chemical composition of the sulfate aerosols determines their relative irritancies, which can be correlated with the permeability of the lung to that specific sulfate salt. The metallic ions associated with sulfate aerosols are also not without toxicity. Since urban air contains sulfuric acid, ammonium sulfate, and metallic sulfates in varying proportions, it is not possible to extrapolate from the currently inadequate toxicological data on single compounds in animals to man as he exists in a complex environment.

No data are available on the toxicity of secondary or complex atmospheric aerosols, since only a very few published reports of animal studies have appeared. The problem is highly complex because of the variability of aerosols from different urban localities and the compositional changes on collection. Toxicity can be approached, at present, only from estimates of composition and toxicity of individual components. Fly ash has little toxicity when inhaled at concentrations less than 100 mg/m^3, but it has definite toxicity at 200 mg/m^3 or greater. Using in vitro tests, metal oxide-coated fly ash has

measurable toxicity which can be ascribed to the insoluble oxides when alveolar macrophages are exposed. The effects of soluble salts of Ni and Cd, for example, have major differences. Nickel and Cd are removed from the lung with relative rapidity but may be stored or bound to intracellular proteins to an extent which is sufficient for accumulation on repeated short-term exposures. Two hr exposures to both Ni (0.5 mg/m^3) and Cd (0.1 mg/m^3) aerosols impair the anti-bacterial defenses of the lung, leading to an increased sensitivity to airborne pathogens in mice. Ciliary beat frequency in trachea can be decreased by Cd and Ni also. Humoral immunosuppression in mice has been reported after a 2 hr exposure to 0.19 mg/m^3 $CdCl_2$ or 0.25 mg/m^3 $NiCl_2$.

12.6.3 Interactions of Gases and Particles

Although man is exposed to a complex mixture of gases and particles, few animal studies have been conducted with mixtures. Sodium chloride and soluble salts (manganous chloride, ferrous sulfate, or sodium orthovanadate) potentiated the effect (increased flow resistance) of a 1 hr SO_2 exposure of guinea pigs. Hypothetically, these particles favored the conversion of SO_2 to H_2SO_4, thus increasing the response.

The effects of chronic exposure to a variety of mixtures of SO_2, H_2SO_4, and fly ash were examined in guinea pigs and monkeys. None of these studies showed effects on pulmonary function. Morphological changes were observed in monkeys after an 18 mo continuous exposure to 2.6 mg/m^3 (0.99 ppm) SO_2 plus 0.88 mg/m^3 H_2SO_4; but the addition of fly ash did not potentiate the response.

When dogs were exposed to SO_2 (13.4 mg/m^3, 5.1 ppm) and H_2SO_4 (0.89 mg/m^3) alone and in combination for 21 hr/day for 620 days, no morphological changes were observed. Sulfur dioxide did not cause any significant changes

in pulmonary function except for an increase in N_2 washout, but H_2SO_4 caused a variety of changes which were interpreted as the development of obstructive pulmonary disease.

In another series of studies, dogs were exposed for 16 hr/day for 68 mo to raw or photochemically reacted auto exhaust, oxides of sulfur or nitrogen, or their combinations. The animals were examined periodically during exposure and at 32 to 36 mo after exposure ceased. After 18 or 36 mo of exposure, no significant changes in pulmonary function were observed. After 61 mo, a few functional alterations were observed in dogs exposed to SO_x (1.1 mg/m^3, 0.42 ppm SO_2, and 0.09 mg/m^3 H_2SO_4) alone and in combination with other pollutants in the study. The animals had been placed in clean air for 32 to 36 mo after exposure ceased, at which time the SO_x group had a variety of morphological alterations. These included a loss of cilia without squamous cell metaplasia, nonciliated bronchiolar hyperplasia, and a loss of interalveolar septa in alveolar ducts. The authors hypothesized that these changes are analogous to an incipient stage of human proximal acinar (centrilobular) emphysema.

Combinations of carbon and H_2SO_4 or SO_2 were investigated also. In mice exposed for 3 hr/day, 5 days/wk for up to 20 wk to a mixture of 1.4 mg/m^3 H_2SO_4 and 1.5 mg/m^3 carbon or carbon only, morphological and immunological alterations were seen in both groups. In hamsters, a 3 hr exposure to 1.1 mg/m^3 + 1.5 mg/m^3 carbon depressed ciliary beat frequency, as did H_2SO_4 alone. Alterations of both the pulmonary and systemic immune systems were found in mice at various lengths of exposure (100 hr/wk up to 192 days) to 5.2 mg/m^3 (2 ppm) SO_2 and 0.56 mg/m^3 carbon, alone and in combination. Generally, carbon and carbon + SO_2 caused more extensive effects than SO_2 alone.

When the interaction of O_3 and H_2SO_4 was studied, the morphological effects to the mixture [10 mg/m^3 H_2SO_4 + 1.02 mg/m^3 (0.52 ppm) O_3] of a 6 mo intermittent exposure of rats and guinea pigs were attributed to O_3 alone. However, combined exposure to 1 mg/m^3 H_2SO_4 and 0.78 to 0.98 (0.4 to 0.5 ppm) O_3 resulted in synergistic effects on glycoprotein synthesis in trachea and certain indices of lung biochemistry. Acute sequential exposure to first 0.196 mg/m^3 (0.1 ppm) O_3 and then 0.9 mg/m^3 H_2SO_4 caused additive effects on increased susceptibility to infectious pulmonary disease and antagonistic effects on depression of tracheal ciliary beat frequency. From these studies, the interaction of O_3 and H_2SO_4 is quite complex and appears to be dependent on the sequence of exposure as well as on the parameter examined.

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APPENDIX I

1.0 SULFONATION BY SULFITE AND BISULFITE

Sulfite is a relatively strong nucleophile and can attack a number of biological compounds by nucleophilic substitution or addition. Either sulfite or bisulfite may be responsible for sulfonation. Nucleophilic substitution through sulfite attack is called sulfitolysis and has been reported for epoxide,[2] disulfide (Reaction 12-3),[3] and thiamine (Reaction 12-4).[4]

$$RSSR' + HSO_3^- \rightleftharpoons RSSO_3^- + R'SH \qquad\qquad 12\text{-}3$$

12-4
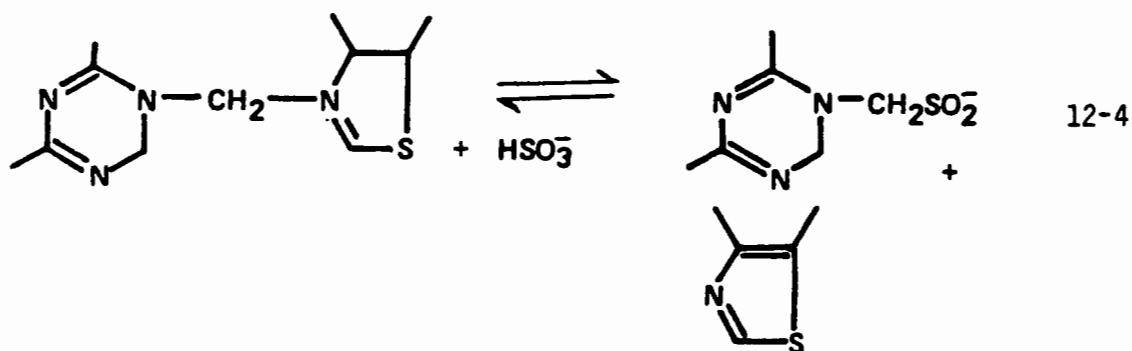
The equilibrium constant for Reaction 12-3 with cysteine at 37°C and pH 7.75 is 8.9×10^{-2}. If sulfite is incubated with rabbit plasma for 45 min, nearly 100 percent of the added sulfite is present as S-sulfonates ($R\text{-}S\text{-}SO_3^-$).

On this basis, Kaplan et al.[5] calculated that chronic exposure to an unspecified concentration of SO_2 would convert 0.16 percent of total plasma

proteins to S-sulfonates. The metabolic significance of this level of plasma S-sulfonates is not yet clearly defined, although Kaplan et al. saw it as toxic. On the other hand, Gunnison and Benton[6] and Shapiro and Weisgras[7] concluded that 0.16 percent is a relatively low level of protein alteration and that sulfitolysis is probably not metabolically significant. S-sulfonation may serve as a vehicle for the widespread distribution and storage of bisulfite in the body. (See Section 12.2.1.3.1).

Bisulfite adds _in_ _vitro_ to aldehydes (Reaction 12-5), ketones (including sugars), conjugated alkenes, quinones, coumerins,[2] the pyridine ring of NAD (Reaction 12-6),[8] the pyrazine ring of folic acid (Reaction 12-4),[9] and the isoalloxazine ring of flavine coenzymes (Reaction 12-7).[10]

$$RCHO + HSO_3^- \rightleftharpoons R\overset{OH}{\underset{}{C}}HSO_3^-$$

<div style="text-align:right">12-5</div>

<div style="text-align:right">12-6</div>

<div style="text-align:right">12-7</div>
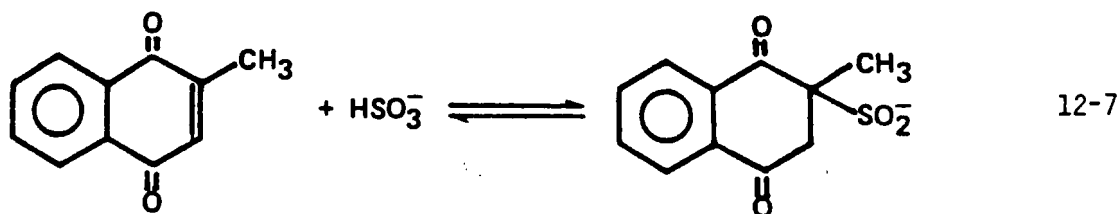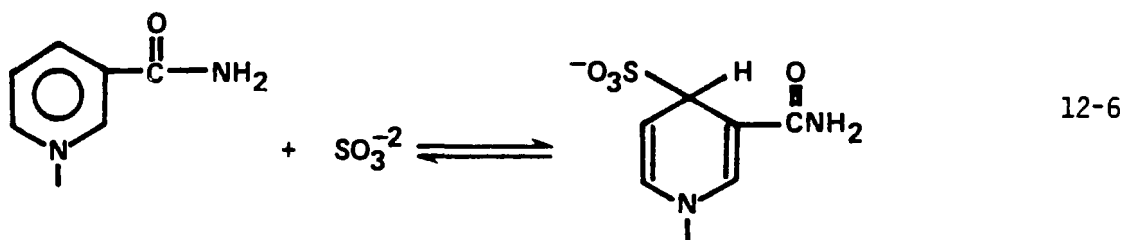
The ionic reaction of bisulfite with NAD^+ and flavins in vitro has been described by several authors. Bisulfite adds reversibly to the 4 position of NAD^+ with an equilibrium constant of 36 M^{-1} at pH 7. The bisulfite adduct is greatly stabilized in the presence of proteins since a stoichiometric reaction of bisulfite at low concentrations occurs with protein bound NAD^+. Enhancement of the reaction of bisulfite with flavins bound to proteins has also been observed. Two reaction mechanisms of bisulfite with NADH are discussed below. The first is an ionic reaction in which bisulfite acts as a general acid catalyst to hydrate the 5,6 unsaturation; this hydration reaction is relatively slow. The second is a free radical oxidation of NADPH to the pyridinium salt.

2.0 AUTOXIDATION OF SULFITE AND BISULFITE

Oxidation of sulfite to sulfate through the free radical chain mechanism in vitro can be initiated by metal ions,[11] ultraviolet irradiation,[12,13] charge transfer complexes from the illuminated dyes,[14-16] electrolytic generation of radicals[17] or enzymatic reactions.[17-22] These reactions are important for their ability to generate free radicals. The autoxidation of sulfite can be initiated by superoxide radical $(\cdot O_2^-)$, but is inhibited by superoxide dismutase.[23,24] This suggests that $\cdot O_2^-$ radical is involved in propagation as well as initiation. Thus, the reactive species generated during the aerobic oxidation of sulfite includes $\cdot O_2^-$, $\cdot OH$, and $\cdot SO_3^-$. The following scheme describes the sulfite oxygen chain reaction.[12-25]

Initiation:

$$SO_3^{-2} + O_2 \rightarrow \cdot SO_3^- + \cdot O_2^-$$

12-8

Propagation:

$$\cdot SO_3^- + O_2 \rightarrow SO_5^-$$

12-9

$$SO_5^- + SO_3^{-2} \rightarrow SO_4^- + SO_4^{-2}$$

12-10

$$SO_4^- + SO_3^{-2} \rightarrow SO_4^{-2} + SO_3^-$$

12-11

$$SO_4^- + OH^- \rightarrow SO_4^{-2} + \cdot OH$$

12-12

$$\cdot OH + SO_3^{-2} \rightarrow OH^- + SO_3^-$$

12-13

$$\cdot O_2 + SO_3^{-2} + 2H^+ \rightarrow 2 \cdot OH + SO_3^-$$

12-14

Termination:

$$\cdot OH + SO_3^- \rightarrow OH^- + SO_3^-$$

12-15

$$SO_3^- + \cdot O_2^- \rightarrow 2H^+ \rightarrow SO_3^- + H_2O_2$$

12-16

$$(H_2O_2 + SO_3^{-2} \rightarrow H_2O + SO_4^{-2}$$

$$SO_3 + H_2O \rightarrow SO_4^{-2} + 2H^+)$$

12-17
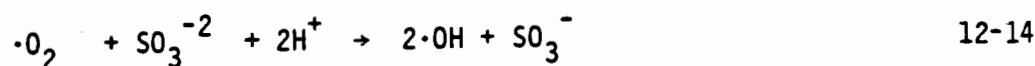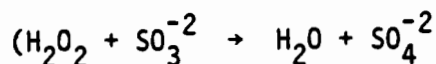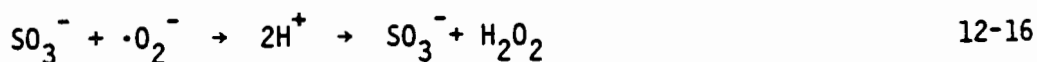
Initiation (Reaction 12-8) is caused by metal ions, ultraviolet light or enzymatic reactions. The chain is propagated by Reactions 12-9 through 12-14, forming sulfate ion. Chain length of the reaction has been estimated at 30,000 moles/mole $\cdot O_2^-$ in the xanthine-xanthine oxidase system[17] and 300 moles/mole $\cdot O_2^-$ in the isolated chloroplast under illumination.[15] The metal initiated autoxidation of sulfite is inhibited by EDTA, organic acids, alcohols, thiols,

amines, and proteins that occur in cells and may act as radical scavengers inhibiting autoxidation.[26,27] Peroxidase initiated sulfite oxidation is not inhibited by these scavengers,[25] suggesting that in vivo the oxidation of sulfite is catalyzed by enzymes. The non-enzymatic autoxidation outlined above produces oxy- and sulfur oxide radicals that may be highly deleterious, since they may cause lipid peroxidation. (See discussion below.)

Evidence for the formation of the highly reactive $\cdot OH$ and $\cdot O_2^-$ species has come mainly from studies of peroxidase catalyzed sulfite oxidation.[22,28] In these studies, methional is used to scavenge hydroxyl free radicals generating ethylene as a characteristic oxidation product. Beauchamp and Fridovich[29] have demonstrated that $\cdot OH$ is responsible for ethylene formation from methional. Methionine is rapidly oxidized to the sulfoxide (Reactions 12-18 and 12-19).[30]

$$R\text{-}S\text{-}R + \cdot OH \rightarrow R\overset{+}{\text{-}}S\text{-}\overset{-}{R} + OH \qquad\qquad 12\text{-}18$$

$$R\overset{+}{\text{-}}S\text{-}R + \cdot OH \rightarrow \underset{\underset{OH}{|}}{R\overset{+}{\text{-}}S\text{-}R} \rightarrow \underset{\overset{\|}{O}}{R\text{-}S\text{-}H} + H^+ \qquad 12\text{-}19$$
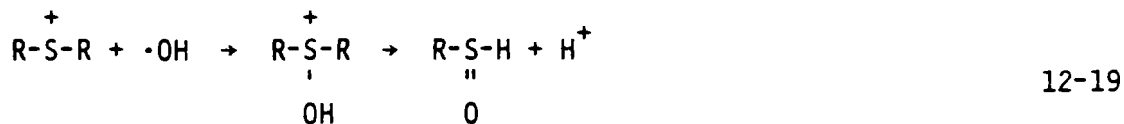
In addition to methionine, tryptophan is also oxidized during the oxidation of sulfite.

Co-oxidation of NADH and NADPH during sulfite oxidation has been reported,[8,21] suggesting the following chain reaction:

$$SO_2^- + Initiator \rightarrow \cdot SO_3^- \qquad \text{12-20}$$

$$NADH \quad \cdot SO_3^- \rightarrow NAD \cdot + SO_3^{-2} + H^+ \qquad \text{12-21}$$

$$NAD \cdot + O_2 \rightarrow NAD^+ + \cdot O_2^- \qquad \text{12-22}$$

$$SO_3^{-2} + \cdot O_2^- + 2H^+ \rightarrow \cdot SO_3^{-2} + H_2O_2 \qquad \text{12-23}$$
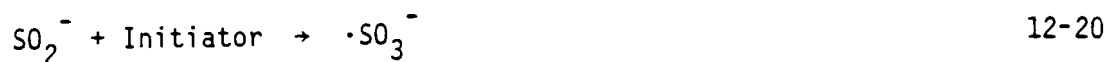
The autoxidation of sulfite could deplete NADH and NADPH needed for metabolism, but the amount of NADH or NADPH oxidized will not be significant at concentrations of SO_2 which occur in the ambient air.

3.0 BISULFITE-INITIATED LIPID PEROXIDATION

Kaplan et al.[31] demonstrated that bisulfite (0.5 to 10 mM) initiates peroxidation of aqueous emulsions of corn oil. Peroxidation was measured by the formation of 2-thiobarbituric acid (TBA) reactive substances. Most likely, these TBA reactive substances correspond to bicyclic peroxides formed during the autoxidation of linolenic acid present in corn oil. The reaction was inhibited by the addition of the phenolic antioxidant BHT (2,6-di-t-butyl-4,4-hydroxymethyl phenol). Addition of manganous ion (10^{-5} to 10^{-3} M) also inhibited the reaction. Therefore, autoxidation initiated by bisulfite seems to proceed through some oxygenated intermediary. It is most probable that the reaction proceeds through $\cdot OH$ or $\cdot O_2^-$ (see Section 12.2.1.1). Kaplan et al. suggest that peroxidation of cell membranes is a mechanism of inhaled SO_2 toxicity. This hypothesis has not been supported by whole animal inhalation data.

4.0 POTENTIAL MUTAGENIC EFFECTS OF SULFITE

This section will review the biochemistry by bisulfite and sulfite. While there is data suggesting a weak mutagenic effect in vitro and in microorganisms, the question of mutagenesis in vivo has not been demonstrated in animals.

As pointed out in Section 3 above, alterations in DNA and RNA produced by sulfite are detected only at high concentrations of sulfite, acid pH and in vitro. Microbial systems validated for chemical mutagenesis have not been used in these experiments. The biological viability of sulfite-induced alterations in DNA remains an important unanswered question. If the alterations were not transcribable, then cytotoxicity, rather than mutation, would be the outcome. Further, the rapid metabolism of sulfite to sulfate in vivo might preclude the accumulation of sufficient sulfite to react with DNA. This is very important for the DNA contained in chromatin of higher organisms where its reactivity towards sulfite is especially obscure. An additional factor, so far not addressed experimentally, is the rate of DNA repair after sulfite damage. Repair, without errors, may be sufficiently rapid to preclude transcription of erroneous information. Lastly, if sulfite damage to DNA were expressed as carcinogenesis, this would undoubtedly be a multistep process involving many stages. It is still unknown how chemical carcinogens would go through this process. However, the most conservative course would be to avoid exposure to all mutagens, since there presently is no known way to reverse carcinogenesis.

4.1 REACTIONS OF BISULFITE/SULFITE WITH DNA AND RNA AS RELATED TO MUTAGENESIS

The reactivity of bisulfite with nucleic acids and subsequent mutagenesis induced by bisulfite have been reviewed by Shapiro[55] and by Fishbein.[56] The deamination of cytosine to uracil in single-stranded, but not double-stranded, DNA is of interest[58] (Reaction 12-26). This reaction also occurs in yeast RNA.[59] The optimum conditions for both reactions are pH 5 and high bisulfite concentrations on the order of 1M. Deamination results in the conversion of GC to AT sites and could be mutagenic. GC to AT in DNA conversion has been

subsequently confirmed. (See the discussions on the effects of bisulfite on cultured cells.) Decomposition of the uracil bisulfite complex is the rate limiting step. The chemistry of this reaction is discussed in detail by Shapiro.[55] He calculated the rate of deamination of cytosine under physiological conditions to evaluate the potential environmental genetic hazard. While it is true that mammalian DNA is double-stranded, during the translational process some regions of single-strandedness in the DNA may be susceptible to attack. Double-strandedness does not completely prevent deamination of cytosine to uracil and, therefore, the introduction of a point mutation. Using estimates of the spontaneous mutation in man at 10^6/gene/generation,[60,61] or approximately 10^{-9}/base pair/generation assuming 10^3 base pairs to a genome,[61] Shapiro calculated that a concentration of 3×10^{-7} M bisulfite is sufficient to double the spontaneous mutation rate. This estimate is probably high since the deamination reaction is second order in bisulfite, whereas Shapiro calculated the rate to be first order at low concentrations of bisulfite. In doing as Shapiro assumes, other general acids or bases could substitute for
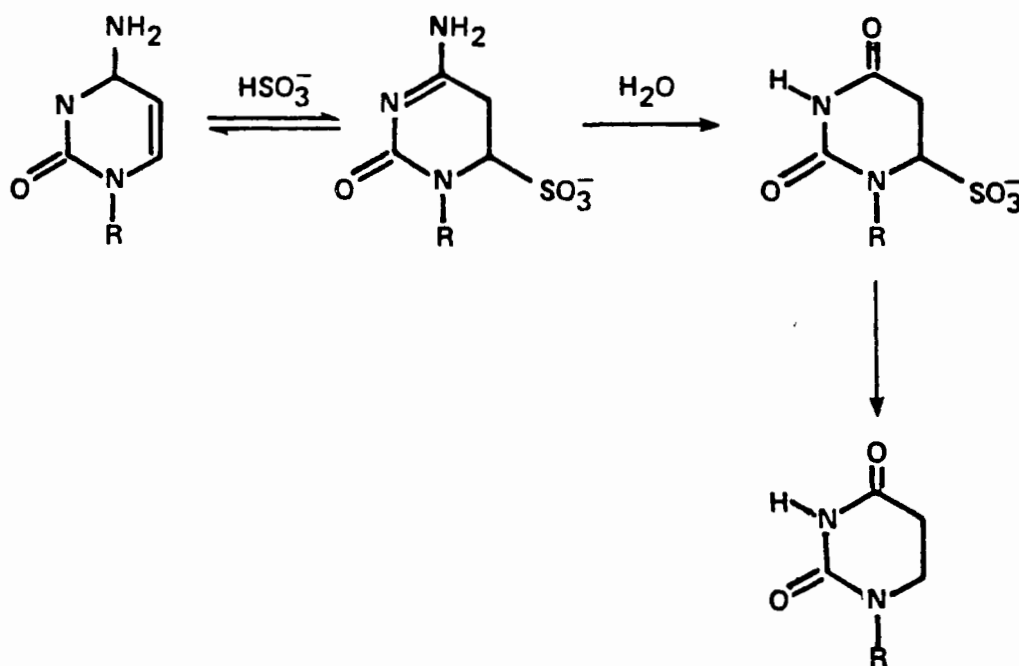
12-26

bisulfite in catalyzing the deamination step (Reaction 12-26). However, Shapiro points out that double-strandedness markedly reduces the reactivity of cytosine. The structure of DNA in eukaryotic chromatin and its reactivity with bisulfite are not known.

Transamination can be carried out via the same chemical mechanism as deamination (Reaction 12-27). The bisulfite adduct readily reacts with primary amines, decomposing to the transaminated base. This reaction has been studied in some detail.[55] If transamination were to occur, then cross-linking of DNA through reactions with other biopolymers containing free amine groups (lysyl groups, for example) is theoretically possible. Thus far, it has been difficult to substantiate covalent cross-linking reactions resulting from this reaction. Cross-linking of single-stranded MS2/phage has been observed. Histones present in mammalian chromatin are rich in lysine and a DNA-histone cross-link might occur in vivo. The biological consequences of such a cross-link are not known at the present time.

12-27
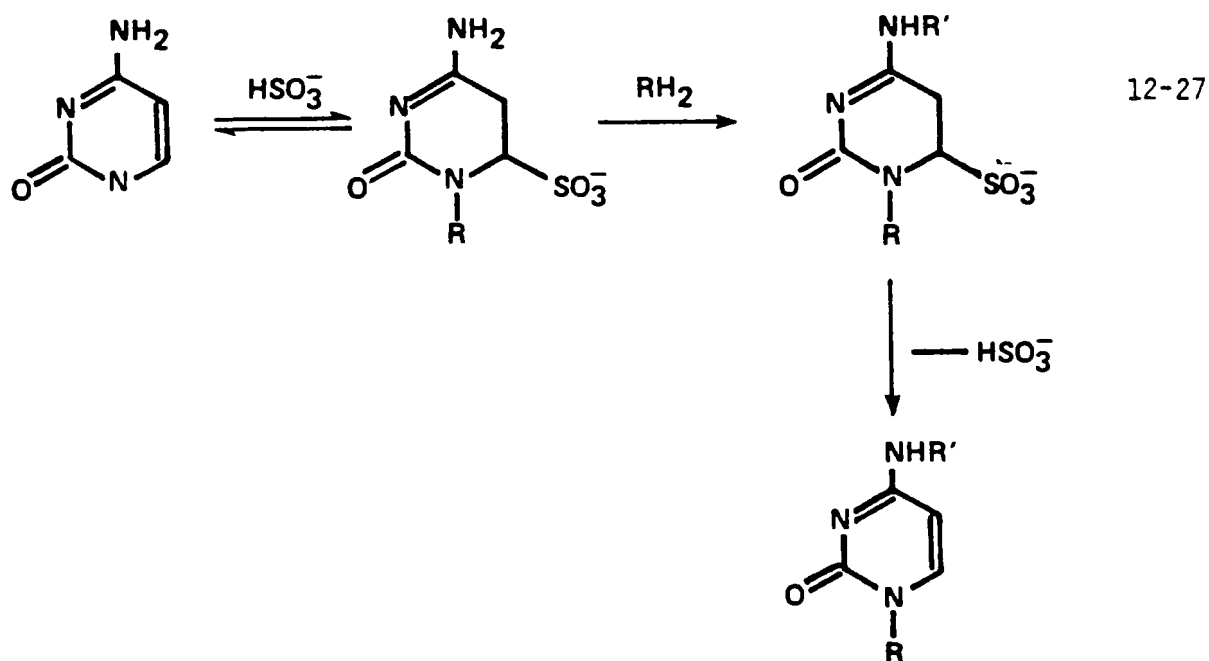
The very addition of sulfite to uracil and cytosine to form reversible adducts could disrupt DNA function. Reaction of these bases with sulfite is likely to reduce their hydrogen bonding with other bases, leading to disruption of the tertiary structure of the gene. Disruption of messenger RNA function and translation could occur. The experiments reported to date are not wholely convincing, but have been reviewed in detail by Shapiro.[55]

5.0 FREE RADICAL REACTIONS WITH DNA

Sulfite catalyzed oxidation reactions are likely candidates as mechanisms for sulfite/SO_2 damage to DNA at low concentrations of DNA. As discussed above, the oxidation of sulfite produces a number of complex free radicals and multistep chain reactions involving reactive oxygen and sulfur species such as $\cdot SO_3^-$, $\cdot OH$, $\cdot OOH$, and $\cdot O_2^-$. The effect of bisulfite-initiated free radical reactions on mutational events has been reviewed by Hayatsu.[62] Sulfite also initiates the free radical catalyzed autoxidation of unsaturated fatty acids. It is possible that the combination of the oxygen and sulfur species generated by bisulfite autoxidation or those generated by lipid peroxidation reactions could damage DNA or RNA. While the deamination and transamination reactions require considerable concentrations of bisulfite to achieve appreciable rates, the free radical pathway need not consume or require large quantities of bisulfite. Thus, free radical reactions could be carried out at trace concentrations which could result from environmental exposure to SO_2 or bisulfite. If so, the free radical reaction initiated by bisulfite assumes greater theoretical interest, although direct evidence for this reaction in vivo is still lacking.

6.0 EVIDENCE FOR SULFITE/SO_2 MUTAGENESIS

Studies on the genetic effects of bisulfite/SO_2 have taken two forms: exposures at acidic pH and high bisulfite concentrations designed to

initiate cytosine deamination; and studies carried out at low bisulfite concentrations and/or neutral pH designed to investigate free radical or more obscure reaction mechanisms.

In viruses, phage, bacteria, and yeasts, experiments carried out with high concentrations of bisulfite support the conversion of GC to AT with intact DNA and, therefore, cytosine deamination reactions.[200-203] However, these studies have not determined whether the cytosine deamination reaction catalyzed by bisulfite can be carried out with double-stranded DNA in chromatin. Studies with microorganisms are complicated since 10^{-2} to 10^{-3}M bisulfite is a growth inhibitor. The inhibition of microbial growth is the principal reason for the use of bisulfite in foodstuffs and particularly in oenology Reactions with RNA and inhibition of protein synthesis by other means might likewise occur.

The effects of SO_2/bisulfite on plants have been well documented, but it is not well established whether these toxic effects are due to inhibition of photosynthesis or to mutations.[55]

The picture of genetic effects of SO_2/bisulfite becomes clouded when considering the experiments on multicellular organisms or cultured mammalian cells. In Drosophila (fruit flies), clear-cut mutagenesis has not been observed in all studies. The results have been muddled by experimental design defects such as the choice of the medium in which the bisulfite was presented to the fruit flies.[205] Reducing sugars in the growth medium could have decreased the bioavailable bisulfite. No definite conclusion can be drawn at the present time.

Experiments with cultured human and animal cells have been reported.[207-212] Cytotoxicity, but not clear-cut mutagenesis, was observed in most of these

studies. For example, human HeLa cells in culture showed decreased growth when exposed to SO_2,[207] and mouse fibroblasts and peritoneal macrophages showed decreased cell viability.[208] Human lymphocytes in culture showed decreased growth, DNA synthesis, and mitotic index when exposed to either SO_2 or bisulfite solutions.[210,211] No mutations or chromosomal breaks were detected in these studies.[57] Inhibition of meiosis has also been reported with mouse, ewe, and cow oocytes exposed to low concentrations of bisulfite.[212] Some of the observed effects may be directly due to the toxicity of SO_2/bisulfite. For example, fuzziness and clumping of chromosomes may represent stages of degeneration of dead cells.

In experiments to detect mutations directly, mice were either injected with bisulfite or fed 1 percent sodium bisulfite in the diet.[213] No effects were found on the oocytes, and a reduced number of chromosomal abnormalities was found in the livers of treated animals.[212] In these experiments, only a small number of animals were exposed to a single dose. The survey for chromosomal abnormalities inappropriately used a model based upon regeneration of liver cells following acute carbon tetrachloride intoxication.[213] In the host-mediated assay using rats and _Saccharomyces cerevisiae_, no effects were observed.[43,232]

At the present time, the equivocal results of these assays leave open the question of SO_2-induced mutations in higher organisms.

7.0 TECHNICAL NOTES ON THE MEASUREMENT OF AIRWAY RESISTANCE AND LUNG COMPLIANCE IN EXPERIMENTAL ANIMALS

7.1 RESISTANCE AND COMPLIANCE

Sulfur dioxide inhalation initiates contraction of bronchoconstrictor muscles in humans[45,233] and in a number of animal species.[98,99,234,235] This

tubular narrowing will in turn inhibit air flow in and out of the lungs. The measured degree of inhibition is called airway resistance. The reciprocal of airway resistance is airway conductance. The actual resistance to air flow in the lungs is due to friction between gas molecules in the gas stream and gas molecules along bronchial walls.[236] Alterations in the cross-sectional area of the trachea and larger bronchi account for major changes in resistance; thus, resistance is a measurement that represents the central airways and is not sensitive to peripheral changes in the lung.[237] Other mechanical factors, such as flow direction, volume history, lung tissue resistance, gas viscosity, and lung volume, contribute directly or indirectly to the measurement of resistance.[236-238] Humoral or pharmaceutical agents,[239,240] mechanical stimuli,[241] respiratory heat exchange,[242] and disease states[238,243] also influence resistance.

Compliance is a ratio of volume change in the lung and the pressure required to overcome elastic resistance of the lung in order to attain the new volume. (Compliance = volume change/pressure change.) This measurement indicates the state or a change in the state of the parenchyma of the lung. Lungs that are stiff (high elasticity) have a low compliance. Compliance is decreased by constriction of alveolar duct smooth muscle, alveolar cellular infiltration, edema, airway closure, pulmonary vascular congestion, fibrosis of the lung, pneumonia and pulmonary distress syndrome in infants.[236,237]

Compliance is determined at periods of no air flow so that the value is not influenced by frictional resistance. It can be measured in two ways. Static compliance is computed by allowing the lung and thorax to inflate (or deflate) to measured volumes in a stepwise fashion; the changes in volumes are then related to the changes in pressures. Dynamic compliance is measured during spontaneous breathing and is calculated at points when air is not

flowing, i.e., during pauses after inflation and deflation. Static compliance equals dynamic compliance at normal tidal volumes (the volume of air moved during normal breathing); however, physiological factors not necessarily related to disease (such as lung volume and lung volume history) can alter the compliance measurement. Dynamic compliance will also decrease with increased breathing frequency or be frequency dependent if there is a non-uniform distribution of ventilation in the lungs.[236-238] It is probable that broncho-constriction following the inhalation of irritants results in non-uniform distribution of ventilation.

Computation of airway resistance and dynamic compliance requires simultaneous measurement of intrapleural pressure ($P_{p\ell}$) and tidal volume (V_T) or flow ($\dot{V}$). Assuming that inertial losses are small, the following relationship occurs during normal breathing. Transpulmonary pressure (P_{TP}) or the pressure difference between the mouth and the intrapleural space at any given time is:

$$P_{TP} = \dot{V}/R + \frac{1}{C/V} \qquad (I)$$

where R is airway resistance and C is the compliance of the lung. Dynamic compliance (C_{dyn}) is determined during tidal breathing at points in time when the flow is zero.

$$C_{dyn} = \frac{\Delta V}{\Delta P_{TP}} = (V_{ins} - V_{exp})/(P_{p\ell ins} - P_{p\ell exp}) \qquad (II)$$

To compute resistance, P and $\dot{V}$ are measured during inspiration and during expiration at points of equal lung volume on the assumption that at that time

inspiratory and expiratory compliance are equal. Equation I can then be
solved for total airway resistance (R).

$$P_{ins} = \frac{V_{ins}}{C} + \dot{V}_{ins} R \qquad (III)$$

$$P_{exp} = \frac{V_{exp}}{C} + \dot{V}_{exp} R \qquad (IV)$$

assume $\qquad \frac{V_{ins}}{C} = \frac{V_{exp}}{C}$

then $\qquad R = \frac{\Delta p}{\Delta \dot{V}} = \frac{(P_{ins} - P_{exp})}{(\dot{V}_{ins} - \dot{V}_{exp})} \qquad (V)$

Electrical subtraction is another method for calculating R.[237] Signals
representing P_{TP} and $\dot{V}$ are displayed on the X and Y axis of an oscilloscope
and a signal proportional to the volume change is subtracted from the total
pressure signal. This is equivalent to subtracting the elastic component of
P_{TP} leaving only the resistive component. The electrical subtraction technique
allows separation of inspiratory and expiratory resistance and determination
of resistance at a specific flow rate as well as at any specified lung volume
over a small tidal range. Electrical subtraction has been programmed for
rapid computer analysis of airway resistance and dynamic compliance,[244] greatly
enhancing accurate and uniform data collection.

These basic mechanical lung function tests, if correctly carried out, can
determine whether a response to a pollutant is located in the small airways
and parenchyma or in the central upper airways. However, when both resistance
and compliance change, it is more difficult to define the site of pulmonary
action.[236,237]

Methods used for obtaining intrapleural pressure and tidal volume or flow
from experimental animals are technically difficult and can impose various

artifacts on the final results. Measurement of V_T or $\dot{V}$ requires the use of either a whole body plethysmograph or a pneumotachograph flow meter. Intrapleural pressure is obtained by a fluid-filled catheter placed directly in the intrapleural space or in the lower one-third of the thoracic esophagus. The plethysmograph or pneumotachograph and the catheter are each connected to calibrated pressure transducers that relay the signals to the recording equipment. To ensure accuracy of resistance and compliance measurements, the equipment should be tested over a range of frequencies to confirm compatibility with the animal signals and to rule out phase angle shifts in the signal. For example, if the frequency response of the equipment is inadequate, identical pressure signals would be artificially decreased or increased at various breathing rates. Also, the P_L signal from a small animal breathing rapidly may be impeded as it travels through the long narrow fluid-filled catheter, and the pulse would not match with the signal in the plethysmograph. Thus, calculation of R and C_{dyn} would yield erroneous or misleading results.

7.2. ANIMAL PREPARATION FOR MEASUREMENT OF PULMONARY FUNCTION

7.2.1 Unanesthetized Guinea Pig

The following procedure was used to measure pulmonary function in guinea pigs for all of the studies[93-97,253] cited in Chapter 12. Guinea pigs were lightly anesthetized with ether and a length of 0.03 I.D. polyethylene tubing containing a wire stylet was pushed through the skin on the back into and out of the chest cavity. The stylet was then removed and the catheter was filled with heparinized saline. This intrapleural catheter was positioned so three small holes were located inside the pleural cavity. The catheter was connected to three-way stopcocks and regularly flushed with saline solution. For the measurement of tidal volume, the guinea pig was placed in a body

plethysmograph with an airtight seal at the neck. (This method was originally described by Amdur and Mead.[189]) In this procedure, the following factors may influence the response of the animal to the pollutant and confound the results: strain of guinea pig, age, existing disease, effects of residual ether anaesthesia, extent of surgical trauma (catheter ± tracheostomy), pneumothorax, volume of saline and heparin used to flush the catheter, and irritability of the animal due to pain, confinement, fit of the neck seal or noise in the room. In addition, the uniformity of conditions within the exposure chamber, principally the temperature, humidity, and rate of flow, can contribute to the degree of animal response.

7.2.2 Unanesthetized Monkey

Studies of pulmonary function in the monkey[246] discussed in Chapter 12 were similar to those for guinea pigs. Disease-free animals were acclimated to the procedure. Pulmonary function tests were conducted while the animal was seated in a restraining chair wearing a face mask. A polyethylene intrapleural catheter was inserted into the chest after subcutaneous administration of 1 percent procaine hydrochloride. Transpulmonary pressure was monitored between the intrapleural space and the face mask and airflow was measured with a pneumotachograph in the face mask. All signals from the animal were analyzed by a computer.

7.2.3 Anesthetized Dog and Anesthetized Cat

The dogs[99] were anesthetized with sodium thiopental, and measurements were taken while the animals were lying on their backs in a plethysmograph. Tracheal and intrapleural catheters were inserted on the day of the experiment. The cats[98] were anesthetized with I.P. pentobarbital sodium, given I.V. gallamine triethiodide (a muscle relaxant), and placed on a

respirator. A tracheostomy and the insertion of an intrapleural catheter were done on the day of the experiment.

Because of the extreme deviation from a normal physiological state, these experiments might better be used to shed light on the mechanisms of SO_2 action on the respiratory system rather than to assess the minimal effective concentration.

7.3 GENERAL COMMENTS ON EXPERIMENTAL TECHNIQUES

Bronchoconstriction is dependent upon intact motor parasympathetic pathways in the human,[87,246-248] cat[87,126] and dog.[249] Although bronchoconstriction is under the control of the same neurological pathways in guinea pigs,[239,271] mucous secretory activity is more pronounced in the guinea pig than in the cat[98] and may contribute to the sizeable difference seen in the response to a given level of pollutant. There is wide variability in airway response to SO_2 in the measurement of R and C_{dyn} between different species.[45,98,99,234] Differences have been noted in airway responsiveness in members of the same species[272] tested on different days as well as between individual animals[239] tested on the same day. In order to normalize these differences, it has become the practice to discuss response in terms of percent change from control period values. Adequate numbers of animals in each group and careful statistical analysis are required for understanding the response of "reactors"[93,233] in studies with such a high degree of variability with so many confounding factors.

13. CONTROLLED HUMAN STUDIES

13.1 INTRODUCTION

Precise evaluation of health effects induced by exposure to air pollutants requires that studies be conducted under rigorously controlled conditions. Controlled studies provide a necessary bridge between epidemiology and animal toxicology data. In general, such studies should provide situations which realistically simulate the exposures experienced by man in his normal environment. However, the complexity and variability of the ambient environment is such that most controlled studies initially have been designed to evaluate the effects of exposure to single pollutants, and then later have been extended to the more complex mixtures of pollutants actually present in the environment.

The high cost and minimal number of subjects who can be studied under controlled conditions make it imperative that studies be conducted under stringent conditions in order to generalize to the entire population. Ideally the design of such controlled trials should include normal individuals of both sexes and all age groups, subjects especially sensitive to some particular pollutant, and individuals from populations suspected to be at special risk. Consideration must also be given to the activity levels of the subjects, ambient environmental conditions prevailing prior to the subjects' testing, and exposure variables that realistically simulate ambient conditions, including such factors as temperature, humidity, duration of exposure, and mode of exposure. Controlled studies also require proper experimental design (including purified air conditions) as well as comprehensive statistical treatment of the data obtained. In addition, adequate (even duplicate) pollutant monitoring equipment with documentation

of quality control are needed. Proper attention must also be given to the presence of potentially interfering pollutants inadvertently present or developing under certain conditions. Ideally not only should physiological and biochemical evidence be obtained, but subjective symptoms and/or changes in performance capability should also be assessed. Since the respiratory tract is the initial target of many air pollutants, proper and sensitive respiratory function measurements are a primary requirement. However, various biochemical systems may be secondarily affected if pollutants (or their reaction products or substances absorbed on particulates) pass into the circulatory and other, systems from the cellular level.

The above criteria need to be applied to any evaluation of clinically controlled studies. However, due to particular restraints placed on investigators, no studies meet all of these ideal requirements. Nonetheless, certain basic information may be derived from a number of studies. This chapter provides an overview of controlled air pollutant exposure studies of certain human health effects of sulfur compounds. It should be noted that laboratory studies utilizing man have been limited to the evaluation of acute effects; thus the potential for subsequent health effects cannot be predicted from such exposures.

13.2 SULFUR DIOXIDE

Exposure of man to sulfur dioxide has been shown to induce a number of physiological responses. Alterations in sensory system responses such as irritation of eyes and nose, changes in odor perception, and dark adaptation have been reported. Various changes in the respiratory system have also been reported varying from cough to altered mucociliary clearance. The following sections address these various functional changes in greater detail. (See Chapter 11 for more detailed discussion of SO_2 deposition).

13.2.1 Subjective Reports

The perception of odor and the sensation of irritation in the eyes, nose, throat, or other parts of the body are difficult to measure precisely. Thus subjects may be observed for qualitative changes (coughing, rhinorrhea, lacrimation) or asked to report whether they detect something in the air they are breathing. Several studies have used such subjective reports as an indication of the effects of SO_2 on human subjects.

A number of early investigators exposed themselves to high concentrations of SO_2 (>500 ppm) and experienced coughing, irritation of the eyes and nose, and difficulty in breathing (e.g., Ogata, 1884; Yamada, 1905; Kisskalt, 1904). In the course of investigating the effects of SO_2 on industrial workers, Lehman (1893) and his associates experienced nasal irritation during exposures of 10 to 15 minutes to 6.5 ppm SO_2. Holmes et al. (1915 -- cited by Greenwald, 1954) carried out an extensive study of 60 subjects, 28 of whom were unaccustomed to breathing SO_2, and 32 of whom were familiar with it. All of the subjects already familiar with the gas seemed to detect it (either as SO_2 or as "something foreign") at 3 ppm. But only 10 of 28 unaccustomed subjects detected something in the air at 3 ppm SO_2. Few subjects found momentary whiffs of 5 ppm disagreeable, although "Long-continued breathing of air containing slightly more than 5 parts per million would probably cause discomfort to most people..." (Holmes et al., 1915). Amdur et al. (1953) noted that during exposure to 1 to 2 ppm their subjects could not usually detect the odor of SO_2; even at 5 ppm most subjects could not smell the gas, although they did complain of dryness in the throat. One subject, however, objected so strongly to 5 ppm SO_2 odor that exposure was terminated. Above 5 ppm the odor was definitely detected by all subjects.

A number of more recent studies have asked subjects to report their subjective experiences (e.g., Greenwald, 1954; Tomono, 1961; Frank et al., 1962; Toyama and Nakamura, 1964; Nadel et al., 1965; Speizer and Frank, 1966a,b; Melville, 1970; Weir and Bromberg, 1972, 1973; Lawther et al., 1975; Horvath and Folinsbee, 1977), but the results seem to be quite variable at exposures less than 5 to 10 ppm SO_2. Also, Frank et al. (1962) have shown that subjective reports are in some situations an unreliable indicator of physiological responses, since coughing and a sense of throat irritation tended to subside in their subjects after a few minutes while other changes in respiratory effects were still maximal.

13.2.2 Sensory Effects

Among the physiological functions that may reflect the effects of exposure to SO_2 are certain sensory processes. These studies have investigated not only odor threshold but also sensitivity of the dark-adapted eye to light and interruption of the alpha (α) rhythm in electroencephalograms (see Table 13-1). Most of these investigations have been summarized by Ryazanov (1962).

13.2.2.1 Odor Perception Threshold--In the Russian studies odor threshold is typically determined in a well-ventilated chamber containing 2 orifices from which emerge 2 small streams of gas, one being very pure air and the other other being a stream of the test gas. The subject sits in front of the apparatus, sniffs both orifices, and points out the odorous one. This experiment is repeated with the same concentration of test gas over a period of several days. The experiment is performed with increasingly reduced concentrations until the subject, in the majority of instances, denies the presence of an odor or gives erroneous answers. The threshold concentration for the most sensitive subject in a group of volunteers is defined as the threshold for odor perception.

TABLE 13-1.   SENSORY EFFECTS OF SO_2

Concentration SO_2 (ppm)	Exposure mins.	Effects	Reference
400	120	Dyspnea	Ogata, 1884
6.5	10 - 15	Nasal irritation	Lehman, 1893
140, 210, 240	30	Marked nasal irritation, sneezing	Yamada, 1908
210, 240	30	Eye irritation, lacrimation	Yamada, 1908
1, 2, 5	--	All subjects detect odor above 5 ppm	Amdur et al., 1953
3, 5, plus	--	Discomfort to all subjects exposed to 5 plus. Some noted disagreeable odor at 5 ppm.	Holmes, 1954 *1915 (see Greenwald 1954)*
0.17 - 4.6	--	Average SO_2 odor threshold was 0.8 - 1.0 ppm	Dubrovskaya, 1957
	--	Positive recognition of SO_2 was 0.47 ppm	*Arthur D. Little, Inc* Odor Threshold, 1968
0.34 - 6.9	15	Light sensitivity increased at 0.34 - 0.63 ppm and above.	Dubrovskaya, 1957
0.23	--	Ocular sensitivity to light increased at SO_2 levels of 0.23 ppm and above	Shalamberidze, 1967
0.2 - 1.7	0.33	Attenuation of α-waves at levels above 0.2 ppm	Bushtueva et al., 1960 *1962*
1 - 10	--	Organoleptic effects at levels 2 ppm and above	Greenwald, 1954

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Using the 2-orifice apparatus described above, Dubrovskaya (1957) conducted sulfur dioxide odor perception threshold tests on 12 subjects. Sulfur dioxide concentrations of 0.5 mg/m^3 to 13 mg/m^3 (0.17 ppm to 4.6 ppm) were used in 530 threshold determinations. Six test subjects sensed the odor of sulfur dioxide in the range 2.6 mg/m^3 to 3.0 mg/m^3; four subjects sensed the odor in the range 1.6 mg/m^3 to 2.0 mg/m^3; one sensed the odor in the range 2.1 mg/m^3 to 2.5 mg/m^3; and one sensed the odor in the range 3.1 mg/m^3 to 3.6 mg/m^3. Thus, the average sulfur dioxide odor threshold concentration was 0.8 ppm to 1 ppm (~2.3 mg/m^3 to ~2.9 mg/m^3), and for the more sensitive of these persons it was 0.5 ppm to 0.7 ppm (~1.5 mg/m^3 to ~2.0 mg/m^3). It should be noted, however, that most of the subjects were of an age at which odor perception was presumed to be most sensitive.

Determination of sulfur dioxide odor thresholds (1968) conducted for the Manufacturing Chemists' Association in the United States gave somewhat lower values than those cited above (Arthur D. Little, Inc., 1968). The concentrations at which first one-half and then all of the panel members could positively recognize the odor were reported to both be 0.47 ppm (1.3 mg/m^3). The details of the test procedure are thoroughly discussed in the report, but one important aspect is reiterated as a reminder that odor thresholds usually represent values derived under ideally suited conditions and with trained individuals. The investigators, who were highly qualified to judge on the basis of substantial experience with consumer evaluation of known flavor and odor situations, derived threshold values under ideal conditions lower than those which would be recognized by the majority of a population under ordinary atmospheric conditions. This does not mean that normal individuals exposed to sulfur dioxide under ideal test conditions could not perceive the 0.47 ppm

level indicated. However, because of background odor and lack of awareness or concern with ambient odor conditions, such individuals in an everyday situation would probably be less responsive to this low concentration.

13.2.2.2 Sensitivity of the Dark-Adapted Eye--The sensitivity of the eye to light while a subject is in darkness increases with time. Several investigations have been made of the effects of inhalation of sulfur oxides on this sensitivity. Typically, measurements of a subject's normal sensitivity are taken in a dark, well-ventilated chamber in complete silence (sudden stimuli, including noise, may affect the subject's response). Each subject is tested once daily following preliminary stimulation at a high light level. Light sensitivity is measured at 5-minute or 10-minute intervals, and a curve of increasing sensitivity to light is established from measurements taken over a period of 7 to 10 days.

Dubrovskaya (1957) studied the effect of inhaling sulfur dioxide in concentrations from 0.96 mg/m^3 to 19.2 mg/m^3 for 15 minutes before measuring light sensitivity during dark adaptation. She reported that light sensitivity was increased by sulfur dioxide concentrations of 0.96 mg/m^3 to 1.8 mg/m^3 (0.34 ppm to 0.63 ppm), that the increase in sensitivity reached a maximum at concentrations of 3.6 mg/m^3 to 4.8 mg/m^3 (1.3 ppm to 1.7 ppm), and that further increases in the sulfur dioxide concentration resulted in progressive lowering of eye sensitivity to light until at 19.2 mg/m^3 the sensitivity was identical with that of the unexposed subject.

In exposures during light adaptation, sulfur dioxide concentrations of 0.6 mg/m^3 to 7.2 mg/m^3 (0.21 ppm to 2.5 ppm) caused slight increases in eye sensitivity. Maximum sensitivity was attained at 1.5 mg/m^3 (0.52 ppm); at higher concentrations the increased sensitivity began to abate. Two human subjects were used in these experiments. The odor threshold was between

2.5 mg/m^3 and 3.0 mg/m^3 for one subject and between 3.0 mg/m^3 and 3.6 mg/m^3 for the other, so that changes in sensitivity to light during dark adaptations were caused by sulfur dioxide concentrations below the odor threshold.

Shalamberidze (1967) investigated the effects of SO_2 and NO_2, singly and in combination, on visual light sensitivity as determined by measures of dark adaptation. According to this report, SO_2 concentrations of 0.6 mg/m^3 (0.23 ppm) and higher caused "a considerable increase in the ocular sensitivity to light" (Shalamberidze, 1967, p. 11). So few details on methods or results were presented, however, that this report cannot be accepted without reservations.

13.2.2.3 <u>Interruption of Alpha Rhythm</u>--The electroencephalogram is a composite record of the electrical activity of the brain recorded as the difference in electrical potential between two points on the head. In the adult, the electro-encephalogram characteristically shows a fairly uniform frequency from 8 cycles to 12 cycles per second in the posterior head regions (alpha). Variations occur with age, the state of wakefulness and attentiveness, or as a result of incoming sensory stimuli from exteroceptive or interoceptive receptors. The dominant frequency (α) is inhibited or attenuated by eye opening and by mental activity.

Subjects with well defined α-rhythms studied in a silent and electrically shielded chamber show a temporary attenuation of the α-rhythm each time they are given a light signal. When the light is excluded, the α-rhythm returns to normal. A concentration of test gas is determined which is so low that by itself it does not cause attenuation of the α-rhythm. A subject breathes the gas at this concentration, and then he receives the light signal. After exposure to this sequence (gas then light) several times (5 to 30 times in

1 day), a subject will show attenuation before he receives the light signal; that is, he responds to the unperceived odor. The unperceived odor thus becomes the conditioning stimulus and brings about the so-called conditioned electrocortical reflex.

Bushtueva et al. (1962) reported that 20-second exposures of six human subjects to sulfur dioxide concentrations from 0.9 mg/m^3 to 3 mg/m^3 (~0.3 ppm to ~1.0 ppm) produced attenuation of the α-wave lasting 2 to 6 seconds; at concentrations of 3.0 mg/m^3 to 5.0 mg/m^3 (~1.0 ppm to 1.7 ppm) attenuation lasted throughout the 20-second exposure. Exposures to 0.6 mg/m^3 (~0.2 ppm) did not cause attenuation of the α-wave. The threshold for attenuation of the α-wave was the same as the odor theshold or the threshold of irritation of the respiratory tract. In other experiments, Bushtueva demonstrated that electro-cortical conditioned reflexes could be developed with sulfur dioxide at 0.6 mg/m^3 (~0.2 ppm) but not with lesser concentrations of the mixture.

13.2.3 Respiratory and Related Effects

A number of studies have documented the various respiratory and cardio-vascular effects deriving from exposure to SO_2 (see Table 13-2). (See Chapters 11 and 12 for further discussion of respiratory effects of SO_2.) One of the first clinical studies of the effects of inhaling SO_2 was reported by Amdur et al. (1953). They had 14 resting subjects breathing SO_2 for 10 minutes through a face mask in concentrations ranging from 1 to 8 ppm. Pulse rate and respiration rate increased and tidal volume decreased during exposure to as little as 1 ppm SO_2. Several investigators attempted to replicate Amdur et al.'s (1953) findings, including McIlroy et al. (1954), Lawther (1955), and Frank et al. (1962). None was able to find consistent respiratory or cardiovascular effects of SO_2 below 5 ppm. Nevertheless, these and other studies have documented a variety of subjective and physiological effects under various conditions of

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Concentration SO_2 (ppm)	Duration of exposure (mins)	Number of subjects	Oral or nasal exposure	Rest (R) or exercise (E)[a]	Effects	Reference
1.0 3.0 5.0	3 3 3	8 - 10 8 - 9 10	0 0 0	R + E R + E R	Light exercise potentiates effect of SO_2 $MEF_{40\%}$ decreased	Kreisman et al. 1976
9 - 60	5	25	N - 0	R	Airway resistance increased	Nakamura, 1964
1 - 8	10	14	Face mask	R	Pulse rate, respiratory increased; tidal volume decreased	Amdur et al., rate 1953
--	10	--	N	R	Could not duplicate Amdur's results	McIlroy et al., 1954
5, 10 20	10 10	18 6	0 - N 0	R R	No changes in pulse rate, respiratory rate or tidal volume (5, 10 ppm) 2 subjects had bronchospasm	Lawther, 1955
1, 5, 13	10	12	0	R	No changes in pulse rate, respiratory rate. Pulmonary flow resistance increased at 5 and 13 ppm	Frank et al., 1962
1.3 - 80	10	8 - 12	Face Mask	R	Bronchoconstriction	Sim and Pattle, 1957
1 - 45	10	46	Face Mask	R	Decreased peak flow, decreased expiratory capacity above 1.6 ppm	Tomono, 1961
2.5, 5.0, 10.0	10	15	0, N	R	SG_{aw} decreased less with nasal breathing	Melville, 1970
4 - 6	10	1	0	R	Airway conductance decreased reflex effect	Nadel, 1965

[a]Intermittent Exercise

Concentration SO$_2$ (ppm)	Duration of exposure (mins)	Number of subjects	Oral or nasal exposure	Rest (R) or exercise (E)	Effects	Reference
15, 28	10	8	O N	R	Pulmonary flow resistance increased less with nasal breathing	Speizer and Frank, 1966[a]
5	10	5	O M	R	MEF$_{50\%}$ decreased less with nasal inhalation	Snell and Luchsinger, 1969
2.5 - 50	10	5	O	R	Increased respiratory and inspiratory resistance	Abe, 1967
6.6 - 7.3	10	variable	ON	R	No changes in airway resistance	Reichel, 1972
1.3 - 80	10	8 - 12	Face mask	R	Bronchoconstriction	Sim and Pattle, 1957
0.5, 1.0, 5.0	15	9		R	MEF$_{50\%}$ decreased at 1 and 5 ppm	Snell and Luchsinger, 1969
1, 5, 13	10 - 30	11	O N	R	Pulmonary flow resistance increased at 5 and 13 ppm but less during nasal breathing; *at 1 ppm, one subject experienced 9% increase in flow resistance, another a 23% decrease*	Frank et al., 1962
16.1	25	7	Face mask O - N	R	SO$_2$ almost completely removal by nasal breathing	Speizer and Frank, 1966b
1, 5, 15	30	12	O	R	Increased in RI at SO$_2$ levels above 5 ppm	Frank et al., 1964
1.1 - 3.6	30	10	O	R	Deep breathing produced no effects	Burton et al., 1969
5	30	10	O	E	MMIR decreased	Newhouse et al., 1978
1 - 23	60	8 - 12	Mask, chamber N	R	Bronchoconstriction	Sim and Pattle, 1969
1	60	-	N	R	No effects observed	McJilton, 1976

Concentration SO_2 (ppm)	Duration of exposure (mins)	Number of subjects	Oral or nasal exposure	Rest (R) or exercise (E)	Effects	Reference
5	60	9	0	R	No effect or <u>mucus transport</u>	Wolff et al., 1975a
5 - 30 1 3	10 50 -	10 13 17	Co$_2$ stimulus Chamber (N) 0	(0) R R R	Deep breathing significantly increased S_{Raw}	Lawther, 1975
10, 15, 25, 50	60 *Intermittent Exercise				At higher conc. of SO_2 mucociliary activity decreased	Cralley, 1942
0.37	120	8	Chamber	E	No pulmonary effects	Bates and Hazucha, 1973; ~~Hazucha and Bates, 1975~~
0.37	120	4 - 12	Chamber	E	No pulmonary effects	Bell et al., 1977
0.40	120	9	Chamber	E	No pulmonary effects	Horvath and Folinsbee, 1977; Bedi et al., 1979
0.75	120	4 - 8	Chamber	E	Significant decrease in $MEFR$; ~~FVC, FEV$_{1.0}$, MMFR, MEFR~~ $FVC, FEV_{1.0}, MMFR$ also decreased	Bates and Hazucha, 1973; Hazucha and Bates, 1975
1.0, 5.0	120	15	N	R	Increase in nasal air flow resistance; decrease in nasal mucus flow	Andersen et al., 1974
5.0	120	11	Chamber	E	Insignificant changes in R_e and P_{aO_2}	von Neiding et al., 1979
5.0	120	10	Chamber (oral)	E	MMFR decreased 8.5% increased tracheobronchial clearance	Newhouse et al., 1978
25.0	120	15	N	R	Increased nasal airfow resistance; decreased nasal mucus flow	Andersen et al., 1974

Concentration SO$_2$ (ppm)	Duration of exposure (mins)	Number of subjects	Oral or nasal exposure	Rest (R) or exercise (E)	Effects	Reference
0.50	180	40 (asthmatics)	Oral	R	MMFR decreased 2.7% recovery within 30 minutes; *3 subjects incurred delayed effects and required medication*	Jaeger et al., 1979
5	180+	10	0	E	Increased tracheobronchial clearance	Wolff et al., ~~1975~~[b] *1977*
0.3, 1.0 and 3.0	96 – 120 Hours	12 (normal) 7 (COPD)	Chamber	R	No difference in response between groups. Slight decrease in pulmonary compliance but of questionable significance	Weir and Bromberg, 1972
1, .0, 5.0 and 25.0	Up to 6 hrs/day	15	Chamber (N)	R	Significant decreases in expiratory flow and FEV$_{1.0}$ decreased mucus flow	Andersen et al., 1974
5	4.5 hours	32 (16 exposed)	Chamber	R	Number of colds similar in both groups but severity less in SO$_2$ exposed subjects	Andersen et al., 1977

exposure to SO_2. Sim and Pattle (1957) performed extensive clinical studies over a 10-month period on an unspecified number of (8 to 12) "healthy males aged 18 to 45." SO_2 was administered either by face mask at concentrations ranging from 1.34 to 80 ppm for 10 minutes or in an inhalation chamber at concentrations of 1.0 to 23.1 ppm for 60 minutes. Regardless of exposure route, the only notable effects of SO_2 were said to be bronchoconstriction (increased resistance to air flow) and high-pitched chest rales at 49 ppm and greater concentrations. They also reported that when ammonia (no value given) was also present in the chamber (9.9 ppm SO_2) the subjective impressions of bronchoconstriction disappeared.

Frank et al. (1962) examined the effects of acute (10 to 30 minute) exposures to SO_2 via mouth in 11 subjects. Each subject received approximately 1, 5, and 13 ppm of the gas in separate exposures at least 1 month apart. The only significant effects were a 39 percent increase (p <0.01) in pulmonary flow resistance at 5 ppm and a 72 percent increase (p <0.001) at 13 ppm. The recovery of some subjects was complete within a few minutes. As in Sim and Pattle's study (1957), other cardiovascular or pulmonary measures did not show any significant effects.

Tomono (1961) tested 46 men for the effects of SO_2 on their pulmonary physiology. The subjects inhaled 1 to 45 ppm SO_2 through a face mask for 10 minutes. Decreases in expiratory capacity and peak flow rate were proportional to the concentration of SO_2. Such effects were detected at a concentration as low as 1.6 ppm. Slight increases in pulse and respiration rates were observed in about 10 percent of the subjects but were not proportional to SO_2 exposures. Nakamura (1964) exposed 10 subjects each to a different concentration of SO_2 (9 to 60 ppm) for 5 minutes. Airway resistance increased an average of 27 percent. Since each subject was exposed to only one concentration of SO_2 and

there was considerable variability in response to the different concentrations, the significance of those isolated findings may be questioned. No significant correlation between dosage and response was discovered. For example, a subject had a 17 percent increase after exposure to 9 ppm, another 9 percent after exposure to 16 ppm, another 75 percent after exposure to 4 ppm and another 22 percent after exposure to 57 ppm.

Snell and Luchsinger (1969) also found significant decreases in pulmonary function consequent to SO_2 exposure. Nine subjects inhaled through a mouth piece SO_2 at concentrations of 0.5, 1.0, and 5 ppm for 15 minutes each, with 15-minute control periods interspersed. Maximum expiratory flow ($MEF_{50\% VC}$) was significantly lower after exposure to 1 ppm SO_2 (p <0.02) as well as 5 ppm (p <0.01). Reichell (1972) found no significant changes in airway resistance in normal subjects and patients with obstructive lung diseases exposed to 6.6 to 7.3 ppm SO_2. Jaeger et al. (1979) exposed 40 normal non-smokers and 40 asthmatics (mild to moderate but with no recent exacerbations) subjects to 3 hours to 0.5 ppm SO_2. Oral inhalation was forced by having the subjects wear a nose clip. These resting subjects were also studied during exposure to ambient air having an average SO_2 content of 0.005 ppm. Three pulmonary function tests (VC, FEV_1 and MMFR) were performed at intervals during the exposure and a more intensive series of tests were made prior to and after the exposure. The only significant (p <0.04) effect observed was a 2.7 percent decrease in MMFR in the asthmatic subjects. This minimal change had little physiological importance. One normal and two asthmatic subjects exhibited adverse reactions--the asthmatics requiring standard asthma medication. No changes in pulmonary functions were observed during 60 minutes of exposure to 1 ppm SO_2 (McJilton et al., 1976).

Nadel et al. (1965) have helped elucidate the mechanism of bronchoconstriction resulting from SO_2 exposure. They exposed seven subjects to 4 to 6 ppm

SO_2 for 10 minutes via mouth in a closed plethysmograph. The mean decrease in specific airway conductance was 39 percent ($p < 0.001$). Injecting the subjects with 1.2 to 1.8 mg atropine sulfate 20 minutes before SO_2 inhalation resulted in only a 3 percent ($p > 0.20$) decrement in specific airway conductance/thoracic gas volume. However, atropine did not affect the coughing or sensation of irritation in the pharynx or substernal area. From this and other evidence, Nadel et al. concluded that the bronchoconstriction induced by SO_2 depends on changes in smooth muscle tone mediated by parasympathetic motor pathways. Thus, when sensory receptors in the tracheobronchial region are irritated by a substance such as SO_2, a reflexive bronchospasm may be triggered.

Apart from fairly consistent bronchoconstriction effects, a common element in these and other reports of the effects of SO_2 has been the notable variability among subjects in their responses to such exposures. In Frank et al.'s study (1962), for example, 9 of 11 subjects showed no effects at 1 ppm, but 1 subject showed a significant ($p < 0.01$) decrease in pulmonary flow resistance, whereas the remaining subject showed a significant ($p < 0.01$) increase. Sim and Pattle (1957) reported that they themselves appeared to be exceptionally sensitive to SO_2 encountered in the course of their research. They experienced persistent and uncomfortable spells of coughing and wheezing upon contact with the gas. Other investigators (e.g., Burton et al., 1969; Frank, 1964; Nadel et al, 1965; Lawther ~~and Bond~~, 1955; Lawther et al., 1975; Jaeger et al., 1979) have reported "hyper-reactors" among their subjects. Indeed, some investigators have suggested that about 10 percent of the total population is made up of especially sensitive persons (Amdur, 1973, 1974; Horvath and Folinsbee, 1977). However, in at least one instance (Andersen et al., 1974), a subject's response was exaggerated even under control conditions, which

raises the possibility of psychological factors contributing to this observed sensitivity.

13.2.3.1 Water Solubility--One of the first points to note is that because of its high solubility in water, SO_2 is readily absorbed when it comes in contact with the moist surfaces of the nose and upper respiratory passages (Frank et al., 1973). This has a number of important implications for the analysis of the effects of SO_2 on respiratory functions. These considerations will be illustrated in the following sections (see Chapter 11).

13.2.3.2 Nasal Versus Oral Exposure--A number of studies have demonstrated significant response differences between the nose and mouth as routes of exposure to SO_2. Speizer and Frank (1966a), for example, compared the effects of SO_2 (10-minute exposures at 15 and 28 ppm) in eight subjects breathing the gas either by nose or by mouth. The subjects coughed less and reported less irritation of the throat and chest when breathing through their noses. Also, pulmonary flow resistance increased less during nasal exposure than during oral exposure.

A second study by the same investigators (Speizer and Frank, 1966b) refined their analysis of these effects, using seven subjects and a specially designed face mask. Air was sampled at various points, including: (1) within the face mask before being inspired, (2) within the subject's nose, and (3) within the subject's oropharynx. Exposures lasted 25 to 30 minutes. The average concentration of SO_2 within the mask was 16.1 ppm; within the oropharynx the concentration was too low for the investigators' equipment to measure. Thus, essentially all of the SO_2 (90 to 99 percent) in the inspired air was removed by the nose. Similar results were obtained by Andersen et al. (1974) in a study that will be described in detail below.

Melville (1970) also compared oral and nasal routes of administration. He used 15 subjects and exposed them (for 10 minutes) sequentially to 2.5, 5, and 10 ppm SO_2. More SO_2 was cleared per minute with nose breathing than with mouth breathing. There was a clear dose-dependent response reflected in measures of the subjects' specific airway conductance (SG_{aw}): as the SO_2 concentration increased, SG_{aw} decreased ($p < 0.05$). This was true regardless of administration route (for 2.5 ppm SO_2), but the average decrease under oral administration was greater (in 80 percent of subjects), than the decrease under nasal administration ($p < 0.05$). During exposure to 5 ppm SO_2 no significant difference was observed in SG_{aw} regardless of whether the 49 subjects breathed through mouth or nose.

Snell and Luchsinger (1969) also examined the differences between nasal and oral exposure using SO_2 at 5 ppm. Five subjects' average maximum expiratory flow ($MEF_{50\% \ VC}$) was 10 percent lower following oral exposure than following nasal exposure. This difference, however, was not statistically significant. See Chapter 11 for further discussion of SO_2 deposition.

13.2.3.3 <u>Subject Activity Level</u>--One of the practical implications of the above findings is that vigorous activity, such as heavy exercise or work, may significantly affect the actual dose received by a person during exposure to SO_2. At some level of ventilation, inhalation of air shifts from nasal to mouth breathing. Studies under way (Horvath, personal communication) suggest that subjects who are nasal breathers at rest move to mouth breathers when ventilatory exchange is approximately 30 L/min. However, it should be remembered that many individuals are always mouth breathers. Kreisman et al. (1976), for example, reported that exercise may potentiate the effect of SO_2 on respiratory function. In their study, subjects inhaled a mixture of SO_2 in air for 3 minutes while exercising on a bicycle ergometer at a pace sufficient

to double their resting minute ventilation rate. Eight subjects recieved 1 ppm SO_2 and nine subjects received 3 ppm. Those receiving 3 ppm showed a significant (p <0.05) decrease in maximal expiratory flow ($MEF_{40\%}$ (P)) compared to a control (untreated air) exposure. However, it is not clear that this change differed significantly from the change in $MEF_{40\%}$ (P) occurring in resting subjects. Bates and Hazucha (1973) and Hazucha and Bates (1975) reported significant decreases in FVC (10 percent), $FEV_{1.0}$ (10%), MMFR (10%), and MEFR (23%) in 4 subjects (who exercised intermittently during the exposure) exposed in a chamber containing 0.75 ppm SO_2. At 0.37 ppm SO_2, Hazucha and Bates (1975) observed no pulmonary function changes. Horvath and Folinsbee (1977) and Bedi et al. (1979) exposed nine intermittently exercised subjects in a chamber to 0.4 ppm SO_2 and found no pulmonary function changes.

Lawther et al. (1975) have demonstrated that simply instructing 12 subjects to take 25 deep breaths by mouth resulted in a significant (p <0.001) increase in specific airway resistance (SR_{aw}) during exposure to SO_2 at 1 ppm. While sitting quietly in an inhalation chamber, the same subjects had previously shown no such increase after breathing concentrations of 1 to 3 ppm SO_2 for an hour. As part of a series of experiments in this study, 17 subjects also received 3 ppm SO_2 by a mouthpiece and were instructed to take 2, 4, 8, 16, and 32 deep breaths at 5-minute intervals. Increases in SR_{aw} due to SO_2 were significantly greater after 16 (p <0.01) or 32 (p <0.001) deep breaths.

Burton et al. (1969), however, found no consistent effects in 10 subjects exposed to SO_2 at 1.1 to 3.6 ppm for 30 minutes, regardless of whether the subjects breathed normally or at a forced hyperventilation rate of up to 2.5 L/sec. One (other) difference between these two studies was the duration of exposure. Burton et al. (1969) exposed their subjects for 30 minutes, whereas, Lawther et al. (1975) maintained exposures for an hour. This raises another

important consideration in reviewing the effects of SO_2 on human subjects, namely, temporal parameters.

13.2.3.4 Temporal Parameters--Early studies (e.g., Lehman, 1893) suggested that workers chronically exposed to relatively high concentrations of SO_2 were less conscious of its presence in the atmosphere than persons not as familiar with the gas. However, Holmes et al.'s data (1915) indicated that subjects already accustomed to SO_2 could detect its odor at lower concentrations than could persons unaccustomed to it. Nevertheless, it would seem plausible that "self-selection" would tend to reduce the number of relatively sensitive persons among the population of workers chronically in contact with supra-threshold levels of SO_2.

As previously noted, a study by Frank et al. (1962) has indicated that subjective reports are not a reliable indicator of physiological responses in any event. After 5 to 10 minutes of exposure to either 5 or 13 ppm SO_2 their subjects' pulmonary resistance measures were just reaching their peaks, while subjective reports of an odor of SO_2 had already subsided.

In a later study by Frank et al. (1964) the increase in pulmonary resistance induced by SO_2 peaked at about 10 minutes and then gradually decreased over the next 15 minutes. This finding corresponds closely to Sim and Pattle's (1957) report that, if lung resistance increased at all in individual subjects, the increase occurred within the first 10 minutes.

Similar short-term responses (within 5 to 10 minutes after the start of exposure) have been recorded by other investigators. Melville (1970) found that percentage increases in specific airway conductance (SG_{aw}) were greatest during the first 5 minutes of up to 60 minutes of exposure to SO_2 by mouth/nasal breathing. At 5 ppm, for example, he noted that SG_{aw} decreased

significantly ($p < 0.05$) within 5 minutes of exposure and stabilized slightly above the values recorded under control conditions of no SO_2.

Similar results were obtained by Lawther et al. (1975), who noted that SR_{aw} increased most during the first 5 minutes of exposure. Recovery to baseline levels generally required about 5 minutes, although 3 "SO_2 sensitive" subjects out of a total of 14 took 10 to 65 minutes to recover from higher exposure levels (up to 30 ppm SO_2). In this last regard, similar findings were reported by Gökenmeijer et al. (1973) for bronchitic patients exposed to 10 ppm SO_2. Respiratory effects were maximal at the end of a 3-minute inhalation period, and recovery required 45 to 60 minutes.

Abe (1967) compared the temporal course of SO_2 exposures. His five mouth-breathing subjects were given 2.5 or 5.0 ppm SO_2. He reported immediate significant ($p < 0.05$) increases in expiratory resistance (42 percent) and inspiratory resistance (25 percent). Effects of repeated exposures are noted by Frank et al. (1964) and Tomono (1961).

Longer term effects (over a period of hours) have been reported by Andersen et al. (1974), who investigated nasal mucus flow rates as well as airway resistance and subjective responses. Nasal mucociliary flow was measured by placing a radioactivity labeled resin particle on the superior surface of the inferior turbinate and tracking its position with a slit-collimator detector. A total of 15 subjects were exposed via an inhalation chamber to increasing concentrations (1, 5, and 25 ppm) of SO_2 for approximately 6 hours per day over 3 consecutive days. Baseline measurements were made under conditions of filtered air on a day prior to experimental exposures. This study found a number of effects reaching their maximum after 1 to 6 hours of exposure. Nasal cross-sectional airway area generally decreased throughout the 6-hour

daily trials, but the decreases were only significant (p <0.05) at 1 ppm and 5 ppm, since there was an overall drop in this measure (approaching a "floor level") by the time 25 ppm was administered on the third day of the study. Significant (p <0.05 or less) decreases in forced expiratory flow ($FEF_{25-75\%}$) and forced expiratory volume ($FEV_{1.0}$) also occurred both within daily exposures and across days (i.e., increasing concentrations), although the within-day decrease in $FEV_{1.0}$ was only significant on day 3 (at 25 ppm) (see Andersen et al., 1974, Figure 7).

13.2.3.5 <u>Mucociliary Transport</u>--Cralley (1942) investigated mucociliary clearance when sophisticated radioactive measurement techniques were not available. A drop of red dye was placed in the active ciliary region of the inferior meatus of a volunteer subject. The rate of mucus clearance was reflected in the time between the dye's introduction and its appearance in the expelled mucus. Exposure to SO_2 at 10 to 15 ppm for 60 minutes produced only a small decrease in the rate of mucus removal. A 30- to 60-minute exposure to 25 ppm SO_2 resulted in a 50 percent reduction in mucociliary transport and a 65 to 70 percent reduction at 50 to 55 ppm. Mucostatis in the anterior region of the nose was observed in 14 of 15 subjects after 4 to 5 hours of exposure to 25 ppm SO_2 (Andersen et al., 1974). In addition, the mucus flow rate in the anterior nose was reduced by 50 percent after 1 to 3 hours exposure to as little as 1 ppm SO_2. At this concentration some subjects also had sporadic mucostasis, although there were pronounced individual differences in these measures even at baseline.

Wolff and his co-workers (Wolff et al., 1975a, 1975b [1977]; Newhouse et al., 1978) have also measured the rate of mucociliary transport. In Wolff et al.'s (1975a) first study, nine subjects were exposed to 5 ppm SO_2 for 1 hour while sitting quietly in an inhalation chamber and breathing through their

mouths. Mucociliary clearance was assessed by having the subjects first inhale a radioactively tagged aerosol and then monitoring its subsequent tracheobronchial deposition and retention during SO_2 exposure. No significant effects were found in mucociliary clearance, except for a small transient change (p <0.05) after 1 hour of exposure.

In their second study, Wolff et al. (~~1975b~~) *1977* used similar methods to compare subjects while resting or exercising. Exercise was performed on a bicycle ergometer for 0.5 hour at a pace to yield heart rates 70 to 75 percent of estimated maximum values. Exposure in this study lasted for 2.5 to 3 hours. The combination of exercise and exposure (via mouth) to 5 ppm SO_2 resulted in a significantly (p <0.05) greater rate of tracheobronchial muco-ciliary clearance. This result contrasts with Andersen et al.'s findings (1974) that nasal clearance rates were reduced by exposure to 5 ppm SO_2. Of course, the two studies focused on different regions of the respiratory tract (tracheobronchial versus nasal), but this in itself provides no cogent account for these contrasting effects. Both of these investigators replicated their findings in later studies [Andersen et al., (1977) and Newhouse et al., (1978)]. Extension of these studies was made by Newhouse et al. (1978) whose 10 subjects breathed either SO_2 (5 ppm) or H_2SO_4 mist (1 mg/m^3) delivered as an aerosol of 0.58 μm MMAD. An aerosol containing a 0.025 percent solution of ^{99m}Tc-albumen was inhaled prior to pollutant exposure. The bolus technique (exposure to short-term peak concentrations) employed achieved deposition of the aerosol, primarily in the large airways. One-half hour later the subjects were exposed to the pollutants. They immediately exercised for the next 0.5 hour. A total of 20 minutes of exercise at approximately 70 to 75 percent of predicted maximum heart rate was performed, followed by an additional 1.5 hours of rest exposure. The

subjects breathed through the mouth to eliminate nasal ventilation and absorption of pollutants. Pulmonary function tests conducted at the end of 2 hours' exposure to SO_2 indicated no changes in FVC or $FEV_{1.0}$ but maximum mid-expiratory flow rate (MMFR) decreased 8.5 percent, possibly due to a reflex bronchoconstriction. No pulmonary changes were found consequent to the H_2SO_4 mist exposures. Tracheobronchial clearance increased in both SO_2 (6 of 10 subjects) and H_2SO_4 (5 of 10 subjects) exposures. The investigators did not present their data in a manner which would provide information as to the relationship between clearance rates and MMFR. It should be noted that even replicated data are in contrast to the replicated observations by Andersen et al. (1977), who showed a slowing of nasal clearance on exposure to 5 ppm SO_2.

Mucociliary transport is a significant aspect of the respiratory system's defense against airborne agents. A disturbance in this function might have important implications for a number of health effects, such as susceptibility to cold-virus infections. Andersen et al. (1974), for example, noticed that 4 of 17 subjects caught colds within a week of their participation in a study where mucostasis generally occurred during SO_2 exposure. Andersen et al. (1977) followed up this observation by inoculating volunteers with a strain of rhinovirus (RV3). The basic design of the study and reactions of the subjects are shown in a table (Andersen et al., 1977, p. 121). Although there was no difference in the number of colds that developed in the two groups of subjects (all nose breathers), cold symptoms were judged (under a double-blind procedure) to be less severe (p <0.05) in the group exposed to SO_2. It was unknown, however, whether this result reflected a direct effect of SO_2 on the host, the rhinovirus, or both. In addition, the average incubation period was somewhat shorter for the group exposed to SO_2 (p <0.06).

Virus shedding (a measure of infection determined from nasal washings) also seemed to be somewhat decreased in the SO_2 exposed group, but not significantly.

13.2.3.6 Health Status--Some studies have considered the preexisting health status of subjects as a variable in assessing the physiological effects of SO_2. Weir and Bromberg, for example, conducted separate studies on 12 healthy subjects (Weir and Bromberg, 1972) and on 7 smokers who showed early signs of chronic obstructive pulmonary disease (Weir and Bromberg, 1973). The subjects were exposed to 0, 0.3, 1, and 3 ppm SO_2 in an inhalation chamber for 96 or 120 hours (smokers or nonsmokers, respectively), with several days separating each trial. The individual variablity among the smokers in their daily lung functions was so great that no effects could be attributed to SO_2 exposure. Also, subjective complaints also appeared to be randomly distributed throughout the course of the study and could not be related to SO_2 exposure levels.

Gunnison and Palmes (1974) compared heavy smokers (7) and non-smokers (13) with respect to blood plasma levels of S-sulfonate after exposure to 0.3, 1.0, 3.0, 4.2, and 6.0 ppm SO_2. Both groups showed highly significant correlations ($p < 0.001$) between SO_2 concentrations and S-sulfonate levels. But there was no significant differentiation between the two groups of subjects in this regard.

Several other studies of SO_2 (e.g., Snell and Luchsinger, 1969; Andersen et al., 1974; Gokenmeijer et al., 1973; Burton et al., 1968, 1969) have included asthmatic patients or smokers, but have not provided even qualitative ratings of their health status. This alone would make it difficult to compare the results of different studies using "healthy" or "impaired" subjects. Morever, the great individual variability among both normal and impaired persons in these studies makes it difficult to reach any conclusions about

the relative importance of an individual's health status in determining his physiological response to SO_2.

13.3. PARTICULATE MATTER

One of the most significant factors influencing physiological responses to SO_2 is the presence of particulate matter in the atmosphere (Amdur, 1969) (see Table 13-3). Particulate matter interacts with SO_2 in at least two distinct ways: as a carrier of SO_2 and as a factor in chemical reactions resulting in the conversion of SO_2 to other forms. In their carrier role, particles may adsorb SO_2 and, depending on their size, solubility, and other characteristics, transport it deep into the respiratory system (see Chapter 11, Section 11.2 for more detailed discussion of deposition.)

This point is illustrated by the results of studies by Nakamura (1964) and Toyama (1962), who reported that sodium chloride (NaCl) aerosol potentiated the response of human subjects to SO_2. In Nakamura's (1964) study, 10 subjects were first exposed to NaCl aerosol (CMD = 0.95 μm; *EPA* estimate of MMAD = 5.6 μm) alone for 5 minutes, allowed to recover for 10 to 15 minutes, exposed to SO_2 alone at 9 to 60 ppm for 5 minutes, allowed 20 to 30 minutes to recover, and then exposed to SO_2 and the NaCl aerosol together for 5 minutes. Airway resistance was greater after the combination exposure than after exposure to SO_2 alone (see Table 1 and Figure 4a, Nakamura, 1964). As noted, the combination condition always followed exposure to SO_2 alone, thus raising the possibility that the effects of the latter exposure were confounded. However, on average, the subjects' airway resistance measures returned to only 4 percent above their pre-exposure control levels, thus making it more likely that the reported effects were independent of preceding conditions.

Toyama (1962) also reported that SO_2 in combination with submicronic (0.22 μm MMD; *EPA* estimate of MMAD = 0.36 μm) particles of NaCl aerosol produced synergistic

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Concentration	Duration of exposure (mins)	Number of subjects	Source	Effects	Reference
SO_2 (1.6 - 5 ppm) NaCl 0.22 μm MMD	5	13	Mask	Synergistic increases in airway resistance with aerosol	Toyama, 1962
SO_2 (9-60 ppm) NaCl (CMD = 0.95 μm)	5	10	Mask	Airway resistance greater after exposure to aerosol than to exposure to SO_2 alone	Nakamura, 1964
SO_2 (0.5, 1.0 and 5.0 ppm) Saline particles 7.0 μm	15	9	Oral	$MEF_{50\%}$ significantly greater decreases in aerosol (NaCl) condition	Snell and Luchsinger, 1969
Ibid	30	9 (asthmatics)	(Mask (Exercise for 10 minutes)	$\dot{V}_{max\,50\%}$, $\dot{V}_{max\,75\%}$, $FEV_{1.0}$ and R_T decrease significantly in aerosol condition	Koenig et al., 1979
SO_2 (1.1 - 3.6 ppm) NaCl 2.0 - 2.7 μg/m³ MMD = 0.25 μm	30	10	Oral	No effect on pulmonary functions	Burton et al., 1969
SO_2 (1-2, 4-7, 14-17 ppm) NaCl 10-30 mg/m³ MMD 0.15 μm	30	12	Oral	Changes in pulmonary function similar to changes due to SO_2 alone not influenced by aerosol	Frank et al., 1964
SO_2 (1 ppm) NaCl 1 mg/m³ MMD 0.9 μ σg = 2.0 μm	60	9 (asthmatics)	Oral	Significant decreases in $\dot{V}_{max\,50\%}$ and $\dot{V}_{max\,75\%}$	Koenig et al 1979
Ibid	60	(normals)	Mask	No pulmonary effects demonstrated	Koenig et al 1979
Ammonium sulfate 100 μg/m³	150	5 (normal) 4 (ozone sensitive) 6 (asthmatics)	Chamber (exercise)	No changes in pulmonary functions	Bell and Hackney, 1977;
Ammonium bisulfate 85 μg/m³ aerosol size distribution 0.4 μm (MMAD)	150	16	Chamber (exercise)	No changes in pulmonary functions	Kleinman and Hackney, 1978; Avol et al., 1979

increases in airway resistance in 13 subjects, even at levels as low as 1.6 to 5 ppm SO_2. There was also a linear relationship between SO_2 concentration and percentage increase in airway resistance.

On the other hand, Burton et al. (1969) were unable to demonstrate comparable effects in 10 subjects exposed to SO_2 (1.1 to 3.6 ppm) in combination with NaCl aerosol (2.0 to 2.7 µg/m³; 0.25 µm MMD; _EPA_ estimate of MMAD = 0.4 µm). There was, however, a great deal of variability within and between subjects in this study, including one or two possible "hyper-reactors" who did show effects below 3 ppm. Frank et al. (1964) studied 12 subjects who were exposed to three conditions of SO_2 and NaCl aerosols. There were six subjects in each group, but the same subjects were not evaluated under each of the three conditions. The purpose of this study was to determine whether acute changes in respiratory dynamics Rl (pulmonary flow resistance) noted to occur during SO_2 exposure were intensified by the presence of sodium chloride particles. The NaCl aerosols had a mean geometric diameter of 0.15 µm _EPA_ (estimate of MMAD = 0.3 µm) and a concentration of 10 to 30 mg/m³; SO_2 concentrations were 1 to 2, 4 to 7, and 14 to 17 ppm. The subjects' response to the SO_2 exposures were as previously noted in that Rl was not affected by the lower levels of SO_2 and progressively increased at the higher levels. The only statistically significant difference (p <0.05) between the effects of the gas alone and the gas-aerosol mixture was a slightly greater average increase in pulmonary flow resistance at 4 to 7 ppm SO_2 than under the combination condition. Addition of the NaCl aerosol resulted in similar changes as observed to SO_2 alone. This effect was interesting in that earlier work was cited suggesting that H_2SO_4 may have been formed in the droplets. (See discussion of similar animal studies in Chapter 12).

Snell and Luchsinger (1969) also compared the effects SO_2 alone and in mixture with aerosols of either NaCl or distilled water. Nine subjects inhaled

SO_2 at 0.5, 1, and 5 ppm alone and in combination with aerosols for 15-minute periods separated by 15-minute control periods. For the saline aerosol condition, decreases in maximum expiratory flow rate ($MEF_{50\% VC}$) were significant (p <0.01) at all exposure levels (0.5, 1, and 5 ppm SO_2) (See Figures 3 and 4, Snell and Luchsinger, 1969). The authors noted that the size of the aerosol particles differed considerably, saline particles averaging around 7 μm in diameter and water aerosols averaging less than 0.3 μm in diameter (see Figure 5, Snell and Luchsinger, 1969). (See also Ulmer, 1974.) Koenig (1979) exposed nine adolescent resting subjects (extrinsic asthmatics) for 60 minutes to either filtered air, 1 ppm SO_2 and 1 mg/m^3 of sodium chloride droplet aerosol or 1 mg/m^3 of NaCl droplet aerosol (MMD 0.9 μm, unable to estimate MMAD, and σ_g of 2.0 μm). Exposure to SO_2 alone was not conducted. Oral breathing was forced on all subjects. Total respiratory resistance (R_T), maximal flow at 50 and 75 percent of expired vital capacity (partial flow volume), $FEV_{1.0}$, and functional residual capacity were measured before, during (30 minutes), and after exposures. No significant changes were found during exposures to filtered air or NaCl aerosol. Significant decreases (p <0.025) were observed in $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$, suggesting that the effect of the SO_2-NaCl droplet aerosol occurred in the small airways. It should be noted that $\dot{V}_{max\ 50\%}$ was significantly depressed (8 percent) only at the midpoint of exposure. However, since possible chemical reactions can occur between dissolved SO_2 and the NaCl droplets (producing sulfite, bisulfite, and hydrogen ions), the pulmonary effects observed cannot be directly attributed to gaseous SO_2 or to the chemical substances produced. Koenig also exposed an unstated number of healthy non-smoking adults to the SO_2-NaCl droplet condition. No changes were observed in $\dot{V}_{max\ 75\%}$. Koenig et al. (1979) exposed nine adolescent extrinsic asthmatics to the same conditions as in her above study but had them also undergo a 10-minute period of moderate exercise

during the exposures. $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$ decreased some 53 and 46 percent respectively after the exercise. Significant changes in $FEV_{1.0}$ and R_T were also observed, suggesting that exercise and SO_2-NaCl exposure resulted in effects on both large as well as small airways.

As chemical interactants, particles such as aerosols of certain soluble salts (e.g., ferrous iron, manganese, vanadium) may act as catalyst to convert SO_2 to H_2SO_4. H_2O from atmospheric humidity or from physiological sources figures prominently in these reactions. The following sections deal with common compounds of sulfur oxides and point up the influence of a number of variables that affect human physiological response to these compounds.

13.4 SULFUR DIOXIDE AND OZONE

Sulfur dioxide and ozone (O_3) may combine to form sulfuric acid on the warm, moist surfaces of the respiratory tract. Studies have not yet demonstrated, however, that a true synergistic bond exists between SO_2 and O_3 (see Chapters 6, 7, and 11).

Bates and Hazucha (1973) and Hazucha and Bates (1975) exposed eight volunteer male subjects to a mixture of 0.37 ppm O_3 and 0.37 ppm SO_2 for 2 hours. Temperature, humidity, concentrations and particle sizes were not measured. Sulfur dioxide alone had no detectable effect on lung function, while exposure to ozone alone resulted in decrements in pulmonary function. The combination of gases resulted in more severe (10 to 20% decrement) respiratory symptoms and pulmonary function changes than did ozone alone. Using the maximal expiratory flow rate at 50 percent vital capacity as the most sensitive indicator, it was evident that after 2 hours exposure to 0.37 ppm SO_2 no change occurred. However, during exposure to 0.37 ppm O_3 a 13 percent reduction was observed, while exposure to the mixture of 0.37 ppm O_3 and 0.37 ppm SO_2 resulted in a reduction of 37

percent in this measure of pulmonary function. The effects resulting from O_3 and SO_2 in combination were apparent in 0.5 hours, in contrast to a 2-hour time lag for exposure to O_3 alone.

Bell et al. (1977) attempted to replicate these studies alone with four normal and four ozone-sensitive subjects. They showed that O_3 + SO_2 mixture had greater detrimental on all pulmonary function measured than O_3 alone. However, only some of these parameters showed statistical significants decrement when compared to O_3. Four of Hazucha and Bates' subjects were also studied by Bell et al. (1977). Two of these subjects had unusually large decrements in FVC (40 percent) and FEV_1 (44 percent) in the first study (Bates and Hazucha, 1973 while the other two had small but statistically significant decrements. None of the subjects responded in a similar manner in the Bell study. Restrospective sampling of the ambient air conditions utilizing particle samplers and chemical analysis in the chamber showed that acid sulfate particles could have been 10- to 100-fold higher in Hazucha and Bates' chamber and thus might have been responsible for the synergistic effects observed. In the Montreal chamber, concentrated streams of SO_2 and O_3 exited from tubes separated by 8 inches (20 cm) under a fan which forced 167 ft^3/min (4.7 m^3/min) of air conditioned laboratory air with SO_2 and O_3 through the chamber and out an exhaust line on the opposite wall. The concentrated streams of SO_2 and O_3 could have reacted rapidly with each other and with ambient impurities like olefins, to form a large number of H_2SO_4 nuclei which grew by homogenous condensation, coagulation, and absorption of NH_3 during their 2-minute average residence time in the chamber.

Horvath's group (Horvath and Folinsbee, 1977; Bedi et al., 1979) exposed nine young men (18 to 27 years old) to 0.4 ppm O_3 and 0.4 ppm SO_2 singly and in combination for 2 hours in an inhalation chamber at 25°C and 45 percent RH.

The subjects exercised intermittently for one-half of the exposure period. A large number of pulmonary function tests were conducted before, during, and after the exposure. Subjects exposed to filtered air or to 0.4 ppm SO_2 showed no significant changes in pulmonary function. When exposed to either O_3 or O_3 plus SO_2, the subjects showed significant decreases in maximum expiratory flow, forced vital capacity, and inspiratory capacity. There were no significant differences between the effects of O_3 alone and the combination of O_3 + SO_2. Although particulate matter was not present in the inlet air, it is not known whether particles developed in the chamber at a later point.

Von Nieding et al. (1979) exposed 11 subjects to O_3, NO_2 and SO_2 singly and in various combinations. The subjects were exposed for 2 hours with 1 hour devoted to exercise which doubled their ventilation. The work periods were of 15 minute duration interspersed with 15-minute periods at rest. In the actual exposure experiments, no significant alterations were observed for $P_{A_{O2}}$, $P_{A_{CO2}}$, pH_a, and thoracic gas volume (TGV). Airway resistance total (R_t) and $P_{A_{O2}}$ were altered in certain studies. $P_{a_{O2}}$ was decreased (7-8 torr) by exposure to 5.0 ppm NO_2 but was not further decreased following exposures to 5.0 ppm NO_2 and 5.0 ppm SO_2 or 5.0 ppm NO_2, 5.0 ppm SO_2 and 0.1 ppm O_3 or 5.0 ppm NO_2 and 0.1 ppm O_3. Airway resistance increased significantly [0.5 to 1.5 cm $H_2O/(L/s)$] in the combination experiments to the same extent as in the exposures to NO_2 alone. In the 1-hour post exposure period of the NO_2, SO_2, and O_3 experiment, R_t continued to increase. Subjects were also exposed to 0.06 NO_2, 0.12 SO_2, and 0.025 O_3 (all in ppm). No changes in any of the measured parameters were observed. These same subjects were challenged with a 1, 2, and 3 percent solution of acetylcholine following control (filtered air) exposure and to the 5.0 NO_2, 5.0 SO_2, and 0.1 O_3 (ppm) as well as after the 0.06 NO_2, 0.12 SO_2, and 0.025 O_3 (ppm) exposures. The expected increase in airway

resistance was observed in the control study. Specific airway resistance (R_t x TGV) was significantly greater than in the control study following the combined pollutant exposures. (See Table 13-4 for a summary of the pulmonary effects of SO_2 and other air pollutants.)

13.5 SULFURIC ACID AND SULFATES

13.5.1 Sensory Effects

A number of studies have been directed toward determining threshold concentrations of H_2SO_4 for various sensory response (see Table 13-5). In a study with 10 test subjects, Bushtueva (1957) found that the minimum concentration of sulfuric acid aerosol (particle size not given) which was sensed by odor ranged from 0.6 mg/m^3 to 0.85 mg/m^3 (average 0.75 mg/m^3). In tests with five subjects (Bushtueva, 1961), a combination of sulfur dioxide at 1 mg/m^3 (0.35 ppm) and sulfuric acid mist at 0.4 mg/m^3 was below the odor threshold. Amdur et al. (1952) reported on 15 subjects (males and females) exposed for 5 to 15 minutes to various concentrations of sulfuric acid mist the subjects breathed via a face mask. It was found that 1 mg/m^3 was usually not detected, while 3 mg/m^3 was detected by all subjects.

Bushtueva (1957) studied the effect of sulfuric acid mist on the light sensitivity of two test subjects. Sensitivity was measured every 5 minutes during the first half-hour of each test, then at 10-minute intervals thereafter. A control curve was established for each subject by seven repeated tests, and then sulfuric acid aerosol was administered for 4 minutes and for 9 minutes at the 15th and 60th minutes, respectively. With sulfuric acid mist of undetermined particle size at a concentration of 0.6 mg/m^3, a just detectable increase in light sensitivity occurred with the first exposure but not with the second. Concentrations in the range of 0.7 mg/m^3 to 0.96 mg/m^3 brought about a well-defined increase in light sensitivity. With 2.4 mg/m^3, increased sensitivity

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Concentration	Duration of exposure (mins)	Number of subjects	Source	Effects	Reference
SO_2 (0.37 ppm) and O_3 (0.37 ppm)	120	8	Chamber (exercise)	Decrease pulmonary functions (in synergistic effect of SO_2 on O_3) FRC, $FEV_{1.0}$, MMFR, $MEFR_{50\%}$	Hazucha and Bates, 1973, 1975
SO_2 (0.37 ppm) and O_3 (0.37 ppm)	120	4 (normal) 4 (ozone sensitive) 4 (from Bates)	Chamber (exercise)	Unable to confirm synergistic effects pulmonary decrement due to O_3 alone	Bell et al., 1977
SO_2 (0.40 ppm) and O_3 (0.40 ppm	120	9	Chamber (exercise)	Unable to confirm synergistic effects changes due to ozone alone	Horvath and Folinsbee (1977); Bedi et al. (1979)
SO_2 (5 ppm) and NO_2 (5 ppm)	120	11	Chamber (exercise)	No changes in P_{aO2}, P_{aCO2}, pHa or TGr $\cdot R_t$ increased	von Nieding et al., 1979
SO_2 (5 ppm) NO_2 (5 ppm) and O_3 (0.1 ppm)	120	11	Chamber (exercise)	No changes in P_{aO2}, P_{aCO2}, pHa or TGr $\cdot R_t$ increased	von Nieding et al., 1979
SO_2 (0.12 ppm) NO_2 (0.06 ppm) and O_3 (0.025 ppm)	120	11	Chamber (exercise)	No changes in pulmonary functions	von Nieding et al., 1979

13-5. SENSORY EFFECTS OF SULFURIC ACID AND SULFATES

Concentration	Subjects	Effects	References
0.75 $\mu g/m^3$	5	Threshold detected by odor - increase in light sensitivity - increase in optical chronaxie	Bushtueva, 1957, 1961
1-3 $\mu g/m^3$	15 (exposed 5-15 min)	3 mg/m^3 detected by all subjects	Amdur et al., 1952

to light was elicited by the exposures at both the 15th and 60th minutes of the test; normal sensitivity was restored in 40 to 50 minutes.

Bushtueva (1961) studied the effect of sulfur dioxide, sulfuric acid mist and combinations of the two on sensitivity of the eye to light in three subjects The combination of sulfur dioxide at 0.65 mg/m^3 (0.23 ppm) with sulfuric acid mist at 0.3 mg/m^3 resulted in no change in sensitivity of the eye to light. An increase of approximately 25 percent in light sensitivity resulted from exposure to either sulfur dioxide at 3 mg/m^3 (~1.0 ppm) or sulfuric acid mist at 0.7 mg/m^3. The combination of sulfur dioxide at 3 mg/m^3 with sulfuric acid mist at 0.7 mg/m^3 resulted in an increase of approximately 60 percent in light sensitivity. Exposures lasted for 4 1/2 minutes.

Bushtueva (1962) demonstrated that combinations of sulfur dioxide at 0.50 mg/m^3 (0.17 ppm) with sulfuric acid mist at 0.15 mg/m^3 or sulfur dioxide at 0.25 mg/m^3 (0.087 ppm) with sulfuric acid mist at 0.30 mg/m^3 could produce electrocortical conditioned reflexes. There are some uncertainties regarding this study.

Bushtueva (1961) studied the effects of different concentrations of sulfur dioxide, sulfuric acid mist, and combinations of the two on the optical chronaxie of three subjects. Optical chronaxie was determined in each test subject at 3-minute intervals as follows: at the start and on the 3rd, 6th, 9th, 12th and 15th minutes. Between the 6th and 9th minutes the subjects inhaled sulfur dioxide, sulfuric acid mist, or their combination for 2 minutes. In each subject, the threshold concentrations of sulfur dioxide and sulfuric acid mist were first determined independently, and then threshold concentrations for combinations of the two were determined. Sulfuric acid mist (750 μg/m^3) increased optical chronaxie.

13.5.2 Respiratory and Related Effects

Amdur et al. (1952) found respiratory changes in all subjects exposed for 15 minutes to H_2SO_4 aerosol at concentrations of 0.35 mg/m^3 to 5 mg/m^3. Vapors from an electrically heated flask containing concentrated sulfuric acid were carried by compressed air into the main air stream and then into a lucite mixing chamber, delivering a mist of MMD 1 μm. The subjects breathed through a pneumotachograph, permitting measurement of inspiratory and expiratory flow rate. In 15 subjects, exposed to 0.35, 0.4, or 0.5 mg/m^3, the respiration rate increased about 35 percent above control values, while the maximum inspiratory and expiratory flow rates decreased about 20 percent. Tidal volume decreased about 28 percent in subjects exposed to 0.4 mg/m^3. These changes occurred within the first 3 minutes of exposure and were maintained throughout the 15-minute exposure period. Lung function returned rapidly to baseline levels after the exposure ended. The tidal volume rose above control values during the first minute after termination of the exposure and then returned to preexposure levels. Breathing through the same apparatus without the acid mist was done as a control, and no such changes were observed. Some subjects showed a marked reaction to 5 mg/m^3. Individual responses were much more varied at this level, the main effect being a decrease in minute volume. The investigators suggest that bronchoconstriction may have been the response to sulfuric acid.

The effect of breathing sulfuric acid mist at different relative humidities (RH) was studied by Sim and Pattle (1957). Healthy males (variable number of subjects), 18 to 46 years of age, breathed 3 to 39 mg/m^3 concentrations of H_2SO_4 at 62 percent RH either via mask or exposure chamber. Subjects were also exposed in the chamber to 11.5 to 38 mg/m^3 concentrations at 91 percent RH. At the lower RH, particles were 1 μm in size. The addition of water

vapor to raise RH increased the mean particle size to 1.5 μm and intensified irritant effects of exposure. For example, the irritancy of wet mist at 20.8 mg/m^3 was much more severe ("almost intolerable at the onset") than that of the dry mist at 39.4 mg/m^3 ("well tolerated by all"). Air flow resistance ranged from 43 to 150 percent above normal in response to the wet mist, compared to increases ranging from 35.5 to 100 percent above normal in response to the dry mist. Two subjects exposed to sulfuric acid mist developed bronchitic symptoms but may have been previously exposed to other substances. Adding ammonia (quantity not given) to the acid mist annulled its irritant properties. There was no consistent evidence that the acid mist caused changes in respiratory functions or blood pressure, pulse rate, or other cardiovascular functions.

Toyama and Nakamura (1964) investigated the synergistic effects of SO_2 in combination with hydrogen peroxide (H_2O_2) aerosol mixtures, the latter of which oxidizes SO_2 to form H_2SO_4. SO_2 concentrations ranged from 1 to 60 ppm; the H_2O_2 concentrations were 0.29 mg/m^3 for particles of 4.6 μm CMD (estimated _EPA estimate of_ MMAD = 13) and 0.33 mg/m^3 for particles of 1.8 μm CMD (_EPA estimate of_ estimated MMAD = 5). Airway resistance increased significantly in the combination (H_2O_2 + SO_2) exposure, particularly for the group of 15 subjects inhaling the larger particles (p <0.01). Toyama and Nakamura (1964) exposed subjects to a mixture of SO_2 and H_2SO_4 aerosols. They used an inadequate method to measure airway resistance. They described the aerosols as having a 4.5 μm diameter. They found a strong constricting effect on the upper airways.

Sackner et al. (1978) studied normal resting young adults and seven asthmatic middle-aged subjects who breathed, by mouth, either sodium chloride or sulfuric acid aerosols for 10 minutes at concentrations of 10, 100, and 1000 μg/m^3. Measurements on these individuals continued for up to 3 hours after exposure. The asthmatic patients represented a wide range of clinical

status and treatment. Neither normal nor asthmatic individuals showed significant alterations of lung volumes, distribution of ventilation, earoximetry, dynamic mechanics of breathing, oscillation mechanics of the chest-lung system, pulmonary capillary blood flow, diffusing capacity, arterial oxygen saturation, oxygen uptake, or pulmonary tissue volume. No delayed effects were observed during a follow-up period of a few weeks.

Kleinman and Hackney (1978) and Avol et al. (1979) reported on the pulmonary responses of six normal and six asthmatic subjects exposed in an ambient environment of 88°F dry bulb and 40 percent relative humidity, and 94 $\mu g/m^3$ H_2SO_4. The asthmatics had pulmonary function test results which ranged widely from normal to abnormal. A sham exposure was followed by 2 consecutive days of acid exposure. Sufficient excess acid aerosol to neutralize the NH_3 present (about 56 $\mu g/m^3$ ammonia neutralization product) was added to the air to provide for the desired acid concentration (75 $\mu g/m^3$). The aerosol MMAD was approximately 0.48 to 0.81 μm. The effective exposure time was 2 hours, with the first 15 minutes of each half-hour devoted to exercise which increased ventilation to twice the resting level. Only one subject was exposed at a time to minimize the effects of ammonia neutralization. The normal subjects showed no exposure-related changes. The lung functions of the asthmatics showed no significant changes. Two asthmatics, the extent of their disease state not given, exhibited increases in respiratory resistance on both exposure days. Nonetheless, it was concluded that there were no convincing adverse short-term health effects of sulfuric acid. However, they also noted the small size of their subject pool and recommended additional studies.

Lippmann et al. (1979) had 10 non-smokers inhale via nasal mask 0.5 μm (σ_g = 1.9) H_2SO_4 at 0 and approximately, 100, 300, and 1,000 $\mu g/m^3$ for 1 hour. The exposures were random over the 4 days of testing. Pulmonary functions

(assessed by body plethysmograph, partial forced expiratory maneuver, and nitrogen washout) were measured before, and at 0.5, 2, and 4 hours post exposure. ^{99m}Tc-tagged monodispersed Fe_2O_3 aerosol (7.5 µm MMAD, $\sigma_g = 1.1$) was inhaled 10 minutes before exposure for the determinations of lung retention of these particles. Tracheal mucus transport rates (TMTR) and bronchial mucociliary clearance were determined. No significant changes in respiratory mechanics or TMTR were observed following H_2SO_4 exposure at any level. However, bronchial mucociliary clearance halftime ($TB_{\frac{1}{2}}$) was on the average markedly altered at all concentrations of H_2SO_4 inhaled. Bronchial clearance was increased (p <0.02) following exposure to 100 µg/m^3 H_2SO_4, while following exposure to 1,000 µg/m^3, it was significantly (p <0.03) reduced. Mucociliary transport in the airways distal to the trachea was affected more by H_2SO_4 exposure than was transport in the trachea. Out of ten subjects four did not respond. "The alterations in bronchial clearance half-time were all transient, which was consistent with the results seen earlier in similar inhalation tests on donkeys (Schlesinger, et al., ~~1968~~ *1978*). However, when donkeys were repeatedly exposed to sulfuric acid at comparable concentrations, four of six animals developed persistently slowed clearance, which remained abnormal for at least several months (Schlesinger, et al., 1978, 1979). Taken together, these results suggest that at the concentrations employed persistent changes could occur in mucociliary clearance in previously healthy individuals and exacerbate preexisting respiratory disease.

Bell and Hackney (1977) presented preliminary data on a limited number of subjects supporting a hypothesis that no adverse short-term (2.5 hours) effects result from exposure to polydisperse ammonium sulfate particles in the respirable size range (see Avol et al., 1979). Sixteen individuals were studied, each being exposed from two to six times to ammonium sulfate. They exercised for

the first 15 minutes of each half-hour. Ventilation volumes were approximately double the resting volume during the four exercise periods. A battery of pulmonary function measurements (FVC, $FEV_{1.0}$, MMF, ΔN_2, RV, TLC, CV/VC, CC/TLC and R_t) were administered to the subjects. Five normal and four "sensitive" (i.e., sensitive to ozone exposures) subjects had 3 successive days of $(NH_4)_2SO_4$ exposures preceded by 2 days of purified air exposures. Ambient temperature conditions were 88°F dry bulb and 40 and 85 percent relative humidity. Six asthmatic subjects were studied at the lower humidity condition. Their first day was a purified air exposure followed by 2 days in the ammonium sulfate condition.

Kleinman and Hackney (1978) and Avol et al. (1979) further evaluated the effects of various sulfate compounds on normal subjects, ozone-sensitive subjects, and asthmatic subjects (requiring medical treatment). The exposures were approximately 2.5 hours in duration, with the subjects exercising the first 15 minutes of each half hour at a pace sufficient to double their ventilation rates. Measurements of pulmonary functions, which included FVC, FEV_1, MEFR, $FEF_{50\%}$, $FEF_{75\%}$, TLC, RV, delta nitrogen (ΔN_2), closing volume, and total respiratory resistance (R_t) were made before and 2 hours after the work-rest regimen began. The ambient conditions were 88°F dry bulb and either 40 or 85 percent relative humidity. Most of the exposure studies were made on five to seven subjects. Four to five sensitive subjects and six asthmatics completed the subject pool. Subjects were first exposed to a control (no pollutant) environment and then to 2 or 3 consecutive days of the pollutants. The asthmatics were not studied in the high humidity conditions, but were exposed to a higher concentration (up to 372 $\mu g/m^3$) of $(NH_4)_2SO_4$. Nominal exposure concentrations were 100 $\mu g/m^3$ for ammonium bisulfate (NH_4HSO_4)

and 85 μg/m^3 for ammonium sulfate [(NH$_4$)$_2$SO$_4$]. The sulfate aerosol size distribution was nominally 0.4 μm MMAD (σ_g 2.5 to 3). There was some ammonia (NH$_3$) in the exposure chamber. Pulmonary functions were unaffected by exposure to the two types of aerosol.

An interesting side observation was made on the asthmatics. On their first day of exposure to NH$_4$HSO$_4$ aerosol, they exhibited worse lung functions in the pre-exposure measurements than they had on a control day. Their functions improved consequent to the pollutant exposure. Subsequent analysis of local ambient conditions showed that these subjects arrived for their aerosol testing after a 3-day period of increased SO$_2$ and ozone levels during a "mild air pollution episode." (See Table 13-6 for a summary of the pulmonary effects of sulfuric acid.)

13.6 SUMMARY

Human experimental studies of the health effects of exposure to pollutants in the ambient environment require strict controls so that their findings can be generalized to the entire population. Although no studies meet all the requirements for strict control, some basic information can be garnered from many published studies.

SO$_2$ has been found to have effects on several physiologic functions. Through subjective reports, the reliability of which has been questioned, a level of 5 ppm has been established for detecting SO$_2$, with considerable variation below that level. Several sensory processes are affected by generally agreed-upon levels of concentration of SO$_2$. The odor threshold averages 0.8 to 1 ppm, with 0.47 ppm set in one study performed under ideal conditions. The sensitivity of the eye to light increases at 0.34 to 0.63 ppm, is maximal at 1.3 to 1.7 ppm, and decreases to normal by 19.2 mg/m^3 during dark adaptation.

13-6. PULMONARY EFFECTS OF SULFURIC ACID

Concentration	Duration of exposure (mins)	Number of subjects	Source	Effects	Reference
$0.35 - 5.0$ mg/m^3 H$_2$SO$_4$ MMD 1 µm	15	15	Mask (rest)	Respiratory rates increased, max. insp. and expiratory flow rates and tidal decreased volumes	Amdur et al., 1952
$3-39$ mg/m^3 H$_2$SO$_4$ MMD 1-1.5 µm	10 - 60	Variable	Mask (rest) Chamber (rest)	Longer particles due to "wet mist" resulted in increased flow resistance cough, rales bronchoconstriction	Sim and Pattle, 1957
SO$_2$ (1-60 ppm) plus H$_2$O$_2$ to form H$_2$SO$_4$ aerosol CMD 1.8 and 4.6 µm	Variable	24	(Rest)	Airway resistance increased especially with larger particles	Toyama and Nakamura, 1964
H$_2$SO$_4$ mist (1000 µg/m^3 MMD 0.5 µm (σg = 2.59)	120	10	Chamber (exercise)	No pulmonary function changes but increased tracheobronchial clearance	Newhouse et al., 1978
H$_2$SO$_4$ aerosol 10, 100, 1000 µg/m^3 MMD 0.1 µm	10	6 normal 6 asthmatics	Oral	No pulmonary function changes, no alterations in gas transport	Sachner et al., 1978
H$_2$SO$_4$ (75 µg/m^3) MMAD 0.48 - 0.81 µm	120	6 normal 6 asthmatics	Chamber (exercise)	No pulmonary effects in either group	Kleinman and Hackney, 1978; Avol et al., 1979
H$_2$SO$_4$ (0, 100, 300, or 1,000 µg/m^3 MMAD 0.5 µm (σg = 1.9)	60	10	Nasal	No pulmonary function effects Broncial mucociliary clearance ↑ following 100 µg/m^3 but ↓ following 1000 µg/m^3 mucociliary clearance distal to trachea more affected	Lippmann et al., 1979

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During light adaptation, the figures increase and decrease similarly but at slightly higher levels of exposure. The alpha-wave has been found to be attenuated by 0.9 to 3 mg/m^3 SO_2 during 20 seconds of exposure.

Studies of the effects of SO_2 on the respiratory system of the body have arrived at conflicting conclusions. Although one study found respiratory effects after exposure to as little as 1 ppm SO_2, others could find no effect below 5 ppm. At the latter level, pulmonary flow resistance increased 39 percent in one study. Respiratory effects have been found to be proportional to the concentration of SO_2 to which study subjects are exposed. In asthmatic subjects, MMFR was significantly reduced after oral exposure to 0.5 ppm SO_2 for 3 hours. Although the bronchoconstrictive effects of exposure to SO_2 have been found to be fairly consistent, subjects vary considerably in response to exposures, and there are some especially sensitive subjects, possibly as much as 10 percent of the population.

Because SO_2 is readily water soluble, and nasal passages are high in humidity, the route of exposure will affect the response of individuals. Subjects report less throat and chest irritation when breathing through the nose, and pulmonary flow resistance increases less in subjects who are nose breathing. Regardless of the route of exposure, 5 ppm SO_2 had no effect on specific airway conductance, although higher levels had a dose-dependent effect; that is, greater concentrations decreased SG_{aw} more than lower concentrations. The average decrease was greater after oral exposure than after nasal administration.

The level of activity of the subjects tested affects the results because the actual dose received is greater when subjects breathe through their mouth, as during exercise. Just having subjects breathe deeply through the mouth

significantly affected specific airway resistance during exposure to 1 ppm SO_2 in one study, although another study found no such effect. Respiratory effects of exposure either by nose or by mouth are greatest after 5 to 10 minutes of exposure. Recovery takes about 5 minutes in normal subjects, but much longer (10 to 60 minutes) in sensitive subjects and those who are asthmatic. Studies of nasal mucus flow rates and airway resistance following about 6 hours of exposure to SO_2 per day for 3 days found some effects maximal after 1 to 6 hours.

An early study found mucus clearance reduced increasingly as length and concentration of exposure to SO_2 increased. Long exposures to 5 ppm SO_2 increased mucociliary clearance in one study; a decrease had been found in nasal clearance rates in another study. Available studies have not found a significant interaction of smoking with SO_2.

The interaction of SO_2 and particulate matter is an important factor in Lunn's experimental studies. Airway resistance increased more after combined exposure to SO_2 and sodium chloride than after exposure to SO_2 or sodium chloride alone in several studies although others have failed to reach the same conclusion. This may have been due to formation of sulfuric acid mist during the study. $MEF_{50\%}$ was found to be significantly reduced after exposure to a combination of saline aerosol and SO_2. After exposure to combined hydrogen peroxide and sulfur dioxide, airway resistance was found to be significantly increased. The combination of SO_2 and ozone may have synergistic effects on lung function. At low concentrations (0.37 ppm) SO_2 had no effect on lung function, ozone impaired lung function, and the combination impaired lung function even more. A similar study did not find the same results. Other studies have found reductions in pulmonary function after exposure to low

levels of SO_2 and ozone combined with SO_2 or to ozone alone, but no synergistic effect of the combined exposure.

Sulfuric acid and sulfates have been found to affect both sensory and pulmonary function in study subjects. The odor threshold for sulfuric acid aerosol has been set at 0.75 mg/m^3 in one study and 3 mg/m^3 in another. Light sensitivity has been found to be consistently increased by 25 percent at 0.7 to 0.96 mg/m^3 concentration of sulfuric acid mist (0.3 mg/m^3). Optical chronaxie has also been found to be increased after exposure of subjects to 750 $\mu m/m^3$ sulfuric acid mist.

Respiratory effects from exposure to sulfuric acid mist (0.35 to 5 mg/m^3) include increased respiratory rate and decreased maximal inspiratory and expiratory flow rates and tidal volume. Several studies of the pulmonary function of asthmatic and normal subjects suggested that pulmonary function was not affected when the subjects were exposed to sulfuric acid. Mucociliary clearance was affected by exposure to sulfuric acid, being significantly increased after exposure to 100 $\mu m/m^3$ and significantly decreased after exposure to 1000 $\mu g/m^3$. Another study found no pulmonary effect of exposure to sulfuric acid, ammonium bisulfate, and ammonium sulfate by normal and asthmatic subjects.

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Chapter 14. Epidemiology Studies Corrigenda

Before listing specific minor errata (insertions/deletions) for text contained

in Chapter 14 of the April 1980, External Review Draft, several general comments

should be noted regarding planned reorganization and certain other major changes

to be made in the chapter. The chapter reorganization and other changes are

based in part on comments received both from within and outside EPA

and further technical information obtained since finalization and release of the

April, 1980, external review version of the chapter.

In regard to reorganization of the chapter, the present introduction (Section

14.1) discussing general epidemiology methodology considerations and the discussion

of air quality measurement considerations (Section 14.2) are to be retained,

with certain specific revisions noted later. Similarly, much of the later discussion

of caveats and limits contained in Section 14.6 is to be retained, again with certain

revisions as noted later. The materials between the above sections (dealing with

evaluation of specific studies). however, is to be reorganized using the following

format:

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14.3 - Acute Exposure Effects
     14.3.1 - Mortality
     14.3.2 - Morbidity
              Adults
              Children

14.4 - Chronic Exposure Effects
     14.4.1 - Mortality
     14.4.2 - Morbidity
              Adults
              Children
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Resequencing of the discussion of specific studies in the above manner both:

(1) better matches the presentation format followed for summary text and tables later

in Chapter 14 and in Volume I; and (2) better organizes discussion

of technical data related to development of health criteria for short-term (24-hour)

or long term (annual average) ambient air quality standards, respectively. Text on

the bottom of pg. 14-14 is, therefore, to be revised to reflect the reorganization

of subsequent materials in Section 14.3 and 14.4, and to indicate that a new

Section 14.5 will contain integrative summary and interpretation discussion

materials of the type dealt with under the present Section 14.6.

Also, at the end of Section 14.1, following the above revisons of text at

the bottom of Pg. 14-14, new text to be inserted is to note that certain criteria

are to be followed, generally, in the selection of specific studies to be

discussed in detail under new Section 14.3 and 14.4. The criteria to be employed

in narrowing down the detailed discussion to potentially key studies are as

follows:

1. The studies have been peer-reviewed and published or are
"in press" to be published, such that final versions of the published reports
are (or can be made) publically available. Also, the results or analyses contained
in the published reports represent completed analyses of data, rather than "preliminary"
analyses subject to change before publication in "final" form.

2. The published information is sufficient to allow for reasonably clear
evaluation of the methodology employed in collection and analysis of
data leading to the results reported (or such information is satisfactorily
alternatively obtained or clarified).

3. Evidence exists for major confounding factors having been appropriately
controlled for or taken into account in the published analyses, e.g. especially
temperature in studies of acute effects and smoking, race, and socioeconomic
status in chronic exposure studies.

4. The published results, together with any alternatively obtained
information, appear to provide a reasonably clear potential basis by which to
define quantitative dose-effect or dose-response relationships for health
effects associated with sulfur oxides and particulate matter. Emphasis
is to be placed on studies yielding information on effects associated
with exposures below 1000 $\mu g/m^3$ (24 hour average) that are most germane for
present criteria development purposes.

In addition to detailed discussion of studies meeting all of the above

criteria, certain other studies failing to meet one or more of the criteria may

also be considered or reviewed, based on their findings likely providing

important information bearing on the overall assessment of epidemiologic evidence

of significance for present purposes.

Following the above modifications of introductory materials in Section 14.1, the next section (14.2) on air quality measurement considerations is to be expanded to include summary statements derived from Chapter 3 discussions of intercomparisons between estimates of particulate matter levels obtained by various measurement techniques. Thus, immediately before the start of Section 14.3 at the bottom of Pg. 14-34, there is to be inserted a relatively brief summary discussion concerning the main conclusions derived from Chapter 3 regarding intercomparisons of particulate matter measurement data obtained by means of high-volume (TSP) sampling, British smoke (BS), and other (e.g., the AISI) particulate measurement techniques. Note will be made of the difficulties and limitations inherent in making such intercomparisons and, based on this, the particulate matter measurement results employed in particular studies discussed in Sections 14.3 and 14.4 are to be expressed there only in terms of units appropriate for the specific measurement methodology employed (e.g., in CoH units or $\mu g/m^3$ of either BS or TSP). Only following summarization of study results in terms of such original measurement units are discussions of any potential interconversions between measurement units to be included as part of later summary and conclusions materials in Section 14.5 and elsewhere (e.g., Volume I).

No attempt will be made here to list myriad changes in sequencing of text materials now under Sections 14.3 to 14.5 of the April, 1980, External Review Draft necessary to accomplish the reorganization of materials into the new Sections 14.3 and 14.4 listed under the revised format outlined above. Rather, only certain planned substantive content revisions (mainly large text deletions) of existing materials in Sections 14.3 to 14.5 of the April draft are summarized below before presentation of more detailed lesser errata corrections for the Chapter.

On pg. 14-47, Table 14-7 is to be deleted along with revisions and reduction in text at the bottom of pg. 14-46 and top of pg. 14-48, discussing the Osaka and Rotterdam studies. The revisions are to note that the Biersteker[315] and Watanabe[100] studies report data or information on quantitative dose-effect relationships, but insufficient information was reported to allow for evaluation of the adequacy of study design (especially in regard to adjustments made for temperature effects).

On pg. 14-51 to 14-52, the discussion of multiple regression studies by Hodgson,[158] Buechley,[159,160] Lebowitz,[170] and Lebowitz et al.[171] is to be shortened considerably. Note is to be made that these studies provide mainly qualitative data on associations between sulfur oxides (SO_x) or particulate matter (PM) and observed mortality effects but generally do not provide clear data on quantitative levels of SO_x or PM likely associated with such effects, with the exception of the Beuchley studies[159, 160] finding significant increases in mortality when 24 hour mean SO_2 levels exceeded approximately $500\mu g/m^3$.

On pg. 14-56, 14-58, 14-59, the extensive quotation of material from Holland et al.[301] concerning the Martin studies[6,11] is to be deleted. Also the rest of the text on pg. 14-59 is to be deleted, along with the text concerning the detailed additional analysis of mortality effects observed in the Martin studies[6,11] that runs from pg. 14-60 to 14-65. Similarly, the rest of the text on 14-65 and 14-66 (top) on further analysis of the 1975 London and 1975 Pittsburgh episodes is to be deleted. The available reports or discussions of the 1975 London episodes do not allow for more detailed analyses of the type indicated on pg. 14-65; and the available report by Riggan et al. (1977)[341] on the Pittsburgh episode contains information only on preliminary analyses that remain to be more definitively completed, peer-reviewed and published.

On pg. 14-70 to 14-71, table 14-16 on qualitative mortality studies is to be moved to the appendices and referred to in Chapter 14 text only briefly, in summary terms. Also, certain studies, such as those by Buck and Brown[199] Wicken and Buck,[19] Burn and Pemberton,[20] are to be added to qualitative studies listed in Table 14-16. Comments on the Winkelstein studies[21-23] and analyses presented on pg. 14-73 to 14-81 would be especially valuable in order to resolve whether to retain such detailed discussion of these results as important quantitative findings or whether to simply list the Winkelstein results in a table of qualitative findings.

On pg. 14-90, the summary table (14-21) is to be revised to show the 24 hour particulate levels at which mortality effects were observed only in terms of the original units ($\mu g/m^3$ BS; CoH units) in which such data were reported (and not possible comparable TSP units). On pg. 14-91, Table 14.22 is to be deleted.

On pg. 14-93 to 14-95, the Table (14.23) on qualitative studies of air pollution and acute respiratory disease is to be moved to the Appendices and only brief summary statements regarding the table kept in the main text of Chapter 14. Comments on studies by Finklea et al.[177,122,123] are to be deleted from the table.

On pg. 14-96 and 14-97, text revisions are to be made that note the exclusion from discussion in the April draft of studies carried out as part of the EPA "CHESS" program. Also, in that connection, explanatory text will be inserted stating that: (1) The manner in which CHESS program study results were reported and interpreted in summary form in early 1970 publications and in more detail in the 1974 "Sulfur Oxides Monograph" raised questions regarding possible inconsistencies in data collection and analyses, as well as interpretation of the reported results;

(2) Of particular concern were questions regarding the adequacy of air quality data measurements (for TSP and SO_2, as well as other pollutants) upon which key quantitative conclusions were based regarding possible air pollution-health effects relationships; (3) Many of the outstanding questions regarding the CHESS studies remain to be clearly resolved and, until such time that they are, the potential usefulness of such studies is extremely limited in terms of yielding well-defined information on air pollution-health effects relationships as they might pertain to development of health effects criteria; (4) Based on the above considerations, CHESS program data sets and analyses will not be further discussed in criteria document drafts, unless questions regarding accuracy of specific data sets and their analyses have been satisfactorily resolved and reports on them adequately peer reviewed.

On pg. 14-102, the last sentence on the page is to be amended to note that, since measurements of air pollution and pulmonary function reported in the Stebbings et al.[82] study and the Stebbings and Fogelman[216] study were not initiated until after the peak of the 1975 Pittsburgh episode, it is impossible to clearly relate any health effects observed in those studies to specific SO_2 or PM levels. Consequently, the rest of the detailed discussion of the Stebbings[82,216] studies on pg. 14-103 and top, pg. 14-104, is to be deleted.

Also, on pg. 14-105 and 14-106, all text dealing with the Stebbings and Hayes[190] report on a 1971-1972 New York "CHESS" Program panel study is to be deleted, as per statements made earlier concerning exclusion from discussion of CHESS Program studies due to unresolved questions regarding their reported results and interpretations. Similarly, the detailed text discussing the French et al.[306] New York ARD "CHESS" Program study is to be deleted from top, pg. 14-109 to top, pg. 14-133, including Tables 14-24 to 14-26 on pg. 14-110 to 14-112.

On pg. 14-107 to 14-109, the discussion of the studies[71, 205-210] by McCarroll and associates is to be shortened (and reference to quantitative estimates of pollutant levels associated with observed health effects deleted). Consideration will be given to including brief summaries of those studies in an appropriate table of qualitative studies.

On pg. 14-113, the detailed discussion of the Kalpalzanov et al.[63] study is to be deleted and its results only briefly summarized in an appropriate table of qualitative studies.

On pg. 14-115 to 14-116, the discussions of the Kevany[15] and Heinman[54] and Sterling[72,73] studies are to be deleted; the results of each are to be summarized in an appropriate table of qualitative studies.

The discussion of the Fletcher et al.[274] and Angel et al.[69] studies on pg. 14-117, is to be moved to the new Section 14.4 on chronic exposure effects, rather than remaining under the text on acute effects as presently situated. Note will be made of difficulties in estimating quantitative levels of SO_x or PM associated with observed health effects, and other problems, which argue for these studies to be included as part of an appropriate table of qualitative studies.

The text on the Verma et al.[65] study (bottom, pg. 14-120; top, 14-121) is to be deleted and that study only mentioned briefly in an appropriate table of qualitative studies. Also, on pg. 14-121, the discussion of the "Ministry of Pensions" study[62] is to be moved to the new Section 14.4 on chronic effects; note will be made of problems with air monitoring data used in that study and other methodological problems which mitigate against useful quantitative information being extracted for present criteria development purposes.

On pg. 14-123, the Shephard et al.[327, 328] discussion is to be deleted and the Lebowitz et al.[180] study results (including top pg. 14-124) briefly summarized in a table of qualitative studies.

Table 14-29, on pg. 14-125 is to be revised as follows: (1) particulate matter measurement data will be expressed only in terms of BS or TSP as originally reported, with a column being added for BS in the table headings along side the TSP ($\mu g/m^3$) heading; (2) "qualitative" studies will be deleted from the table, including those by McCarroll et al.,[205,206] Cassell et al.,[208, 209] Greenburg et al.,[196] Stebbings et al.,[216] Stebbings and Hayes,[190] Heimann,[54] and British Ministry of Pensions.[62]

On pg. 14-131 to 14-134, certain of the studies included in Table 14-30 as yielding qualitative information on air pollution-health effects might be appropriately deleted, except for ones providing data specifically elucidating associations between health effects and SO_x or PM. Comments on which studies should be retained as meeting such criteria, and which should be deleted as useless for present purposes, would be helpful.

The extensive discussion of the Irwig et al.[98] and Melia et al.[(new ref. #342)] reports on the British school children study, on pg. 14-139 to 14-149 (top), is to be deleted. Essentially no reference in the main body of Chapter 14 is to be made to either the Irwig et al. or Melia et al. reports in view of the preliminary nature of the analyses alluded to in the referenced papers and the lack of any peer-reviewed published reports on "final" or completed analyses of the British school children study.

On pg. 14-151 (top), the discussion of the study by Tsunetoshi et al.[38] is to be deleted and the results briefly summarized in a qualitative studies table.

Similarly, the Suzuki et al.[183] study discussion on pg. 14-151 (bottom) is to be deleted and that study summarized in a qualitative studies table, as is also the case for the Toyama et al.,[312,317] Tani[319] and Yoshii[319] studies on pg. 14-152.

On pg. 14-152 to 14-158, all text is to be deleted regarding discussion of the EPA "CHESS" studies reported by Chapman et al.[212] for Utah "CRD" and Chicago "CRD" prevalence rate data sets. Also, on pg. 14-158 (bottom) and 14-159 (top) discussion of the Yoshida et al.[176] is to be deleted and results of that study briefly summarized in a qualitative studies table.

Comments focusing on the discussion and interpretation of the studies by Rudnick[182] and Douglas and Waller[90] on pg. 14-159 to 14-163 would be highly useful, as would comments on the Lunn et al.[96, 97] studies discussed on pg. 14-163 to 14-165. Rudnick[182], Douglas and Waller[90], and Lunn et al.[96,97] appear to to provide at least some reasonably well-defined air quality data by which quantitative health effects - SO_x/PM air pollution relationships might be delineated (they have been interpreted by leading experts in such a manner). This, together with otherwise apparently sound methodological features, argue for these studies being strongly considered as potential key studies in arriving at final conclusions regarding the epidemiology data base for SO_x and PM.

On pg. 14-165 to 14-177, all text is to be deleted regarding discussion of CHESS studies reported by Hammer et al.[214] and French et al.[306] (on New York "LRD" data), French et al.[306] (on Utah "LRD" data), and Hammer[113,257] (on Southeast or Birmingham vs. Charlotte "LRD" data). This is in keeping with statements presented earlier regarding exclusion of CHESS studies from consideration in view of questions that remain to be resolved concerning data collection, analyses and interpretation of results for CHESS Program studies. Of all the various CHESS

studies to be deleted at this time, the Hammer[113, 257] "Southeast LRD" study appears to provide the most extensive and thorough data analyses potentially leading to reliable quantitative estimates of air pollution (SO_x/PM)-health effects relationships. Also, there appears to be a reasonable possiblity of resolving questions concerning the Hammer study[113,257] within the time frame of finalization of the present document. Comments on that study would, therefore, be helpful in determining its possible future consideration for inclusion in the criteria document as a potentially key quantitative study.

Comments focused on the Van der Lende et al. studies[74-77] discussed on pg. 14-178 would also be quite useful, in view of its having been interpreted by a number of experts as yielding important information on quantitative health effects - air pollution (SO_x/PM) relationships. Similarly. comments would be useful on the Becklake[33] and Manfreda et al.[85] studies as potentially finding lack of evidence of health effects at SO_2 and TSP levels around 100 $\mu g/m^3$ or less, as discussed on pg. 14-178 and 14-179.

On pg. 14-179 (bottom) and pg. 14-180 (top), the discussion of the Kagawa et al.[218, 264] studies is to be deleted and, at most, briefly summarized within a qualitative studies table. The same applies for the Zapletal et. al[87] study discussed at the top of pg. 14-180.

Comments would be especially valuable regarding the discussions on pg. 14-180 to 14-186 regarding the studies by: Holland et al;[101,102] Bennett et al.[103]; Colley and Reid[112]; Ferris[115]; Mostardi and Leonard[177]; Mostardi and Martell[258]; and Shy et al.[215] (Cincinnati school children pulmonary function study). At least some of these studies appear to provide potentially useful information by which quantitative health effects - air pollution (SO_x/PM) relationships might

be defined, whereas others may be sufficiently flawed methodologically (e.g. in failure to control for smoking, etc.) so as to be rendered essentially useless for present criteria development purposes.

On pg. 14-186 to 14-188, all of the text is to be deleted regarding the "CHESS" studies reported on by Shy et al.[215] (New York pulmonary function data) and Chapman et al.[213] (Birmingham and Charlotte pulmonary function data).

Comments would be useful regarding the Neri et al.[34,35] studies, discussed on pg. 14-189, as well as the other studies discussed on pg. 14-190 to 14-195. However, the discussion of Irwig et al.[98] results, on pg. 14-193 (bottom), is to be entirely deleted in view of the "preliminary" nature of the results thus far reported.

On pg. 14-196 to 14-197, Table 14-40 is to be revised, including: (1) addition of a column heading for BS ($\mu g/m^3$) along side TSP ($\mu g/m^3$) and listing of particulate matter measurement data under only one of the columns according to the original form or units reported for a given study; and (2) deletion of CHESS Program studies (Goldberg et al.,[109] House et al.,[108] Nelson et al.,[114] Hammer,[113,257] Shy et al.,[215] Chapman et al.[213]) and qualitative studies (Kerrebijn et al.,[99] Yoshida et al.,[176]) consistent with deletions in text noted above. The present Summary and Conclusions section (14.6) of Chapter 14, starting on pg. 14-199, is to be designated as Section 14.5 under the proposed chapter reorganization format outlined on the first two pages of the present materials. Reflecting the planned format change, the first paragraph on pg. 14-199 is to be appropriately revised to note under points (3) and

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(4) that acute and chronic exposure effects discussions appear under Sections 14.3 and 14.4, respectively, of the newly reorganized chapter. Point (5) at the end of the first paragraph is to be deleted.

On pg. 14-200, the last part of the last sentence of the first paragraph (text starting with "--not for the purpose...") is to be deleted as unnecessary. The next paragraph on pg. 14-200 is to be revised to make reference to Table 14-41 as summarizing the results of key studies discussed earlier in the chapter as providing valid information on quantitative relationships between acute exposures to sulfur oxides or particulate matter and mortality and morbility health effects. Reference is also to be made to Table 14-42 as containing similar summarization of key quantitative studies concerning chronic exposure effects.

Table 14-41, on pg. 14-201 and 14-202, is to be revised as follows: (1) additional column headings for COH and BS measurement results in $\mu g/m^3$ are to be provided along side the TSP ($\mu g/m^3$) heading; (2) results for particulate matter measurements will be entered under one of the three (BS; COH; TSP) columns only, as per the original units or form reported for a given study; and (3) numerous deletions of entries from the revised table are to be made. Such deletions are to include: (a) the first four sets of entries designated as being for British, Dutch, Japanese, and USA studies under episodic mortality; and (b) the morbidity study entries for Stebbings and Hayes,[190] McCarroll et al.,[163] Cassell et al.,[208,209] and Stebbings and Fogleman.[216]

On pg. 14-203, changes analogous to the first two types listed above

for Table 14-41 are to also be made in Table 14-42. Entries are to be deleted

from Table 14-42 for studies by Winkelstein,[188] Zeidberg and colleagues,[16-18]

Hammer et al.,[214] Goldberg et al.,[109] House et al.,[108] Nelson et al.,[114]

Hammer,[113,257], Shy et al.,[215] and Chapman et al.[213]

From pg. 14-205 to pg. 14-208 (top, before heading for Section 14.6.2),

all text for present Section 14.6.1.1 is to be deleted. The text under

Section 14.6.2 (pg. 14-208 to 14-214), however, is to remain, as is the text

under Section 14.6.3 (pg. 14-215 to pg. 14-251).

On pg. 14-245, Figure 14-8 is to be deleted and the differences between

evaluations of key studies between Holland et al.[301], WHO[312] and other reviewers

briefly discussed only in new text inserted on pg. 12-244. Study results for the

Osaka (1962), Rotterdam (1960's), France (1973), Tokyo (1970), and Southeast

USA (1969-71) entries in the figure will not be discussed. The mistaken data

entry for "Chicago-(1972)" in the figure actually refers to Mostardi's[177,258] studies

in Ohio (1972), and the entry in the key to the right for Apling et al., Waller

(1977-78) London is for Apling et al.; Weatherly and Waller (1977-78) London.

Discussion of differences in the reviewers' evaluations of study results will note

where the particular review "translated" original estimates of health effects-associated

particulate matter levels associated with health effects from original COH or

BS units to approximate corresponding TSP levels.

Lastly, at the end of Chapter 14, copies of summary tables now appearing

only in Volume I of the document (as Tables 1-19 to 1-22) are to be inserted to

summarize the evaluations of different reviews for key quantitative studies.

The tables will be the same as present Tables 1-19, 1-20, and 1-21, except for those modifications discussed for those tables earlier, under present corrigenda materials for Chapter 1. Appropriate text will also be inserted to discuss the reviewers' evaluations summarized in the tables and definite statements made regarding which studies appear to be generally viewed as being valid and conclusions that can appropriately be drawn based on those study results.

14. EPIDEMIOLOGICAL STUDIES OF THE EFFECTS OF ATMOSPHERIC CONCENTRATIONS OF SULFUR DIOXIDE AND PARTICULATE MATTER ON HUMAN HEALTH

14.1 INTRODUCTION

In the preceding chapters of this volume (Chapters 11, 12, and 13), information was assessed regarding the uptake, deposition, and absorption of sulfur oxides and particulate matter and various health effects demonstrated to be associated with these pollutants by means of animal toxicology and human clinical studies. Such studies offer the advantage of being able to study biological processes specifically associated with particular pollutant exposures under highly controlled laboratory conditions.

The animal toxicology studies are particularly valuable in providing both qualitative characterization of the full ranges of health effects caused in mammalian species by SO_2 and particulate matter exposures and information on the mechanisms of action underlying such effects. However, considerable caution must be applied in extrapolating quantitative dose-effect relationships defined in animal studies to humans.

Of course, some such definition of quantitative dose-effect relationships can be more directly ascertained by means of human clinical studies. Such studies, however, are also somewhat limited, in terms of the kinds of health effects potentially characterized by them. More specifically, only the effects of short-term (a few hours) exposures or perhaps a few repeated short exposures are typically investigated in such studies. Also, the nature of the effects studied are generally limited to detection of onset of relatively transient changes in pulmonary or cardiac functions and, at times, related physiological or biochemical parameters. In addition, restrictions arising from human rights

considerations often result in limitations that preclude thorough investigation
of health effects experienced by the most sensitive members of the population.

Community health (epidemiology) studies offer several advantages that go
beyond what can be determined by animal toxicology or human clinical studies,
in that health effects of both short- and long-term pollutant exposures (including
the presence of other pollutants) can be studied and sensitive members of
populations at special risk for particular effects identified. In addition,
epidemiology evaluations are not limited to the study of more or less transient
physiological or biochemical effects but also include investigation of both
acute and chronic disease effects induced by SO_x and particulate matter pollution
and associated human mortality as well. Information from epidemiology studies,
then, together with the results from animal and human clinical studies, help
to provide more complete understanding of the health effects of environmental
air pollutants such as sulfur oxides and particulate matter.

Before proceeding with evaluations of epidemiology studies in this chapter,
certain methodological considerations should be discussed as background for
the critical review that follows. Epidemiology is the study of the etiology
and natural history of disease in populations. Epidemiologic studies examine:
(1) the distribution of diseases in populations and their subgroups; (2) the
interplay of agent, host, and external environment; and (3) epidemics or
changes in the homoeostasis in populations. As such, epidemiologic studies
are important in understanding air pollution. They can be conducted in clinical
settings or among populations in communities (or subcommunities) to examine
the relationship between air pollution concentrations and health effects.
Such relationships may be found to be spurious (accidental), indirect (occurring
in the same place and/or time), or direct (such as when subclinical or clinical

disease nearly always follows exposure). The consistency of a relationship in different times and places and the strength of that relationship will generally determine the likelihood of the relationship being causal. The tendency for certain events to occur together (dose and response or stimuli and response) also strengthens the conviction that the relationship may be causal.[235,237,238,242,244] A. B. Hill added the concepts of the specificity of results and the demonstration of a biological gradient as other patterns of results highly indicative of likely causal relationships existing.[240]

There are, however, complications associated with estimating dose and measuring effects by means of community health studies. For example, certain competing risks, such as cigarette smoking and occupational exposures must be identified and taken into account in experimental design and statistical analyses of study results. Other confounding factors, such as socio-economic status, race, and weather, must also be evaluated. In all studies, the researcher accepts the exposures as they occur. Exposures are not subject to manipulation, although ambient levels change during the course of a study. It is always difficult to evaluate the long-term effect of large fluctuations in the levels of air pollution around a given mean value compared to small fluctuations around the same mean.

Population studies involve the comparisons of groups of people residing in different areas (spatial) or the change in certain measurements in the groups over time (temporal). There is no guarantee that the populations residing in different areas are anything like each other and lifelong exposure is usually not considered. There are always possible errors and biases, effects of response rate, effects of perception, and various methodological problems of both a measurement and a statistical nature.

Many epidemiological studies of the health effects of air pollutants rely on descriptive methods. When possible, covariables and confounding variables are described, and occasionally used in analysis. Health indices may use available data such as mortality statistics. Analytical approaches are more likely to involve the collection of a greater amount of data on individuals and more reliance on statistical analysis. They usually provide information on other key variables in addition to the specific dependent and independent variables (health indices and exposure levels, respectively). They usually test specific hypotheses, searching for associations between occurrence of particular diseases and potential causal agents. Prospective studies are those which start with risk or causative factors and proceed to the disease. They usually employ standardized statistical measurements and have better control of other variables. Retrospective studies (like case-control studies) start with the disease and examine risk or causative factors. They encounter difficulties in (1) ascertaining cases (a group of individuals who meet certain criteria for the presence of a certain disease process) and controls, (2) obtaining pertinent records, and (3) obtaining data on and measuring of risk factors. Such studies, however, at times lack the best probability estimates of risk. Epidemiological studies in the clinical setting, for example, involve the use of clinical techniques on patient populations to assess the effect of the environment on cases and controls.[249]

Health risks may be evaluated, according to Lowrance (1976), in four steps: identifying health effects; quantifying these effects at various concentrations of pollutant; estimating the number of people exposed at those concentrations; and calculating overall health risks associated with the given degree of concentration. In this regard, it is more difficult to determine the health effects of specific amounts of sulfur oxides emitted by specific

sources, or suspended particulate matter of specific types emitted by specific sources than it is to demonstrate a health effect of pollution in general. In addition, acute, readily detectable effects and chronic and often delayed effects due to cumulative exposures must be of concern. Also, there are limits to relating the varieties of effects to combinations of pollutants, isolating of the effects of individual pollutants, and isolating of air pollution effects from other causal contributing factors.

Making valid observations of air pollution exposures are probably the most difficult aspects of community studies. To make observation even more difficult, there is lack of consistency in the measurement techniques used over time in the United States and in other countries. (See Chapters 2, 3, and 5.) No completely satisfactory methods, for example, have been devised for deriving equivalency relationships among data for smoke, CoHs, or high-volume results, although some efforts have been made (see Chapter 3). Also, the specific measure of particulate air pollution (BS, TSP, CoH, etc.) most relevant to health effects is not yet clearly established. Few particles greater than 15 µm in aerodynamic equivalent diameter appear to reach the lower respiratory tract; but the possible significance of larger particles still needs exploration. The relative importance of individual physical/chemical characteristics of fine and coarse mode aerosols needs further exploration. (See Chapters 2, 6, and 11).

In studying the health effects of particulate matter, one difficulty is the variety of ways in which particulate pollution has been measured. Most of the measurements of particulate matter made in Great Britain and on the European continent have used the British Standard Smoke (BS) method. This is a nongravimetric method, using the light reflectance from a stained filter paper. The reflectance is calibrated against a standard Coal Smoke and given in $\mu g/m^3$.

In essence it measures the blackness of the spot. The interpretation of standard smoke measurements is influenced by the relative prevalence of black and white, grey, or other colored particulates. This method collects the smaller particle sizes that can penetrate into and be deposited deeply in the lung. Comparisons have been made in Great Britain between British Standard Smoke and total suspended particulates (TSP) as measured by the high-volume sampling methods; and TSP values have been found to generally be consistently higher than BS values at BS levels below 500 $\mu g/m^3$, reflecting the fact that high-volume samplers collect particles over a wider range of sizes. Some of these particles are not likely to penetrate into the lung, but can be deposited in the upper airways--nose and pharynx--where they can have an effect either directly or secondarily when swallowed. From certain British data and other analyses discussed in Chapter 3, a correction factor can be applied to "convert" British Smoke data to total suspended particulates as measured by the high-volume method, the measure of particulate pollution in many studies in the United States. Other studies, especially in New York, have measured coefficients of haze (CoH). Only limited information currently exists, however, regarding the relating of this measure to TSP measurements.

There are very few pollutants which have been measured over long periods of time in a great number of cities. This shortage of data is associated with two related problems. First, to the extent that the variation in the available air pollution data does not reflect the variation of all mortality- or morbidity-inducing pollutants, the estimates of the effect of sulfur oxides and particulate matter may be biased. Ambient air pollution represents a complex mix of materials, which makes the identification of the causative agent, or agents, difficult. Thus, sulfur oxides or particulate matter levels may represent indices of pollutant mixes containing other toxic agents more directly associated with health effects found to vary with SO_x and particulate matter air concentrations.

A third feature of many pollution data sets is significant colinearity. In general, places which have high particulate levels also tend to have high SO_2 levels. Although this does not limit our ability to find a "pollution" effect, it does limit an effort to partition the effect among the various pollutants being considered. With coal burning, for example, concentrations of SO_2 and particulate matter tend to fluctuate together, making it difficult to separate the relative contribution of each pollutant to any effects seen.

An additional difficulty in relating air quality to health is the possibility of a lag between an initiating exposure and its effect. The latency between the initiating insult and the detection of cancer is often many years and some health effects of air pollution may be subject to similar delayed response. On the other hand, a high concentration of sulfur oxides or particulate matter may immediately initiate some responses. In reality, time lag is a complex problem involving the weighted average of exposures in various time periods. However, almost all studies use limited data on lagged exposure and most use only current air quality to proxy the previous exposures. In serial measurement studies, the failure to consider the appropriate lagged exposures will probably result in biasing the estimated effect toward zero.

Many observational studies have estimated exposures from data obtained at monitoring sites used to represent large areas, 2 to 5 km in radius. Thus, measurements at these sites may not correspond to exposure for some individuals in the area respresented. The estimate of exposure is even less representative for persons working in other areas or significantly exposed at work. In addition, most persons spend more time indoors where the air pollution mix can be quite different.

In serial measurement studies, the average exposure in the community may not equal the ambient air quality at the monitoring site. However, if a change in air quality at the monitoring site corresponds to a proportional change in the community exposure, the monitored air quality can be used as a surrogate for actual exposure. Cross-sectional studies present a different problem when using data from a central monitoring site to measure exposure. The relationship between community exposure and central station ambient air quality may change from community to community. When many monitoring sites have been selected to monitor sources, it is possible that the dependence between community exposure and monitored ambient air quality is a function of the air quality.

Many studies have found that meteorological factors help determine ambient pollutant levels. Many studies have found that meteorological factors affect health. There is obviously a complex interaction between meteorological conditions and air pollutant levels in space and time. The meteorological variables which have been shown to be critical include: temperature, relative humidity, wind speed (and direction), precipitation, and the adiabatic lapse rate. Also included are barometric pressure, solar radiation, and other meteorological indices. Studies in which the meteorological variables are not considered along with the pollutant levels or exposures are usually judged to be lacking in critical information or in environmental factors which may influence the health indices (as well as the factors which may influence the pollutant levels themselves). Occupational exposure to pollutants can certainly have a major effect on the host, and possibly on the host's family. Interactions may also occur between the occupational pollutant exposure and the ambient pollutant exposure. Thus, studies of acute and/or chronic effects of the

SO_2/TSP complex should consider the occupational exposure effects as well.
Lifelong exposure to other pollutants from any source will influence chronic
diseases. Housing ventilation, filtration, the generation of pollutants in
indoor environments, and temperature and humidity conditions in those environ-
ments will all have a relative role in the influence on human health. As
such, they play a significant role in the effects of the SO_2/TSP complex on
the health indices. The status of the host and the host's history and genetic
makeup will influence the ways the pollutants may have an effect and on what
indices.

In addition to the SO_2/TSP exposure variables, and the health indices
(the independent and dependent variables, respectively), there are many
variables which may act as either covariables or intervening, confounding, or
spurious variables. In addition, there are temporal and spatial factors which
must be considered. Covariables are those factors which also help determine
occurrence of and variation in the dependent variable or the independent
variables. Intervening variables are those factors through which an independent
variable may have an effect on a dependent variable. Confounding variables
are those factors which, because of their direct or indirect relation to
either dependent or independent variables, have a tendency to confound the
picture unless they are taken into account. Spurious variables are those
factors which happen to be totally unrelated variables that fluctuate in time
or space in a parallel fashion to either the dependent or independent variable,
and thus may be associated with either one due to the influence of variable
time or the variable space (or similar variables).

It is important to eventually determine some form of quantitative relation
between the exposure dose and the health effect response. This will differ

with regard to type of response and will always have a time component as an additional dimension. Some attempts have been made to do this for health status as a whole.[245]

The quantification of dose-response relationships will yield a family of curves specific for different health effects and specific for factors of age, sex, etc., as well as for the addition of other environmental variables. This hypothetical family of curves might show that a given increase in exposure amount may increase the frequency of some effects, whereas those same amounts may not increase other health effects. Susceptible populations may not only have a curve that is higher than that for nonsusceptible populations, but it may have a different shape. Extrapolation of dose-response curves is a form of theoretical model building or hypothesis generation. Extrapolation does not provide the empirical evidence of effect at any given level.

Dose-response curves could be utilized as sets of damage functions for pollutants to be applied to the dose estimates for all segments of the population. Data gaps may require judgments and assumptions to be used in order to derive estimates of relationships occurring within those gaps. Although only estimates, they may be useful to suggest what changes in dosage may lead to a relative change of effects in the population exposed. Absolute change estimates may be more speculative. Certainly in a qualitative sense, one would continue to expect decreases in overall risk for those effects with decreasing pollutant levels.

Demographic and anthropomorphic measures are usually covariables. Disease occurs differentially in males and females, and at different ages. Disease may occur differentially in different race or ethnic groups independent of social status. Height and weight (body mass) have been shown to be highly

pertinent in terms of functional characteristics such as lung volume and pulmonary flows.

Smoking should be a key variable in the examination of the effects of pollutants on the health indices. Other behavioral variables which may influence the status of the host or susceptibility to certain diseases include: alcohol consumption, diet, exposures in recreational activities and hobbies, exercise, other recreation and other activities including vehicular driving.

Biological factors in the host which will influence the effect of pollution on the health indices include: resistance, susceptibility, immunity, present disease of the type being studied, and co-morbidity. Often these are not measured or measurable. Co-morbidity and present disease, however, should be known and considered. Familiar factors, including genetic factors, and exposure to microbes that can produce acute illness, also play a role in the status of the host, and thus, the potential pollutant effects.

Social economic status and cultural factors will also influence the host, not only in terms of the possibility of an effect of a pollutant on a host, but also the perception of the effect and the medical care received by the host. In comparing different areas, socio-cultural differences are often critical.

The MRC questionnaire or variations thereof has come to be the most commonly utilized tool to derive health indicators of respiratory disease. Such questionnaires generally include information on demographic variables, anthropomorphic variables, acute and chronic respiratory disease history, and may also seek information on family respiratory history, occupational exposure histories, and residential histories.[249] Standardized questionnaires have become the tool of choice. Some inter-observer variability with the MRC

questionnaire, however, has been noted; and variations have been noted with self-administration of the questionnaires. Nevertheless, comparisons of interviewer- and self-administered questionnaires have generally found good agreement. (c.f. Higgins, 1974; Lebowitz, 1980).

Questionnaires to derive information on acute changes (diaries) have been developed. The period of recall is considered critical. Such diaries have been utilized most effectively in conjunction with medical practices, house visits, phone calls, and pulmonary function testing. Frequent monitoring and follow-up with direct contact (visits or calls) are considered necessary. Motivated and understanding subjects have improved the amount and quality of the response.[234,249]

The most commonly used pulmonary function tests in epidemiological studies are peak flow and spirometry. The peak expiratory flow rate (PEF or PEFR) is the maximum flow rate during a maximum expiratory flow volume (MEFV maneuver). The instrument in general usage is the Wright peak flow meter. It is used often to measure serial changes. It predominately shows large changes in upper airway function. It has a great deal of variability and poor ability to be calibrated. However, it is a useful adjunct of acute studies; it is not otherwise generally suggested.[234,249]

Spirometry tests normally measure the forced vital capacity (FVC) and the forced expiratory volume (FEV). They are the simplest, most repeatable, valid, and among the most discriminating tests reflecting mechanics of breathing.[234,249] The subject must be coached through the MEFV maneuver.

Other tests have been used occasionally. These are more complex and are used in specialized studies to look at different properties of lung mechanics.[234,249]

Observational studies of the health effects of air pollution are sometimes viewed as natural experiments in which the exposure to pollutants varies over groups or over time. However, this view overlooks the effects of other factors influencing mortality or morbidity which may also vary over the study units. These factors are typically not subject to control by the investigator. Ideally, the influence of such variables is minimal and can be quantified. In practice, this ideal is not always achieved.[231]

Cross-sectional prospective studies compare health index differences to air pollution levels during the same time period across several locations. Such studies attempt to relate differences in community health indices to differences in air quality across communities. The adjustment for concomitant variables such as age, personal habits, and occupation is the most sensitive part of the analysis of cross-sectional data. Retrospective studies start with the disease and seek risk or causative factors. They encounter difficulties: (1) in ascertaining cases (a group of individuals who meet certain criteria for the presence of a certain disease process) and controls; (2) in terms of the inadequacy of the records utilized; (3) in obtaining and measuring risk factors; and (4) in the lack of true probability estimates of risk. Prospective studies are those which start with risk or causative factors and proceed to the disease. They usually employ standardized statistical measurements and have better control of other variables.

Randomization cannot be used in all cases to avoid selection effects. The influence of extraneous factors is sometimes partially controlled by studying population groups which are as similar as possible and which are exposed to similar environmental conditions except for air pollution level. Typically, investigators also use some method of adjustment to correct observed

associations between sulfur oxides or particulates and the health measures for differences between populations or over time in these extraneous factors. The adequacy of these adjustments depends entirely on the selection of factors and their interrelationships. Moreover, the degree of success in adjusting for selection effects is unknown. Therefore, replication and reanalysis of studies are essential to establish a pattern of association while minimizing selection effects.

Although there have been many literature reviews on SO_x and particulate matter effects,[245-248,251,301,304,107, 311, 313,314] they do not all suit the purposes of an air quality criteria document. A more exhaustive and less personal review assessment than appears in some is necessary. As a starting point in the present assessment, important information discussed in Chapter 3 is summarized regarding critical appraisal of SO_2 and particulate matter air quality measurements employed in community health epidemiology studies evaluated in this chapter. Then, the ensuing discussion of epidemiology (community health) studies is subdivided into three main subsections: Section 14.3 deals with mortality studies; Section 14.4 discusses studies relating morbidity to short-term pollutant exposures; and Section 14.5 discusses morbidity associated with long-term studies. Within each of these chapter subsections, a number of different health end points are discussed. For example, under the mortality section, studies of effects of acute air pollution episodes on deaths and death rates are delineated, as well as studies on long-term mortality trends. Under both the long- and short-term morbidity sections, studies are discussed which deal with health end points such as chronic bronchitis, respiratory diseases, pulmonary function, and aggravation of cardio-pulmonary symptoms. The main focus of this chapter is to describe the studies used and consider the interpretation of individual study results.

14.2 AIR QUALITY MEASUREMENT CONSIDERATIONS

The critical assessment contained in Chapter 3 of this document regarding practical applications of measurement approaches employed in Great Britain and the United States for determinations of air concentrations of oxides of sulfur and particulate matter are concisely summarized here as background information important for the ensuing discussion of community epidemiology studies. The information presented in part concerns published information on the relative specificity, sensitivity, accuracy, precision, and reliability of the methods discussed when used under optimum conditions in the hands of technically-expert analysts. Much more emphasis, however, is placed on evaluation of results actually obtained in the course of practical applications of the measurement methods, often by less technically-skilled personnel. That evaluation draws mainly upon published commentary on quality control assessments for the different applications. Also, the major focus here is on British and American air measurement approaches most widely used in acquiring SO_2 and particulate matter data utilized in published quantitative community health studies of interest later.

14.2.1 British Approaches

14.2.1.1 British SO_2 Measurements--As noted earlier, the lead dioxide gauge was used extensively in Britain during the years prior to 1960. However, use of the hydrogen peroxide method was gradually interspersed with the lead dioxide gauge during the course of the 1950s, often being coupled in tandem, as it were, with the apparatus for smoke measurements. Much of the early (1950s) British epidemiology data discussed later in this chapter has been related to SO_2 measurements obtained by the hydrogen peroxide method, especially where 24-hr SO_2 values are used. Nevertheless, it is useful to compare the

results obtained with the two methods, since some British air quality data of
historical interest are derived from the lead dioxide method.

In 1962, as part of the establishment of the British National Air Pollution
Survey, a working party was set up to compare the lead dioxide gauge with the
hydrogen peroxide method, which was then chosen as the standard method for use
in the Survey. As quoted in <u>Atmospheric Pollution</u>, 1958-1966 (WSL, 1967): [344]

> The hydrogen peroxide method is subject to the limitation that
> its reaction is not confined to sulphur compounds; the lead dioxide
> method has the limitation that the extent of the reaction can be
> substantially influenced by weather conditions. Despite limitations,
> both methods estimate pollution by sulphur compounds; the hydrogen
> peroxide method is somewhat more complicated, but has the outstanding
> advantage that it can measure concentrations of pollution over short
> periods; the lead dioxide method is simple in operation, but it is
> incapable of measuring concentrations over short periods.

> Even so, it was considered desirable to compare the results
> from the two types of instrument under controlled conditions. A
> statistical analysis was made by Warren Spring Laboratory of results
> from a group of 20 sites at which both lead dioxide and hydrogen
> peroxide instruments had been operated over a period of 48 months.
> The 20 sites selected were those with a reasonably complete set of
> results from March 1957 to February 1961 at which the two instruments
> were not more than 100 feet apart.

> The correlation between 829 pairs of results from the 20 sites
> over a period of four years was highly significant, showing that
> both instruments were predominantly affected by the same pollutant,
> sulphur dioxide.

The WSL (1967) [344] report presents a plot of these data shown below as Figure
14-1, with the lead dioxide data reported as mg $SO_3/100cm^2$ day.

The ± 2σ confidence limits shown in Figure 14-1 correspond to ± 1.8 mg
$SO_3/100$ cm^2/day for a given hydrogen peroxide reading and ± 0.18 mg SO_2/m^3 for
a given lead dioxide reading. The WSL (1967) [344] report concludes:

> "The analyses carried out indicated that there is no generally
> applicable calibration for relating lead dioxide and hydrogen peroxide
> results. The conversion from lead dioxide to hydrogen peroxide
> reading is not recommended except to give a rough indication of the
> levels of concentration concerned, the degrees of approximation
> being as indicated by the preceding paragraphs."
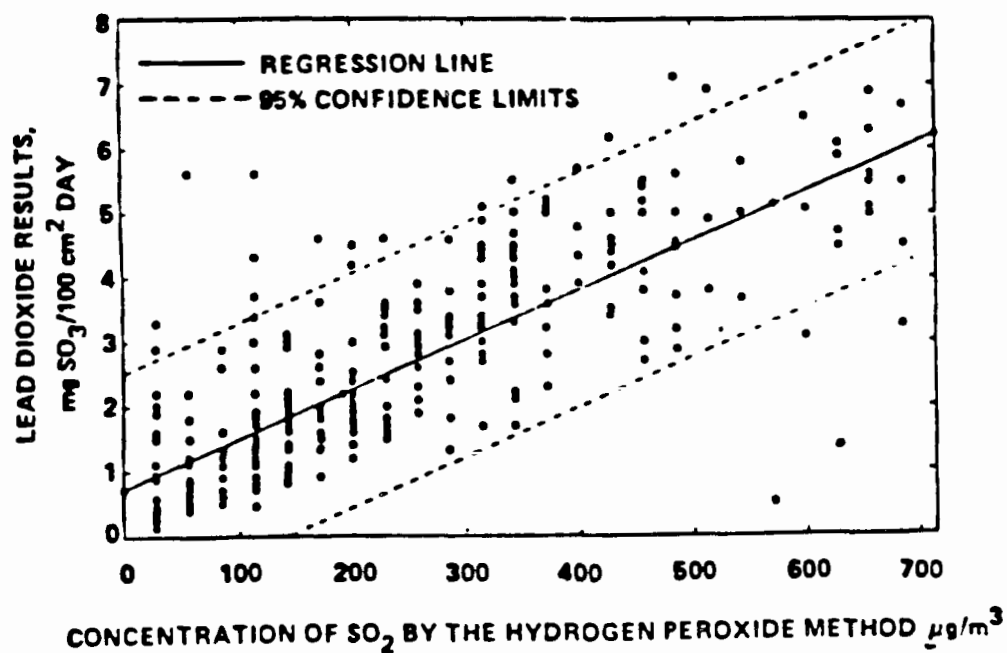
Figure 14-1 A comparison of lead dioxide and hydrogen peroxide methods for sulfur dioxide showing wide variations between simultaneous measurements. The solid line is the regression line, and the dotted lines are the 95 percent confidence limits. From WSL (1967).*344*

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In other words, estimates of SO_2 levels derived from lead dioxide sulfation rate measurements, especially 24-hr estimates, can only be roughly compared with SO_2 estimates obtained by the hydrogen peroxide method at other geographic sites or at later times at the same location(s). Also, from the data in Figure 14-1, comparisons between sulfation rate readings may only be meaningful when such readings differ by the equivalent of about 180 $\mu g/m^3$ of SO_2. Some of the types and magnitudes of errors encountered in the British application of lead dioxide gauges to measure SO_2 levels are summarized in Table 14-1. As shown in Table 14-1, several problems (e.g., humidity and temperature effects) result in the lead dioxide method being essentially useless for 24-hr. measurements and in their otherwise having a rather large (± 180 $\mu g/m^3$ 2σ) error band associated with them.

Based on some of the above problems, when the National Survey began in 1961 it was recognized that the lead dioxide method could not provide the 24-hour SO_2 measurements necessary for correlation with mortality and morbidity effects investigated by epidemiology studies. The hydrogen peroxide method for SO_2 was, therefore, adopted as being more valid than the old lead dioxide gauge sulfation method. Because many of the staff making the measurements would be the same people who had been servicing particle deposit gauges and the lead candles without detailed technical knowledge of the analyses, however, an Instruction Manual (IM) issued by WSL in 1966 had to be quite detailed and clearly readable by people with no training in analytical techniques.

As mentioned above, the lead peroxide method was selected because its sensitivity, reliability and precision were demonstrated to be much better than that obtained in comparison to the lead dioxide method. More

TABLE 14-1. SUMMARY OF EVALUATION OF SOURCES, MAGNITUDES, AND DIRECTIONAL BIASES OF ERRORS
ASSOCIATED WITH BRITISH SO$_2$ MEASUREMENTS

Time period	Measurement method	Reported source of error	Direction and magnitude of reported error	Likely general impact on British SO$_2$ data
Pre-1961	Lead Dioxide	Humidity (RH)	Reaction rate increases with RH.	Variable positive bias, especially in summer.
		Temperature (T)	Reaction rate increases 2% per 5° rise.	Variable positive bias, especially in summer.
		Wind speed (WS)	Reaction rate increases with WS.	Variable positive bias, under high wind cond.
		(Overall errors)		Can be up to ± 180 µg/m^3 (2σ).
1961-1980 (British National Air Pol. Survey)	Hydrogen Peroxide	Siting of Sample Line Intake:		
		a. too near boiler chimneys	50 - 100 µg/m^3 overestimation.	Occasional (prob. rare) positive bias.
		b. too near vegetation	50 - 70 percent underestimation.	Occasional (prob. rare) negative bias.
		Sample Line Adsorption:		
		a. Good care & cleaning	10 µg/m^3 underestimation.	Possible general 10 µg/m^3 negative bias.
		b. Average care	20-25 µg/m^3 low from 50 µg/m^3.	Occasional 40-50% negative bias.
		c. Poor care (insects, dirt)	Probable greater underestimation.	Likely rare 50-90% negative bias.
		Flow Meter Problems:		
		a. Daily normal conditions	± 3 percent variation.	Negligible impact. Presumed ±3% precision of data.
		b. 8-port unit with only one weekly flow reading	± 5 percent variation.	-5% negative bias on high SO$_2$-BS days. +5% positive bias on low SO$_2$-BS days.
		Allowable Filter Clamp Leakage	1-2 percent underestimation.	Negligible impact. Presumed ±2% precision of data.
		Poor Clamp Care & Technique	5-10 percent underestimation.	Likely occasional 5-10% negative bias.
		Grade B Glassware Usage	2-5 µg/m^3 underestimation.	Negligible impact.
		Improper Alkalinity Buffering	5-10 µg/m^3 underestimation.	Occasional 5-10 µg/m^3 negative bias.
		CO$_2$ in Demineralized in H$_2$O	40 µg/m^3 low from 50 µg/m^3 monthly mean.	Occasional negative bias of up to 80%. [b]
		Atmospheric Ammonia	25 µg/m^3 underestimation on 10% of summer samples in urban areas. <80 µg/m^3 low on ind. days & 40 µg/m^3 low monthly summer mean in country areas.	≥25 µg/m^3 neg. bias on 10% of summer samples in urban areas. Occasional neg. bias in country areas- up to 80 µg/m^3 daily data & up to 100% monthly mean in summer.
		Titration Error:		
		a. Normal-sharp color change of indicator at pH 4.5	±5 µg/m^3 error in determination.	Presumed ± 5 µg/m^3 precision of data.
		b. Gradual color change of indicator at pH 4.5	±10 µg/m^3 error in determination.	Actual ± 10 µg/m^3 precision level. [c]
		c. Rounding off to 0.1 ml of alkali volume added.	±5 µg/m^3 error in determination.	Added ± 5 µg/m^3 precision error. [c]
		Evaporation of reagent:	≤15 µg/m^3 overestimation, especially in summer months.	15-100% pos. bias for SO$_2$ data <100 µg/m^3. 7.5-15% pos. bias for SO$_2$ of 100-200 µg/m^3. 3.25-7.5% pos. bias for SO$_2$ of 200-400 µg/m^3. ≤3.25% pos. bias for SO$_2$ data >400 µg/m^3.
		Temperature and Pressure:		
		a. Corrections - normal	5% underestimation.	General 5% neg. bias in SO$_2$ data.
		b. Large ΔP at filter	10% underestimation.	Occasional ~ ±10% negative bias in SO$_2$ data.

[a] Data from 1965-1968 most clearly impacted.

[b] Data from 1966-1967 most clearly impacted.

[c] At ≤50 µg/m^3 uncertainty due to these two errors is ~ 7 µg/m^3 or 14%. That is, 68% of the data are within 14% and 5% are >28% in error.

specifically, the British Standard for sulfur dioxide determination by the hydrogen peroxide method states that replicate determinations can be expected to be within ±20 $\mu g/m^3$ for concentrations up to 500 mg/m^3 and within ±4 percent for concentrations above 500 $\mu g/m^3$; and an OECD Working Parting stated the accuracy of the method to be $\pm10\%$ at levels >100 $\mu g/m^3$. However, as summarized in Table 14-1, numerous sources of errors have been encountered in the practical application of the method in collecting data for the British National Survey over the past 15-20 years.

Certain of the sources of error listed in Table 14-1, it can be seen, resulted in relatively small errors, whereas others produced errors ranging up to 50-100% in magnitude. Also, some errors appear to have been restricted to affecting data from only limited locations (usually unspecified as to specific names of localities) or during only limited time periods. Many of these types of errors appear to have been detected fairly quickly and steps taken to successfully correct or minimize them. Still other sources of errors exist (e.g., those from reagent evaporation), which have likely affected essentially all British National Survey SO_2 data. Some of these appear to remain uncorrected to this date, in some cases more than 10 or 15 years after they were first detected and brought to the attention of Warren Spring Laboratory officials responsible for overseeing quality control for the entire National Air Pollution Survey. See Chapter 3 for a more detailed discussion of each type of error.

Taking the above information into account for present purposes, it would be extremely difficult to determine precisely which errors affected particular National Survey data sets employed in British epidemiology and other studies discussed later in this chapter. That would likely require a thorough examination, on a time- and site-specific basis, of records detailing information on

how each pertinent data set was collected and WSL quality control assessment
reports for the data sets. Alternatively, in later evaluations of British
epidemiology studies one could accept the following overall evaluation and set
of conclusions by the WSL (1975) regarding British National Survey air pollution
data (emphases added):

> The actual degree of accuracy attained in the Survey is not known.
> Input data are scrutinized by WSL staff, and subjected to computer
> checks, and any reflectances, titres, or air flows which are abnor-
> mally high or low or show unusually abrupt changes from one day to
> the next are queried and data known to be invalid are excluded from
> the annual summary tables. Such checks can however eliminate only
> some of the gross errors. More information will become available on
> accuracy when current (1974) plans to institute additional quality
> control, e.g., on reagent solutions, are put into operation.
> However, although the accuracy of the Survey data cannot at present
> be quantified, many of the errors discussed in the previous para-
> graphs will cancel out when data are averaged over periods of a few
> months or a year, or for groups of sites. The remainder tend to
> show up as anomalies when data are compared with past or subsequent
> data at the same site or with data from other sites; anomalies of
> this kind have been commented upon throughout the Reports. Members
> of Warren Spring Laboratory staff have devoted a large effort over
> the years to site visiting and checking on procedures. It is their
> experience that the vast majority of the instruments are maintained
> and operated with reasonable care and accuracy. The Laboratory is
> therefore confident that the accuracy is sufficient for the type of
> data analyses carried out in the present series of reports.

Presumably, it is the opinion of the WSL and British epidemiologists that the
accuracy of the survey data is also sufficient to meet the original objectives
of the Survey, ie. to assess the benefits accruing from the Clean Air Act of
1956, which requires use of the survey air quality data along with community
health endpoint evaluations in order to define quanititative air pollution/health
effects relationships. That this presumption is likely correct is further
attested to by the long history of reliance on these data by British epidemio-
logists, such as in the making of statements regarding such quantitative relation-
ships in innumerable journal articles and reviews appearing during the past
twenty years, up to and including the very recent review by Holland et al. (1979).[301]

14.2.1.2 <u>Daily Smoke Measurements of the United Kingdom National Survey</u>--The general technique for the British Smoke shade (BS) measurement is described in detail in Chapter 2, and a detailed critical assessment of the measurement procedure is provided in Chapter 3 to allow for evaluation of the precision, accuracy, and reliability of the measurements. Also, details of the BS measurements are provided by an Instruction Manual (IM) issued by (Warren Spring Laboratory in 1966. At the start of the National Survey in 1961 (WSL, 1961) it was recognized: "The daily instrument, while comparatively simple in design and operation gives reliable results <u>in good hands</u>* and seemed the best choice for the National Survey." WSL circulated the specifications of the apparatus and methods to all the cooperating organizations as careful, uniform work was essential if the results from the different sites throughout the country were to be comparable. However, WSL found that detailed instructions were necessary as most of the Local Authority staff making the measurements had no training in analytical techniques. These methods were reviewed by an O.E.C.D. Working Party and a report "Methods of Measuring Air Pollution" (OECD, 1964) was prepared, which was accepted into the British Standards Specification 1747, Parts 2 and 3. The Manual of Instruction (WSL, 1966) incorporated the improvements in techniques, "but apparatus and procedures are specified in much greater detail to assist operation by observers with <u>no technical knowledge</u>."*

Partly due to the lack of analytical training of survey monitoring site operators, and other factors as well, various errors were encountered in carrying out BS measurements for the National Survey.

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*Underline added for present emphasis.

Table 14-2 summarizes information discussed in Chapter 3 on the sources,
magnitudes and directional biases of errors associated with British smoke
measurements during the past 30 to 40 years. For example, prior to 1961, the
use of weights for sealing purposes led to highly variable errors in BS
measurements due to leakage at filter clamps, and steps were taken to require
screw-down clamps as standard procedure as part of the later British National
Survey work implemented after 1961. It is not clear to what extent any specific
British BS data sets from the 1950s may have been affected by the clamp leakage
problem, but one must assume that such errors could not have often been very
large or serious and that the WSL took appropriate steps to eliminate or
invalidate any data in gross error as they were detected via their quality
control efforts in the late 1950s. Analogously, there is evidence that WSL
did take steps to inform users of pre-1961 BS data of errors arising from (1)
comparing reflectance on filters to photographs of painted stains and (2) use
of reflectance readings below 25 percent, where the stain was too dark to use
the Clark-Owens DSIR curve. However, it also appears that only a few investigators
(e.g., Commins and Waller, 1970) took steps to go back and correct published
reports based on the affected pre-1961 data and to publish revised analyses
taking into account corrections for the pre-1961 data errors.

Probably of much greater concern than the pre-1961 BS measurement errors
are those encountered after the establishment and initial implementation of
the British National Survey in 1961. These include certain errors, e.g., the
"computer error of 1961-1964," which were eventually detected by WSL and
resulted in steps being taken to correct affected BS data in National Survey
data banks. It is clear, however, that whereas users of the affected data may
have been informed of such errors by WSL, virtually none of them have taken

TABLE 14-2. SUMMARY OF EVALUATION OF SOURCES, MAGNITUDES, AND DIRECTIONAL BIASES OF ERRORS
ASSOCIATED WITH BRITISH SMOKE (PARTICULATE) MEASUREMENTS

Time period	Measurement method	Reported source of error	Direction and magnitude of reported error	Likely general impact on published BS data
1944-1950s	Smoke filter	Leakage at clamp. Weights used to make the seal.	Highly variable under-estimation of BS levels.	Probable widespread highly variable negative bias.
Pre-1961		Comparing reflectance to photographs of painted standard stains.	Depending upon observer and value of R.	Probable widespread relatively small negative bias.
		Reflectance (R) below 25%, stain too dark with use of Clark-Owens DSIR curve.	50-100% underestimation.	Occasional 50-100% negative bias in some data sets.
1961-1964		Computer not following proper calibration curve.	$\leq$80% underestimation at low R if not corrected by WSL (See Moulds,1961) and discussion of clamp size correction factor.	Negligible for BS <~100 $\mu g/m^3$. Increasing negative bias up to 80% as BS values increase over 100 $\mu g/m^3$.
1964-1980		Clamp correction factor for other than 1-inch clamp.	Uncertain; derivation cannot be verified. Possible $\pm$20%.	Possible underestimate for 2-inch and 4-inch clamps. Possible overestimate for 1/2-inch and 10 mm clamps.
		Flow rate - normal 1 day. Flow by 8-port with 1 reading per week.	+3% variation. -10% underestimation. +10% overestimation.	Presumed $\pm$ 3% precision level. 10% negative bias on high BS days. 10% positive bias on low BS days.
		Variability of reading reflectance.	$\pm$2 units of R	Error increases with BS level from $\pm$10% at 50 $\mu g/m^3$ up to $\pm$20% at 400 $\mu g/m^3$.
		Averaging reflectance instead of averaging mass/cm^2.	Highly variable under-estimation due to non-linearity of R.	Probable small negative bias at low BS levels, could be large at high BS.
		Use of coarse side of filter facing upstream.	6-15% underestimation.	Occasional negative bias of 6-15%.

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TABLE 14-2 (continued).

Time period	Measurement method	Reported source of error	Direction and magnitude of reported error	Likely general impact on published BS data
		Reading of wrong side of stained filter.	50-75% underestimation.	Occasional negative bias of 50-75%.
		Leakage at filter clamp a. Normal, with good care b. With inadequate care. c. Careless loading where uneven stains are produced.	1-2% underestimation. 2-8% underestimation. 10-20% underestimation.	General 1-2% negative bias. Occasional 2-8% negative bias Occasional 10-20% negative bi
		Use of wrong clamp size a. Stain too light R>90%. b. Stain too dark R<25%.	Highly variable over-estimation. Highly variable under-estimation.	Data usage not recommended. Data usage not recommended.

steps to (1) alert recipients of publications containing analyses based on the affected data of the likely inaccuracies or ranges of error involved; (2) to reanalyze the study results based on the affected data sets; or (3) to reissue or publish anew any revised analyses. In fact, even some Warren Spring Laboratory quality control literature prepared and published during the 1960s or 1970s and still in use may contain incorrect information and recommended standard procedures for BS measurements based on analyses "contaminated" by computer errors or other problems summarized in Table 14-2 and discussed in more detail in Chapter 3.

In regard to determining which British BS data sets and related epidemiology studies are affected by different post-1961 National Survey errors, it is again presently very difficult, as was the case with British SO_2 measurements, to specify with any confidence the nature and magnitude of specific errors impacting particular studies. This would probably require thorough examination of records and WSL quality control reports concerning each of the pertinent data sets. On the other hand one can project that certain data sets and British epidemiology studies were almost certainly affected by some subset of BS measurement errors and these are taken into account in evaluating such studies later this Chapter. For example, published reports of the "Ministry of Pensions" [62] (1965) and Douglas and Waller [96] (1966) studies contain specific reference to usage of National Survey data from the 1961-64 period and, therefore, the results of those studies should be reevaluated in light of measurement errors reported by the WSL for that period.

14.2.2 American Approaches

14.2.2.1 American SO_2 Measurements--Turning to American measurement approaches, different types of measurement methods for a given pollutant were adopted by

various local, state, and federal agencies in establishing or expanding air quality monitoring systems that proliferated across the United States during the 1950s and 1960s. Rather than discuss methods used for SO_2 measurements by all of the different American air monitoring systems, main emphasis is placed here on the discussion of only certain key American applications of measurement methods for SO_x that are of crucial importance for later discussions of quantitative relationships between health effects and atmospheric levels of sulfur dioxide. These include mainly applications of SO_2 measurement methods as employed in the EPA "CHESS Program" as the single largest attempt to define quantitative relationships between air pollution and health effects.

In regard to sulfur oxides measurement approaches used in the United States, lead dioxide or other "sulfation rate" measurement methods were, as in Britain, widely employed prior to the early 1960s for assessing SO_2 air levels. However, probably to a somewhat greater extent than in Britain, sulfation rate measurement techniques continued to be used later into the mid or late 1960s by some monitoring programs in the United States or in connection with certain community health epidemiology studies, as discussed later in this chapter. As shortcomings of the "sulfation" methods became more widely recognized, however, their use was generally abandoned and more specific methods for the measurement of SO_2 or other sulfur oxide compounds were adopted, as was done in Britain. The hydrogen peroxide acidimetric method (see OECD, 1965) selected for use in the British National Air Pollution Survey, however, was not very widely adopted in the United States for SO_2 measurements. Rather, versions of West-Gaeke (1956) colorimetric procedures were much more widely used in the USA. Conductivity measurements for SO_2 (Adams et al., 1971). based on an acidimetric method adaptation often used in automatic instruments and most suitable for measuring

periods of around 24 hours, later began to be applied in the operation of some American air monitoring networks in the 1970s.

The West-Gaeke method was the method mainly employed in the EPA "CHESS Program" for determining SO_2 air levels for inclusion in analyses of community health end point data in "CHESS" epidemiology studies. The application of that method in the CHESS Program was accordingly most thoroughly discussed in Chapter 3. The types of errors in measurement associated with CHESS SO_2 data are summarized in Table 14-3, along with notation of some factors affecting earlier sulfation methods. Much of the information on the former subject is derived from a 1976 Congressional Investigative Report (IR)[107] which contained a thorough evaluation of EPA CHESS Program air quality measurements and other aspects of the Program.

Looking at the types of errors associated with earlier American use of sulfation rate lead dioxide methods, similar effects of temperature, humidity, etc., as affected analogous British SO_2 methods are seen to apply here to American data as well.

Turning to American applications of SO_2 measurements since the widespread abandonment of sulfur dioxide sulfation rate methods in the mid to late 1960s, several different types of errors were identified as being associated with EPA CHESS Program SO_2 measurements via a thorough evaluation of the CHESS Program, as reported in the IR[107] (1976). As can be seen, the magnitudes of some errors in CHESS SO_2 measurements spanned about the same range as those seen for British National Survey SO_2 measurements and, at times, derived from analogous sources of error, e.g., evaporation or other loss of reagents. In the case of the American CHESS Program data, however, the specific overall impact of the various detected errors on particular CHESS data sets appears to have been more definitively defined by the work of the IR[107] (1976); more specifically, it

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TABLE 14-3. SUMMARY OF EVALUATION OF SOURCES, MAGNITUDES, AND DIRECTIONAL BIASES OF ERRORS
ASSOCIATED WITH AMERICAN SO_2 MEASUREMENTS

Time period	Measurement method	Reported source of error	Direction and magnitude of reported error	Likely general impact on American SO_2 data
1944-1968	Lead dioxide.	Humidity (RH).	Reaction rate increases with RH.	Variable positive bias, especially in summer.
		Temperature (T).	Reaction rate increases 2% per 5° rise.	Variable positive bias, especially in summer.
		Windspeed (WS).	Reaction rate increases with WS.	Variable positive bias, especially in summer.
		Saturation of Reagent (sulfation plate mainly).	Variable underestimation beyond pt. where 15% of PbO_3 on plate reacted.	Possible large negative bias, especially for 30-day samples for summer monthly readings.
		(Overall Errors).		Generally wide ± error band associated with data. Possible negative bias up to $\geq$100%, mainly in summer, with 30-day reading.
1969-1975 (EPA CHESS PROGRAM)	West-Gaeke Pararosaniline.	Spillage of reagent during shipment.	18% of total volume 50% of time; occasional total loss	Half of SO_2 data likely negatively biased by mean of 17%; some up to 100%.[a]
		Time delay for reagent-SO_2 complex.	SO_2 losses of 1.0, 5, 25, and 75% at 20, 30, 40, and 50°C, respectively.	Usually small (<5%) negative bias, but consistent negative summer bias up to 25% at 40°C temp, extreme.[b]
		Concentration dependence of sampling method.	Underestimation of unspecified magnitude at daily SO_2 >200 $\mu g/m^3$.	Probable general negative bias in daily, monthly, and yearly SO_2 data.[b]
		Low flow correction.	±10% to 50% variable error.	Usually error of < ±10%; occasionally up to ± 50% in daily, but dampened statistically in annual mean.[b]
		Bubbler train leakage.	Small underestimation error of unspecified magnitude.	Slight negative bias suspected.[b]
		(Overall errors).		From Nov., 1970, to Dec., 1971, data biased low by 50-100%. From Nov., 1971, to conclusion of CHESS Program in 1975, fall-winter data appear valid but summer data biased low by maximum of 60-80%. From 1972 to 1975 annual average data approximately 15-20% low. Daily data highly random, not useful.[c]

[a]November, 1970, to April, 1973, CHESS Program data impacted before error corrected.
[b]Applies to CHESS Program SO_2 data from all years 1970-1975.
[c]As summarized by Congressional Investigative Report (IR, 1976).[07]

appears that the CHESS data generally tended to be somewhat negatively biased in comparison to other local or state SO_2 data from monitoring sites proximal to the CHESS sites, with the local and state data judged by the IR[107] (1976) to be reasonably accurate and reliable. The specific magnitude of the negative bias for particular years of CHESS data is summarized in Table 14-3, and appears to have been around 30-40% in some circumstances and up to around 100% in other cases.

14.2.2.2 American High-Volume TSP Sampling Measurements

As discussed earlier, the hi-volume TSP sampler, since its development in the early 1950s, has been the instrument most commonly used in United States for measurement of atmospheric particulate matter; and high-volume TSP readings have most typically been used in American epidemiology study evaluations of associated air pollution-health effects relationships. In contrast, other particulate matter measurement approaches (e.g., the coefficient of haze method) saw only relatively limited application during the 1950s and early 1960s in certain American locations and were infrequently used in estimating quantitative relationships between airborne particulate matter and health or welfare effects. Accordingly, major emphasis is placed below on the critical appraisal of certain key applications of hi-volume TSP measurements in the United States. As before, in discussing American applications for measurement of oxides of sulfur, the present summarization focuses most heavily on evaluation of applications of TSP measurement methods employed as part of the EPA "CHESS Program," as the single most extensive and comprehensive use of such methods as part of American community health epidemiology studies. Much of the information is derived from the 1976 Congressional Investigative Report (IR), which included a thorough analysis of EPA CHESS Program TSP measurements and comments regarding certain local or state TSP measurements.

The main sources, directions and magnitudes of errors identified as possibly affecting American TSP measurements are summarized in Table 14-4. In addition to various sources of minor errors inherent to the basic TSP sampling method, certain other nuances of procedures included in the Federal Reference Method (40 CFR 50, Appendix B) may have resulted in the introduction of an additional slight negative bias in TSP data obtained by American researchers. This, more specifically, pertains to the manner in which flow rate calculations are made upon which final TSP concentration determinations are based.

The Federal Reference procedure calls for the averaging of the initial and final recorded airflow rates. However, as described in Appendix 3-A of Chapter 3, the uncontrolled flow rate drops more rapidly at the start of the run than at the end of the run. Therefore, a linear approximation leads to an overestimate of the *average* flow rate, which will reduce the *calculated concentration* measured value. Consequently, all TSP data computed in this manner have a slight negative bias which is likely usually of the order of 5 percent; on occassion, however, under circumstances where the flow rate may have fallen below 40 ft^3/min, larger errors (up to approximately 15 percent) may have been introduced. Assuming that monitoring site operators in the United States adhere to the recommended Federal Reference Method procedures, then this type of bias is likely inherent in essentially all American TSP data collected without flow rate control or recording. Despite such problems, it can be seen that the maximum range of uncertainty derived from the various errors associated with American TSP measurements is generally less than 20 percent in either a positive or negative direction on a random (±) basis.

TABLE 14-4. SUMMARY OF EVALUATION OF SOURCES, MAGNITUDES, AND DIRECTIONAL BIASES OF ERRORS
ASSOCIATED WITH AMERICAN TOTAL SUSPENDED PARTICULATE (TSP) MEASUREMENTS

Time period	Measurement method	Reported source of error	Direction and magnitude of reported error	Likely general impact on published TSP data
1954-1980	Staplex Hi Vol TSP	Time Off (Due to power failure).	Variable underestimation.	Negligible impact, rare negative bias.
		Weighing error.	±2% random variation.	Negligible impact.
		Flow measurement (with control).	±2% random variation.	Negligible impact.
		Flow measurement (without control) a. Constant TSP--Average of flows.	.	
		1. Low TSP level.	2% underestimation.	Negligible impact.
		2. High TSP level.	5-10% underestimation.	Possible 5-10% negative bias.
		b. Rising TSP-Average of flows.	10-20% underestimation	Possible 10-20% negative bias.
		c. Falling TSP-Average of flows.	10-20% overestimation.	Possible 10-20% positive bias.
		Aerosol evaporation on standing.	1-2% underestimation.	Probable negligible impact.
		Condensation of water vapor.	5% overestimation.	Possible 5% positive bias.
		Foreign bodies on filter (Insects).	Generally small over-estimation.	Possible 5% positive bias.
		Windblown dust into filter during off-mode.	Generally small over-estimation.	Occasional (rare) positive bias.
		Wind speed effect on penetration of dust into the Hi-Vol shelter.	Less penetration at high windspeed.	Occasional (rare) negative bias.
		Wind direction effect due to Hi-Vol Asymmetry	Higher penetration when normal to sides.	Probable increase in random (±) error.
		Artifact formation, NO_3^- $SO_4^=$	5-10 µg/m³ overestimation.	Occasional positive bias.

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TABLE 14-4 (continued).

Time period	Measurement method[a]	Reported source of error	Direction and magnitude of reported error	Likely general impact on published TSP data
1969-1975 (EPA CHESS Program).	Fed. Reference Method Standard Hi-Vol Sampler	Loss of sampling material in field.	No specific estimate of magnitude of error; but would be underestimation.	Probable slight negative bias in Utah winter data. No known impact on other CHESS TSP data.
		Loss of sampling material in mailing.	Reported 4-25% apparent loss; max. likely due to crustal (sand, etc.) fall-off from selected Utah sampling sites.	Probable general small <10% negative bias; occasional 25% negative bias.
		Evaporation of organic substances.	No specific estimate of error magnitude, but not likely to exceed 5% underestimation.	Probable slight negative bias of <5% for TSP data from urban/industrial areas.
		Windflow velocity and asymmetry.	No specific estimate of error magnitude; but most likely to increase random variation or small underestimation.	Negligible impact or slight negative bias.
		(Overall errors).		Generally <10% negative bias; occasional 10 to 30% negative bias.[a]

[a] As summarized by Congressional Investigative Report (IR).

Errors in addition to general TSP measurement errors reported by the 1976 Congressional Committee Investigative Report (IR, 1976) to affect CHESS Program TSP measurements during 1969-1975 are broken out and listed seperately in Table 3-5. Some of those errors (e.g., loss of sample materials in filter removal from the field monitoring apparatus) were reported by the IR (1976) as likely affecting only very restricted CHESS data sets. Others, e.g., errors due to loss of sample in mailing, appear to have been more widespread and presumably impacted on many CHESS data sets. It is interesting to note, however, that the IR (1976) concluded that the net effect of all of the errors was to introduce, in general, a slight negative bias of 10 to 30 percent into CHESS TSP data, which is not much beyond the range of different types of errors (e.g., linear flow corrections) more generally associated with American applications of TSP measurements. Section IV C 3 of the IR (1976) further concluded that:

> "...the TSP data were by far the best quality data taken in the CHESS monitoring program. Differences measured between High and Low sites are probably reasonable estimates of the differences of TSP exposures as received by populations in these areas."

It appears reasonable to concur with the IR (1976) and, accordingly, to accept CHESS TSP measurements as reasonable estimates of TSP exposures of CHESS Program community health study populations, taking into account that such data may by biased low by no more than 10 ~~or, at most,~~ *to* 30 percent.

14.3 AIR POLLUTION AND MORTALITY

14.3.1 Introduction

Mortality represents the ultimate end point of many disease processes. Estimates of mortality rates are generally fairly accurate in most places for most time periods. On the other hand, mortality rate is not necessarily a

sensitive indicator of the effect of pollution at any given place or time, since it may be related to various lengths and types of exposures. Also, recorded cause of death may or may not be accurate, necessitating additional care in assessing reports of pollution-associated increases in cause-specific mortality. Daily mortality varies greatly and its relationship to fluctuations in ambient air levels may be fortuitous or may represent a trend that started anywhere in the past (days, weeks, or years earlier). Despite the above problems, numerous studies have attempted to determine possible relationships between air pollution, including elevated levels of SO_x and particulate matter, and documented increases in mortality rates.

Studies of mortality tend to fall into three broad categories: (1) episode studies examining the effects of very high pollution levels lasting, at most, for a few days; (2) studies in which short-term fluctuations in pollution and mortality are monitored over more extended time-periods for a particular population, and (3) cross-sectional studies in which mortality and pollution are compared across different geographic areas. The earliest mortality studies had limited estimates of pollution, and the numbers of deaths were compared with those from other periods of time with the hope that similar conditions prevailed except for air pollution. Often the differences are large enough to be convincing in spite of the lack of complete information on other pertinent data.

Short-term effects studies are usually limited to a well-defined population that is followed through time. Since the period of time is relatively short, it is usually safe to assume that the population has remained constant with respect to age and composition. These studies are very sensitive to temporal

variables such as influenza cycles, ambient temperature and other meteorologic factors, season, day of the week, and even holidays. Confidence can be best placed in those studies of this type where the contributions of such factors are either controlled for or otherwise properly adjusted for or taken into account.

Long-term studies usually compare mortality rates over long periods of time such as one to twenty years. The comparisons are usually cross-sectional, that is, between geographic areas. Temporal factors are less important, but the demographic characteristics of the study areas are critical. Among the more important factors are age, race or ethnic differences, sex, socioeconomic status, in-out migration, smoking habits, and general health care. The location of monitoring sites in each area is also extremely important in long-term studies. If the monitors in some geographic areas are in industrial locations while the monitors in other areas are in residential locations, the differences that are ascribed to ambient air pollution may actually represent other differences between industrial and residential locations.

14.3.2 Acute Episodes

Detailed study of the human health effects associated with episodes of severe air pollution spans a period of less than 50 years. The earliest reliable documentation of such episodes describes an incident in the Meuse Valley of Belgium in 1930.[1]

An intense fog covered the Meuse Valley from Liege to Huy[1,201] from December 1 to 5, 1930, and was accompanied by an anticyclonic high pressure area with low winds and large amounts of fine particulate matter. Sixty deaths associated with the fog occurred among residents of the Valley on

December 4 and 5. The people who died were sick for only a short time. Although there were no other immediate deaths, several persons affected by the fog died much later from complications associated with fog-induced injuries. The death rate in the area was 10.5 times normal. The illnesses abated rapidly when the fog dispersed.

A similar but smaller event occurred in Donora, Pennsylvania.[149] Donora was blanketed by a dense fog during late October 1948, which adversely affected 43 percent of the population. Twenty persons died during or shortly after the fog, and 10 percent of the population was classified as being severely affected. No pollution measurements were made during the incident but the investigators concluded that no single chemical agent was responsible. Sulfur dioxide, its oxidation products and particulate matter were undoubtedly significant contaminants. During subsequent inversion periods, presumably not as severe as the one in October 1948, daily averages of sulfur dioxide as high as 0.4 ppm (~1140 $\mu g/m^3$) were recorded.[205]

A pollution episode also occurred on December 5 to 9, 1952 in London.[2,202-204] Monitoring sites near the center of the fog averaged 1.98 mg/m^3 British Smoke (BS) with an average maximum of 2.65 mg/m^3; the maximum BS reported was 4.46 mg/m^3 for a 48 hr sample. The corresponding mean values for SO_2 were 0.91 ppm, 1.26 ppm and 1.34 ppm. Four thousand excess deaths were noted during the fog. As shown in Figure 14-2, the death rate began to rise within 24 hours of the beginning of the pollution episode and fell abruptly to slightly elevated levels when the fog abated. Most deaths occurred among people with pre-existing disease, including bronchitis (tenfold increase in deaths) and coronary heart disease (threefold increase). It has been noted that influenza present in London at the time may have also influenced the reported death rate.[301]
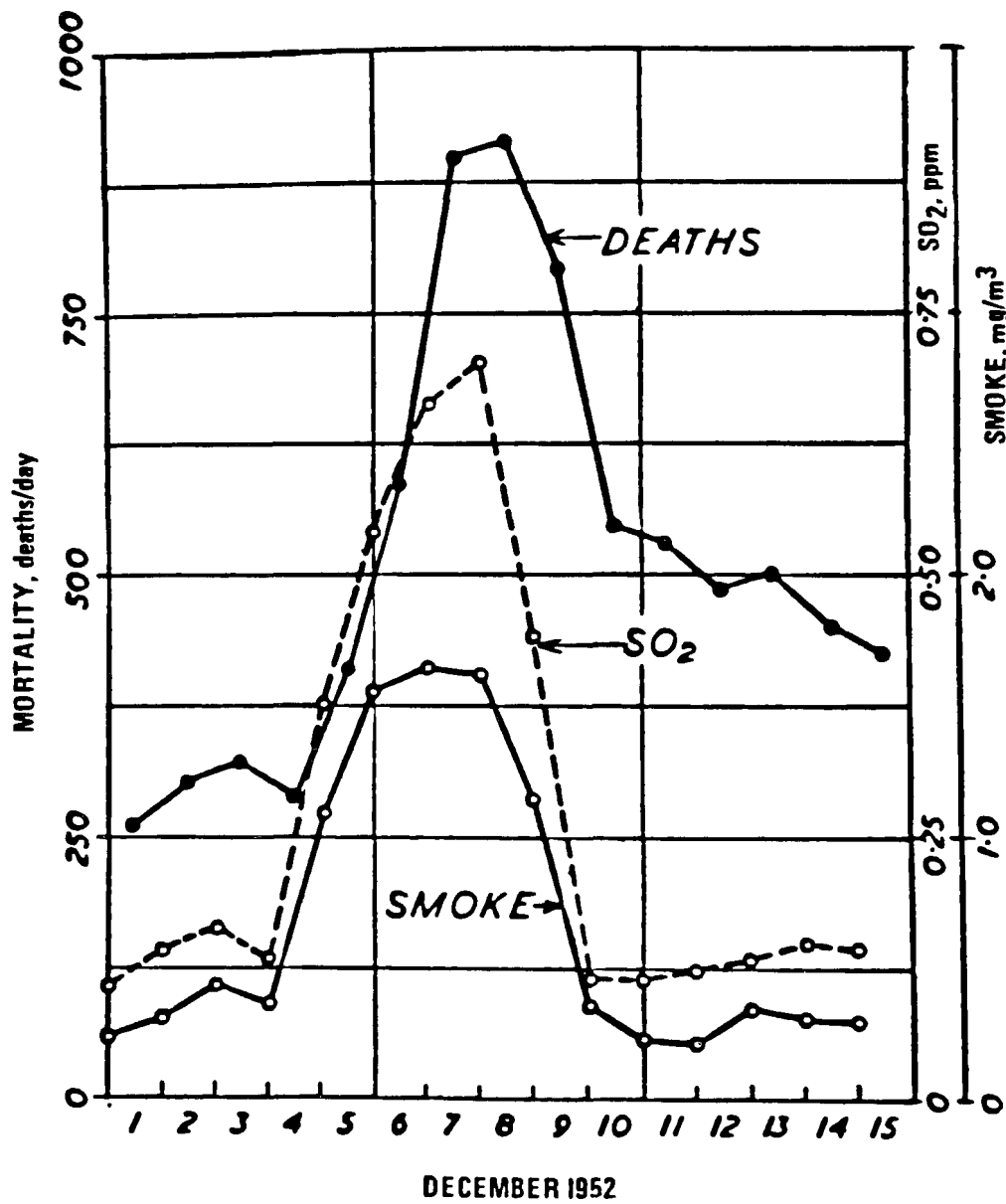
Figure 14-2. Daily air pollution and deaths, London, 1952[203]

Excess mortality in London during lesser episodes[11-14] was assessed by various statistical techniques for comparing observed and expected mortality. The expected mortality rates were estimated from the mean number of deaths occurring during the same dates over a number of years, from observed deaths during previous or subsequent weeks, or by deviation from 15-day moving averages of daily mortality. Aerometric data obtained for the various studies are not entirely comparable; thus the study results only allow for crude comparison. It has also been noted that the published concentration levels may not be representative of the acutual exposures of all of the affected population.[312]

The information on mortality and maximum 24-hr pollution measurements for BS and SO_2 are presented in Table 14-5. The maximum 24-hr concentrations of SO_2 during the 1952 and 1962 episodes were almost identical, and 1962 maximum TSP measurements were 75 percent of the 1952 maximum, but far more deaths occurred in 1952. This raises questions concerning the influence of factors other than pollutant levels. The maximum smoke concentration recorded in 1952 was the highest ever observed and yet is believed to have underestimated the actual concentration, because the filter became completely saturated and additional deposition had little effect on the intensity of the black spot produced on the instrument's filter tape. In 1962, publicity about the hazards of episodic conditions may have motivated the population, particularly the elderly, to avoid exposure as much as possible. Interpretation of the other data in Table 14-5, however, argue against this possibility. In 1956, the memory of the 1952 episode should still have been clear and, therefore, at least as many precautions should have been taken. However, more excess deaths occurred in 1956 than in 1962, even though concentrations were less than those

TABLE 14-5. EXCESS DEATHS AND POLLUTANT CONCENTRATIONS DURING SEVERE AIR POLLUTION EPISODES IN LONDON (1948-75)[2],[3],[219-221],[301]

Date	Duration, days	Estimated excess deaths	Maximum 24-hr pollutant concentration, $\mu g/m^3$	
			Smoke (BS)	SO_2 (H_2O_2 titration)
Nov. 1948	6	750	2780	2150
Dec. 1952	4	4000	4460	3830
Jan. 1956	4	1000	2830	1430
Dec. 1957	4	750	2417	3335
Jan. 1959	6	250	1723	1850
Dec. 1962	5	700	3144	3834
Dec. 1975	2	100-200	546	994

measured in 1962. Thus, the influence of publicity on minimizing exposure is only one possibility. A second possibility is that influenza in 1952 may have increased mortality. A third possibility is that the composition of air pollution changed between 1952 and 1962 as a result of the 1956 British Clean Air Act. The act limited the combustion of high-volatile coal for domestic heating and thereby affected the amount of tars in the atmosphere. Such alterations in the composition of air pollutants could have delayed or altered the atmospheric transformation of SO_2 to more toxic materials.[301]

Regardless of whether any of the above explanations apply, one clear conclusion from the major London episodes is that increases in mortality are associated with severe increases in air pollution. During the most severe episodes, maximum 24-hour concentrations exceeded 1400 $\mu g/m^3$ (0.5 ppm) for SO_2 and 1700 $\mu g/m^3$ for smoke (BS). A less severe episode in 1975, resulting in 100-200 estimated excess deaths, had maximum 24-hour concentrations of about 994 $\mu g/m^3$ (0.35 ppm) for SO_2 and about 546 $\mu g/m^3$ for smoke.[220,221,301] It has been suggested[301] that mortality levels during this episode may have been affected by a concurrently occurring physician's strike in London; but the strike referred to actually occurred the week before the air pollution episode. Thus, one would have to assert that it was the return of the physicians to work that may have contributed to the observed increases in mortality as an alternative to the induction of mortality by the elevations in air pollution.

One study. by Gore and Shaddick,[8] has associated sharp increases in mortality with four milder episodes of high air pollution between 1954 and 1956 in London. Using a 7-day moving average of deaths, the authors concluded that significant increases in the number of deaths occurred when 24-hour mean BS concentrations exceeded 2000 $\mu g/m^3$ and the 24-hour mean SO_2 concentration was at least 1150 $\mu g/m^3$ (0.4 ppm).

The data from the London air pollution episodes do not clearly delineate the effects of specific pollutants acting alone or in combination. However, during these periods characterized by heavy fog, low wind speed and high humidity, the conditions for the formation of secondary pollutants may have been better than usual. One of these conditions could be the presence of impurities in the particulate matter that could serve as catalysts for the reactions that form secondary pollutants, such as the transformation of sulfates from sulfur dioxide (SO_2). Holland et al. (1979)[301] draw attention to iron as an impurity in coal as possibly being involved in catalyzing atmospheric conversions of certain sulfur compounds to more toxic forms. The concentrations of sulfates were not recorded, but according to current knowledge they could have likely been very significant components of the pollution, related both to the particulate matter and the precursor SO_2. In addition, the effects of low temperatures may have been important.

Episodes of acute air pollution have also occurred in the United States, but no single event has reached the proportions of the major London episodes. Studies have been consistent, however, in showing that increases in total mortality, and in some cases cause-specific mortality and morbidity, were associated with the major episode in Donora in 1948 and, also, with episodes in New York City.[150-153] In these studies, increases in mortality have generally been related to 24-hour mean SO_2 concentrations above 1000 $\mu g/m^3$ (Table 14-6), together with measured particulate matter above 5.0 coefficient of haze units (CoHs). Ingram and Golden[154] estimated that 5.0 to 6.0 CoHs was approximately equivalent to 570 to 720 $\mu g/m^3$ of BS as monitored in England.

The estimates of excess mortality reported from the five New York episodes were derived by comparing daily deaths during periods of high air pollution

TABLE 14-6. ACUTE AIR POLLUTION EPISODES IN THE UNITED STATES

Location	Date	Reference	Estimated excess deaths	24 Hour pollutant concentrations*		
				SO_2, max $\mu g/m^3$ [a]	particulates, CoHs[b]	$\mu g/m^3$ TSP
Donora, Pa.	Oct. 1948	(149)	20	max: >1140 (0.4 ppm)	---	---
Detroit	Sept. 1952	(230)	↑ infant mort.	2620 (1.0 ppm)		>200
New York City	Nov. 1953	(151)	200	1000 - 1500 Max (1 hour) 2288 (0.86 ppm)	5.0	570
New York City	Dec. 1962	(150)	90	1890 (0.72 ppm)	6.5	800
New York City	Jan 1963	(150)	?	1830 (0.7 ppm)	6.0	720
New York City	Jan-Feb 1963	(153)	405-647[c]	1570 (0.6 ppm)	7.0	880
New York City	Feb.-Mar. 1964	(153)	50	1570 (0.6 ppm)	5.0	570

*Conversions:
[a] 1 ppm SO_2 = 2620 $\mu g/m^3$

[b] 5-6 CoH = 370-720 $\mu g/m^3$ TSP

[c] Influenza outbreak also present

with daily deaths for the same period in the years immediately before or following the episode[151,152] or by calculating daily deviations from a 15-day moving average of daily deaths.[150] The number of deaths in New York City was reviewed for excess mortality in relation to the air pollution episode of November 1953 by Greenburg et al.[151] Excess deaths were related to elevated concentrations of sulfur dioxide and suspended particles. Average daily smoke shade (particulate matter) measured in Central Park was in excess of 5.0 CoH units (568 μg/m^3 TSP), while the SO$_2$ rose during the episode from the typical New York City 24 hr average of between 400 μg/m^3 to 532 μg/m^3 (0.15 to 0.20 ppm) to 24 hour averages of 1000 to 1500, and reached a maximum level of 2288 μg/m^3 (0.86 ppm), which was probably a half-hour value. For this episode, there was a lag effect and excess deaths were distributed among all age groups. The number of deaths, although not showing the marked rise seen in some of the London episodes, was above average for comparable periods before and immediately after the incident. For the period November 15 to 24, 1953, the average number of deaths per day was 244, whereas during the 3 years preceding and following 1953, the average was 224 deaths per day for the same calendar period.

A later New York City episode (1962) was also studied by Greenburg et al.,[152] but they did not discern any excess mortality. McCarroll and Bradley[150] and McCarroll,[163] however, did find evidence of excess mortality arising from acute episodes in New York City in November and December of 1962, January and February of 1963, and February and March of 1964. In their studies, those workers compared 24-hour average levels of various pollutants with New York City mortality figures, employing daily deviations from 15-day moving averages. Pertinent air quality measurements were performed at a single station in lower Manhattan, and fluctuations in the values at this station were known to correlate

well with those at another station 6.5 miles away. Excess deaths during the first episode peaked on December 1, 1962 one day after the daily average for sulfur dioxide concentrations peaked at 1886 $\mu g/m^3$ (0.72 ppm) and smoke shade levels peaked at 6.5 CoH units (800 $\mu g/m^3$ TSP) during a period of atmospheric inversion and low ground-wind speed. The increased death rates were shared by the 45 to 64 age group and those over 65. A later episode, occuring around January 7, 1963, was associated with an SO_2 concentration above 1834 $\mu g/m^3$ (0.7 ppm) and a smoke shade value of 6.0 CoH units (720 $\mu g/m^3$ TSP). Some days did not have excess mortality. During another episode between January 29 and February 13, 1963 a peak death rate was apparently superimposed upon an elevated death rate average due to the presence of influenza virus in the community; daily pollutant levels averaged about 1570 $\mu g/m^3$ (0.6 ppm) for SO_2 and 6.0 for CoH units (720 $\mu g/m^3$ TSP). A fourth episode of excess mortality (April 1963) did not show sharp increases in air pollution. A fifth episode (February to March 1964) again showed simultaneous increases in air pollution and mortality. SO_2 was over 1570 $\mu g/m^3$ (0.6 ppm) and TSP was 570 $\mu g/m^3$ (5 CoH).

Severe air pollution also encompassed the New York City area during the Thanksgiving weekend, November 23 to 25, 1966. The maximum 24-hour average of hourly SO_2 values, as measured by electroconductivity, was 1,340 $\mu g/m^3$ (0.51 ppm) on November 23, and 1,230 and 1,020 $\mu g/m^3$ (0.47 and 0.41 ppm) on the 24th and 25th. The maximum hourly concentration was 2,670 $\mu g/m^3$ (1.02 ppm). Smoke shade values were above 5 CoHs (570 $\mu g/m^3$ TSP) on the 3 days. The average number of daily deaths during the 7 days of the air pollution episode was 261 compared with the expected value of 237 for control periods in 6 surrounding years.[229]

In Detroit[230] a rise in infant mortality and deaths in cancer patients occurred over a 3-day period in September, 1952, accompanied by a rise in the 3-day mean suspended particulate matter above 200 μg/m^3 and an instantaneous SO$_2$ maximum of 2,620 μg/m^3 (1.0 ppm). This is not believed to be related to cold temperatures that often characterized the London episodes.

Direct, precise comparisons of the pollution data from the London and United States episodes, it has been asserted,[301] cannot be made because of differences in the methods used for measuring air pollution concentrations. However, even rough comparisons accomplished by interconversion of BS, CoH, and TSP (by means of the approaches discussed in Chapter 3) suggest that the pollution must have been much greater in London. This is consistent with the respective health findings indicating that, in a population of approximately the same size, the estimated number of excess deaths was much higher in London. than in New York. Of course, these differences may have also been caused by a number of factors, including the accuracy with which the air measurements used reflected exposure for the total population, and the fact that the concomitantly occurring pollutants may have been quite different and might have acted together to increase the impact on human health. It is known also that acute episodes of excessive mortality have not been associated with all days of high pollution in New York or London.[152,163]

Investigations in Rotterdam (Brasser et al.[302]; Joosting[303]; Biersteker[315]) indicate that a positive association exists between air pollution and total mortality as shown in Table 14-7. Biersteker[315] found excess mortality to be associated with 24 hour smoke and SO$_2$ levels of approximately 500 μg/m^3 (OECD smoke) and 1000 μg/m^3 (sulfur dioxide method), respectively. Brasser et al.[302] found similar relationships when the SO$_2$ value of 500 μg/m^3 per 24

TABLE 14-7. OTHER ACUTE AIR POLLUTION EPISODES

Location	Date	Reference	Estimated excess deaths	24 Hour mean pollutant concentrations	
				SO_2, $\mu g/m^3$[a]	TSP ($\mu g/m^3$)
Osaka	Dec. 1962	100	60	262	1000
Rotterdam	varies	232	varies	300-500	d

[d]Particulates to SO_2 ratio of 1:3-1:4 (303)

hours is surpassed for a few days. This effect may begin to occur at lower concentrations, somewhere between 300 and 500 $\mu g/m^3$ SO_2 (0.11 to 0.19 ppm) per 24 hours, based on SO_2 measurements made with the hydrogen peroxide titrimetric method.[232,302] The Rotterdam episodes of January to February 1959 and December 1962 have also been discussed by Joosting.[303] Particulate levels are generally low in Rotterdam. On comparing particulate and SO_2 concentrations, Joosting has characterized the ratio of particulates to SO_2 as low (1:1), moderate (1:1.5 to 1:2), and high (1:3 to 1:4). Rotterdam is in the last category, whereas London is in the first.

Watanabe[100] (Table 14-7) found 60 excess deaths (about 20 percent) associated with a 1962 air pollution episode in Osaka, Japan, in which the 24-hour mean SO_2 concentration exceeded 260 $\mu g/m^3$ (0.1 ppm) together with concentrations of TSP greater than 1000 $\mu g/m^3$, both measured at a central station. Low temperatures may have been partly responsible for these effects.[312]

When a marked increase in air pollution is associated with a sudden dramatic rise in the death rate or illness rate that lasts for a few days and both return to normal shortly thereafter (as documented in the above studies), a causal relationship is strongly suggested. Sudden changes in weather, however, which may have caused the air pollution incidents, must also be considered as another possible cause of the death rate increase.[232] On the other hand, the consistency of the above associations between SO_2 and particulate matter elevations and increases in mortality render it extremely unlikely that weather changes alone provide an adequate explanation for all such observations. This view is further reinforced by (1) the fact that at least some episodes (e.g., the 1952 Detroit one) were not accompanied by sharp falls in temperature; and (2) other weather changes of similar magnitudes to those accompanying the

above pollution episodes are not usually associated with such dramatic increases in mortality in the absence of greatly increased levels of SO_2, particulate matter, or other pollutants.

14.3.3 Mortality Associated with Short-term Variations in Pollution

A number of investigators have reported on relationships in the United States between mortality and daily variations in air pollution during non-episodic periods.[155-160,170,171]

Schimmel and Greenburg[155] used more than 500,000 death certificates for New York City in a study of daily mortality from January 1, 1963 to December 31, 1968. The study attempted to relate fluctuations in mortality to daily SO_2 and smoke shade, after adjusting for weather and other temporal factors, and recognized the problems of auto- and cross-correlation. The authors concluded: "...that with a high degree of probability a certain portion of deaths would not have occurred at the time they did, in the absence of air pollution." By using their fully adjusted model, their estimate of excess deaths was 18.2 per day. Pollution estimates only came from a single station (Harlem), where SO_2 averaged 0.17 ppm (450 $\mu g/m^3$) for the study, while smoke shade averaged 2.1 CoH units (203 $\mu g/m^3$ TSP). The authors attributed approximately 20 percent of the excess deaths to SO_2 and 80 percent to smoke shade, but it has been noted that this represents stretching interpretation of the epidemiologic data to a point of precision beyond that allowed by existing techniques.[301] Schimmel and Greenburg[155] also performed cause-specific analyses for ten different cause categories. Estimated excess deaths were high in both the respiratory disease category and the coronary heart disease category. The linear regression model of Schimmel and Greenburg assumes that excess deaths rise in proportion to the increase of the SO_2 or smoke shade levels over the range of values they studied.

Schimmel and Murawski[156,157] expanded the death certificate data to include information through 1972. Using a revised model, they revised their estimate of premature deaths to be 2.8 percent (about 7 deaths per day) and stated that the lower estimates were "...explained by a fuller correction for seasonal trends and temperature effects." They found a colinearity of temperature and SO_2, but a curvilinear term for temperature may be more appropriate due to the known increase in mortality at extreme temperatures. They estimated the percent excesses attributed to SO_2 and to smoke shade. Based on separate analyses for the years 1963 to 1966, 1967 to 1969, and 1970 to 1972 the authors concluded that the reduction in SO_2 levels had not resulted in decreased estimated premature deaths due to SO_2. They further stated that "the SO_2 association with mortality is not really a measurement of SO_2 effects but, rather, SO_2 is to be viewed as an index of the effects of the more volatile components of combustion activity."

Schimmel[187] has presented additional data and analyses for the 14-year period of 1963 to 1976, leading to results and conclusions similar to those derived from the earlier papers by Schimmel and Murawski.[156,157]

Several reviews[184-186,301,312] have been critical of the findings and interpretations reported in the above Schimmel papers.[155-157] Some of the same criticism may also apply to certain other studies of the short-term effects of air pollution on mortality. With particular reference to the Schimmel papers, various reviewers noted that large standard errors for reported SO_2 effects, and others, complicate interpretation of the Schimmel findings. Also, it was pointed out,[301] it is not particularly surprising that some weak, but statistically significant, relationships were found (especially in the earlier Schimmel papers) in view of the enormous numbers of regression analyses

carried out and the consequent likelihood that at least a few statistically significant associations would be found by chance alone. Conversely, it was noted[18/] that, because of considerations not taken into account in Schimmel's later papers, one cannot rule out a possible significant contribution of SO_2 to mortality levels observed in New York City--although Schimmel and his colleagues failed to find any significant *changes in* associations between ~~decreases in~~ SO_2 levels and ~~decreasing~~ *recorded* mortality rates over the ~~same time~~ *1963-1972 time* span. One factor that may strongly limit the potential for Schimmel's statistical approach (to convincingly demonstrate significant associations, or lack thereof, between various air pollution parameters and mortality) was his use of air quality data from a single monitoring site in New York City. Thus, the crucial air quality measurement data imputs, upon which virtually all of the rest of his analyses very heavily depend, may not have adequately represented exposures for the entire New York City population studied.[312]

Hodgson[158] used multiple regression methods to examine the relationship between deaths and air pollution concentrations in New York City. He concluded that much of the variation in deaths could be explained by the ambient concentrations of SO_2 or particulate matter (as measured in CoHs) but the monthly average data used provided no useful quantitative information.

Multiple regression analyses were used also by Buechley[159] to relate daily deaths in the New York/New Jersey metropolitan area from 1962 to 1966 to concentrations of SO_2 measured at a single monitoring station. For this analysis, the data were adjusted for season, temperature, day of week, and an influenza epidemic. Beuchley's results have been interpreted to indicate that on days on which the 24-hour mean SO_2 concentration exceeded 500 $\mu g/m^3$ (0.19 ppm), deaths were 2 percent higher than expected;[301] on days when the 24-hour

mean SO_2 concentration was 30 $\mu g/m^3$ (0.01 ppm) or less, deaths were 1.5 percent less than expected (see Figure 14-3). The authors indicated that measurement of particulate matter (CoHs) did as well as SO_2 in predicting deaths, but no data were given. Extension of the analysis through 1972[160] gave indications of the importance of temperature and influenza regarding short-term variations in the number of deaths. The extended analysis again indicated the association between pollution and deaths but gave no additional information on the relative significance of SO_2 or particulate matter.

Lebowitz[170] studied relationships between air pollution exposure and mortality in New York (1962 to 1965), Philadelphia (1963 to 1964), and Los Angeles (1962 to 1965), and Lebowitz et al.[171] performed similar studies in Tokyo (1966 to 1969). These investigators developed a model in which higher air pollution concentrations (one standard deviation above season mean) were treated as stimuli; deaths, using various lag periods were treated as responses to these stimuli. Although no definitive levels were reported, significant relationships between periods of heavy pollution and increases in the number of deaths were found in each area studied. New York winter pollutant averages were 484 $\mu g/m^3$ (.182 ppm) SO_2 and 150 $\mu g/m^3$ TSP (2.12 CoH). Philadelphia winter average TSP was 100 $\mu g/m^3$ (1.6 CoH). Los Angeles winter average SO_2 was 390 $\mu g/m^3$ (.148 ppm). Adverse temperature and humidity changes were shown to be very important as well, but did not account for all mortality increases more directly attributable to or closely associated with increases in air pollution.

A number of reports have investigated relationships between mortality and air pollution in England during periods with no unusual air pollution episodes.[5-14] For most of these studies, 15-day moving averages were constructed and the effects of pollution were assessed in terms of daily deviations from these
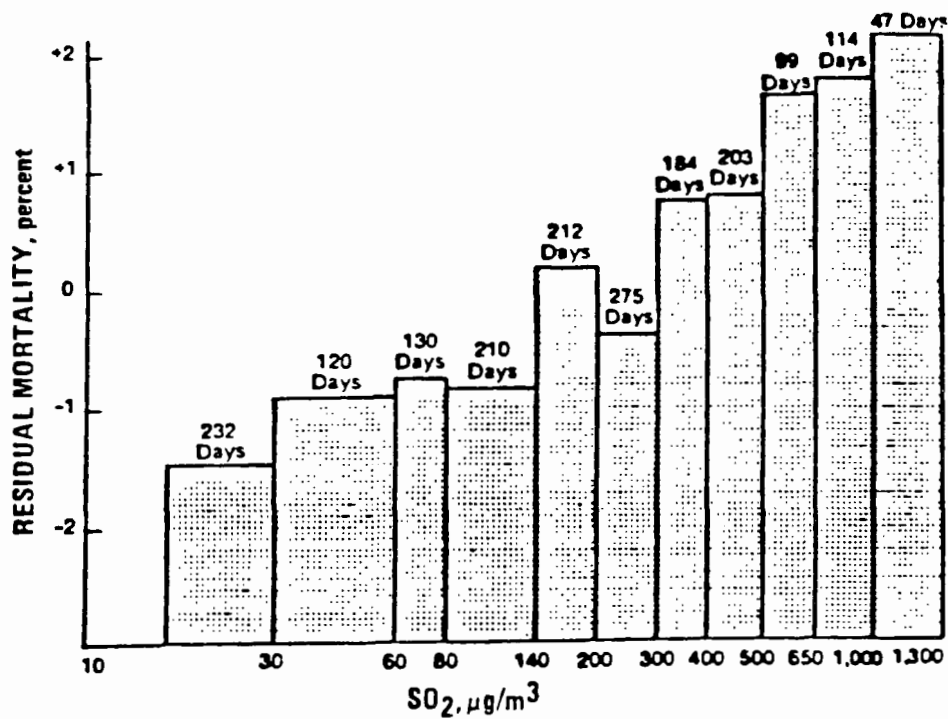
Figure 14-3. Residual Mortality as a Function of SO_2 for the New York – New Jersey Metropolitan area, 1962 to 1966[159]

baselines. Increases in daily deaths during the winter of 1958-59 were found to be associated with concentrations of BS >750 $\mu g/m^3$ and SO_2 >660 $\mu g/m^3$ (0.25 ppm).[13] Increases in daily deaths were not associated with pollutants at lower concentrations. Similar studies in Sheffield[14] were not as consistent. Increases in deaths were associated with very high concentrations of pollutants, but random variations in the number of deaths were so large that firm conclusions could not be drawn.

Among the most important British studies bearing on acute health effects of sulfur oxides and particulates at levels near present 24 hour air quality standards are those of Martin and Bradley[11] and Martin.[6] The first of these studies related daily mortality from all causes and from bronchitis and pneumonia to the level of SO_2 and smoke in London during the winter of 1958 to 1959. The authors found a considerable number of coincident peaks in pollution level and daily mortality. The correlation of mortality from all causes with pollutants measured on the log scale was 0.613 for smoke (BS) and 0.520 for SO_2. Neither temperature nor humidity was significantly correlated with mortality.

Though the authors emphasized the relationship between change in pollution level and change in number of deaths, an influenza epidemic occurring during part of the study may have influenced part of their results. The authors, however, provided the number of deaths, smoke levels, and SO_2 levels from November 1, 1958 to February 28, 1959 in the published report on the study. A further analysis of these data was performed by Ware et al.[304] but excludes the month of February, in which an epidemic of Type A influenza also had a significant influence on daily mortality. For the remaining 92 days, the deviation of daily mortality from the 15-day moving average (truncated at each end of the series) was computed, and the average of these deviations is given for intervals for smoke level in Table 14-8 and SO_2 level in Table 14-9.

TABLE 14-8.   MEAN DEVIATION OF DAILY MORTALITY FROM 15 DAY MOVING AVERAGE, BY LEVEL OF SMOKE (LONDON, NOVEMBER 1, 1958 - JANUARY 31, 1959)

Smoke level, $\mu g/m^3$ BS	Number of Days	Mean Deviation
100-199	6	-17.84
200-299	14	-11.63
300-399	16	-10.31
400-499	19	-5.57
500-599	9	18.46
600-699	6	18.80
700-799	7	5.31
800-1199	10	17.17
1200+	5	31.37

TABLE 14-9.   MEAN DEVIATION OF DAILY MORTALITY FROM 15 DAY MOVING AVERAGE, BY LEVEL OF SO_2 (LONDON, NOVEMBER 1, 1958 - JANUARY 31, 1959)

SO_2 level, $\mu g/m^3$ BS	Number of Days	Mean Deviation
100-199	16	-11.38
200-299	28	-10.78
300-399	22	8.50
400-499	12	13.45
500+	9	21.25

These tables suggest 500-600 $\mu g/m^3$ BS and 300-400 $\mu g/m^3$ SO_2 as levels above which increased mortality is seen, although this is not intended to suggest a threshold for response. In fact, the data suggest a gradient of mortality over the entire range of air quality seen. Although temperature and humidity were not correlated with daily mortality, both pollution level and daily mortality increased throughout the period of study, and the possibility of other extraneous seasonal variables contributing to this association cannot be ignored. On the other hand, it has been suggested[301] that the use of 15-day moving averages may underestimate the magnitude of effects associated with some episodes of high air pollution and, thusly, even more marked increases in mortality might be attributable to the increases in SO_2 and particulate matter.

A similar analysis was carried out by Martin for the winter of 1959-60.[6] This winter had fewer incidents of high pollution. The significant positive correlation between mortality and pollution was, however, still present although the coefficients were somewhat lower than in the previous year. Tables 14-10 and Table 14-11 show Martin's results combining high pollution days from 1958 to 1959 and 1959 to 1960, after excluding days on which pollution had fallen from a previously higher level. The mean deviation was positive in every group. Bronchitis mortality was also significantly, though less strongly, correlated with pollution level, but pneumonia mortality was not correlated with pollution.

Holland et al. (1979) discuss the above findings on mortality as follows (emphasis added):

> The nearest approach to an episode of high pollution in London in the last 10 years has been one lasting about two days, on December 15-16, 1975. On that occasion, the 24-hour average concentration of smoke (BS) rose to 546 $\mu g/m^3$, and that of sulfur dioxide to 994 $\mu g/m^3$. A comparison of the crude weekly totals of deaths for the

TABLE 14-10. MEAN DEVIATION OF DAILY MORTALITY FROM 15 DAY MOVING AVERAGE, BY LEVEL OF SMOKE (LONDON, 1958 to 1960)

Smoke level, $\mu g/m^3$ BS	Number of Days	Mean Deviation
500-599	9	5.2
600-699	6	13.0
700-799	9	9.2
800-1199	8	15.6
1200+	7	40.0

TABLE 14-11. MEAN DEVIATION OF DAILY MORTALITY FROM 15 DAY MOVING AVERAGE, BY LEVEL OF SO_2 (LONDON, 1958 to 1960)

SO_2 level, $\mu g/m^3$	Number of Days	Mean Deviation
400-499	9	9.0
500-599	6	11.6
600-799	9	16.0
800-899	6	19.2
900+	5	39.6

weeks around that time shows an excess of 100 to 200 in the week of the fog; but, as in a number of the other episodes, there was also a fall in temperature that may have been a contributory factor (11, 12). Relationships between short-term changes in mortality and low temperatures have been recognized for many years, having been demonstrated in London data as far back as the nineteenth century (13, 14).

In addition to studies of the major episodes of high pollution, attention has also been paid to day-to-day variations in mortality in London since 1952. Gore and Shaddick (15) calculated seven-day moving averages of deaths in the inner area (County of London) only, over winter periods from 1954 to 1956, and they found sharp increases in association with four foggy periods. Their own assessment was that the increases in deaths were particularly marked when pollution (as 24-hour averages) exceeded 2000 $\mu g/m^3$ smoke (BS), with 0.4 ppm (1149 $\mu g/m^3$) sulfur dioxide. This was a very conservative judgment, and there were increases in deaths in their series with smoke and sulfur dioxide concentrations of the order of 1000 $\mu g/m^3$ and 750 $\mu g/m^3$, respectively. Such changes may, in part, have been attributable to other associated environmental conditions, such as cold weather (that is, within minimum temperatures falling below freezing point), but, as in other studies of the kind, there is no satisfactory way of distinguishing the effects of these factors. It is important in trying to elucidate the influence of temperature independent of other meteorologic variables to compare like with like. Thus, cold Januarys should be compared with warm Januarys, and cold Julys with warm Julys. Most work has shown an association between respiratory disease and cold weather (e.g., see reference 16).

The main series of studies on day-to-day variations in deaths in Greater London is that by Martin and colleagues. In most of their studies, 15-day moving averages have been calculated and the short-term effects of pollution have been assessed in terms of deviation from these. (The moving average for each day refers to the average number of deaths for the day in question, together with seven days on each side of it.) The general seasonal trends and the direct effects of epidemics (notably of influenza) are eliminated in this way, although there is a risk of underestimating the magnitude of effects associated with some episodes of high pollution. In the winter of 1958-1959, when there were many days with high pollution, Martin and Bradley (17) reported a marked association between daily deviations in deaths, and concentrations of smoke or sulfur dioxide. These increases in deaths were consistently related to day-to-day increases in concentrations of the pollutants, and the authors originally assessed their results in terms of the increments in pollution only. They also showed that there were significant correlations between deviations in deaths and the actual concentrations of pollutants on the same day. No correlation technique such as this, however, can show the full impact of pollution. The effects are sometimes delayed by about one day, but since there is no uniformity in any such lag effects during a winter season, it cannot be dealt with simply by introducing a one (or more) day lag between the pollution and mortality figures.

Martin and Bradley displayed their results in detail in tabular form, so that days with elevated pollution could be linked with changes in mortality in the most appropriate way. Subsequently, increases in deaths (of 20 or more on a total of the order of 200-400 per day) were considered to be associated with 24-hour mean concentrations of smoke (BS) >750 µg/m³ and SO_2 >0.25 ppm (710 µg/m³) (18). It was not possible then, by this technique, to detect variations in daily deaths at lower concentrations, and this finding has not been contradicted in any way by subsequent events. Indeed, with a general decline in pollution levels in London such that 24-hour (BS) smoke concentrations are now seldom, if ever, as high as 750 µg/m³, there is still no evidence of associations of any day-to-day variation in mortality with relatively minor peaks in pollution.

Not mentioned by Holland et al. (1979)[301] in their above analysis is the fact that Martin and his colleagues reported that they found no significant association between excess mortality and temperature. As stated by Martin and Bradley[11] in discussing their findings for the winter of 1958 to 1959 (emphasis added):

Temperature is the climatic factor most frequently considered to have an association with fog mortality. Russell (1924, 1926) drew attention to the importance of cold weather as a factor in increasing mortality rates during fogs, but his investigations were based on weekly means and his results are not, therefore, applicable to the immediate effects of individual incidents. By itself, unless well below freezing point, temperature appears to have comparatively little immediate effect on winter mortality and this is exemplified by the low correlation coeficient (-0.030) which was found during the winter of 1958-59. A range of 30-38°F is characteristic of most winter fogs and temperatures consistently below 30°F are the exception. At the other extreme several fogs each associated with a mortality peak were found in November and December. 1958, with temperatures substantially over 38°F. As yet details have not been collected of a sufficient number of incidents to estimate mathematically the effect of temperature on fog mortality, but apart from the exceptional incidents with very low temperatures it appears on present information to have a comparatively minor influence.

See Appendix 14-B for more detailed review of literature on associations between mortality and temperature.

Also overlooked by Holland et al. (1979)[301] in their above analysis is the fact that other tests (beside correlation techniques) of possible associations

between mortality, SO_2 and particulate matter levels and temperature changes can be utilized to assess results reported by Martin and colleagues. The report by Martin and Bradley[11] presents a daily mortality-BS-SO_2 data set in tabular form. That detailed presentation of data allows for the validity of some of the above blanket statements by Holland et al.[301] to be evaluated by means of certain nonparametric statistical tests.

Timing of Observations

The mortality data from Martin and Bradley are reported on the calendar day of the date of death, that is 0001-2400. The SO_2 and smoke data for the given day are an average for seven Greater London stations obtained from the 24-hr collection values recorded from the bubblers and filters which were turned off at 0900 the same day. The meteorological observations for London (Croydon) give the maximum temperature between 0900 to 2100. The assignment of the minimum temperature is less certain. As stated in the footnote of the meteorological observations table "Minimum temperature night period 21-9 h. and are entered to day of reading."

If strictly interpreted, the recorded daily minima may not be independent since the temperature at 2400 may be the minimum on day 1 and the temperature at 0100 may also be the minimum on day 2. That is, some of the minima in the table could be 1 or 2 hours apart and other minima values could be 46 to 47 hours apart. With this timing uncertainty in mind, we can model these data as follows.

The recorded minimum temperature recorded on day 1 influences the pollution level recorded over the time period 0900, day 1 to 0900, day 2. Because mortality from relatively low pollution levels would take a period of time to occur, we expect the mortality on day 3 to be influenced by the pollution

recorded on Day 2. Such a delay is not unreasonable since there is likely to be a finite time from the stimulus which may lower resistance to a preexisting low grade infection until the crisis stage is reached or for other fatal effects to be manifested. In addition, respiratory patients in hospitals might be placed in oxygen tents, with heroic measures taken to keep them alive from day 2 to day 3.

A careful inspection of the mortality and temperature tables lead us to the period December 8 to December 24, 1958 for the detailed study. This choice was made because of the fact that daily mortality rates tended to steadily increase over the winter period, November 1958 to February 1959. This upward trend may have been caused by a combination of several of the following factors:

1. Decreasing Temperatures : The monthly mean minima are shown in Table 14-12 with the corresponding average for the years 1931 to 1950. Note that while temperatures in November and December were warmer than normal, those in January and February were somewhat colder than normal.

TABLE 14-12.
MINIMA TEMPERATURE DATA FOR LONDON (Croydon)

Month	1958 to 1959 mean minima	1931 to 1950 average minima
November 1958	40.6	40.1
December 1958	38.1	37.0
January 1959	31.5	36.1
February 1959	34.7	35.7

2. Presence of Influenza in London

Martin and Bradley report that an influenza epidemic occurred during this winter period. The peak in mortality and peak in pollution occurred almost on

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the same days in February 1959; however, this may not have been happenstance but indicitive of a true pollution effect of exacerbation of the preexisting disease.

3. Cumulative Dosage Effect

A repeated dosage of pollution to a susceptible individual may serve to lower the bodily resistance to such a point that an insult which might have produced mild discomfort in November could produce a pulmonary crisis in February. This would result in gradually increasing mortality trends over the course of the winter, likely peaking in February along with peak pollution levels and influenza effects.

By choosing December 1958, which was relatively warm, we avoid possible temperature complications, the influence of the later influenza outbreak, and the "sampling without replacement" problem as potential alternative explanations for mortality effects varying as a function of SO_2 and particulate matter pollution levels.

The pollution levels and minimum temperatures given in Table 14-13 were all in the range where Holland et al.[301] stated that no discernible mortality (20 or more on a total of the order of 200-400 per day) effect should be observed (that is, when BS $\leq$ 760 $\mu g/m^3$, SO_2 $\leq$ 0.18 ppm, T minimum $\geq$ 33°F).

In order to establish the robustness of these pollution data during this period, the day-to-day variation is evaluated by a sign-test. If we assume that SO_2 and BS are independent of each other, then during the 17-day period, the 16 day-to-day changes should occur randomly. Therefore, one could expect 8 days when SO_2 and BS rise or fall together and 8 days when they do not rise and fall together. As shown in Table 14-13, there are only 2 days of opposite

TABLE 14-13. POLLUTION AND TEMPERATURE DATA FOR LONDON, DECEMBER 1958

Date December	Total deaths (all causes)	Smoke BS ($\mu g/m^3$)	SO_2 (ppm)	Minimum temperature (°F)	Heating degrees (60-T min)*
8th	307	720	0.175	37	23
9th	305	290	0.117	36	24
10th	288	400	0.112	35	25
11th	285	440	0.113	36	24
12th	308	430	0.118	38	22
13th	291	340	0.078	36	24
14th	289	540	0.105	33	27
15th	334	760	0.162	36	24
16th	343	670	0.134	39	21
17th	319	560	0.122	40	20
18th	307	560	0.121	42	18
19th	284	300	0.058	46	14
20th	297	150	0.042	50	10
21st	256	190	0.054	45	15
22nd	297	430	0.084	39	21
23rd	311	520	0.128	38	22
24th	296	430	0.106	39	21

*Heating degrees are expressed in terms of 60°F—the minimum
temperature (°F) recorded for a given day at London (Croydon).
This assumes that residential space heating is utilized proportionally
in relation to decreases in outside ambient temperature below 60°F.

variation (Dec. 9-10 and Dec. 11-12). The chi-square test with 1-degree of freedom is 2 $(6)^2/8 = 9$ (P = 0.003), so one rejects the null-hypothesis of no association and accepts the alternate hypothesis of BS - SO_2 association. The averaging of air quality data from 7 monitoring stations apparently removes the routine or expected experimental errors, and the average is robust as expected. One can also perform the same test on smoke (Day 2) vs temperature as heating degrees (Day 1) data, and SO_2 (Day 2) vs minimum temperature as heating degrees (Day 1). Because of the one-day offset, we have 15 variations with null expectations of 7.5 each. For BS there are only 2 days with opposite variation, so that the chi-square test with 1-degree of freedom is 2 $(5.5)^2/7.5 = 8$ (P = 0.005) which demonstrates the close association of smoke (BS) with heating degrees. Repeating the evaluation, but for SO_2 and temperature (heating degrees), there are 4 days with opposite trend so that the chi-square with 1-degree of freedom is 2 $(3.5)^2/7.5 = 3.26$ (P = 0.07) which is on the edge of statistical significance and highly suggestive of an association between SO_2 and temperature.

These evaluations show how the sign test can demonstrate an association in cases where one expects, from prior knowledge, an association to exist.

Mortality Association with Temperature and Pollution

Because temperature is assumed to be offset from mortality by 2 days, we have only 14 day-to-day changes and an expectation of 7 similar changes and 7 dissimilar changes if mortality Day 3 is independent of the minimum temperature Day 1. The data set gives a total of 4 opposite sign changes, so that the chi-square test with 1 degree of freedom is 2 $(3)^2/7 = 2.57$ (P = 0.13). Note, if we test mortality Day 2 with temperature Day 1; P $\cong$ 0.50. Thus, temperature does not appear to be statistically significantly related to

mortality during the December, 1958, period studied. Performing similar computations with both BS and SO_2 on Day 2 and mortality on Day 3, however, there are 15 possible changes and only 3 were in the opposite direction, leading to a chi-square test with 1-degree of freedom of $2 (4.5)^2/7.5 = 5.4$ (P = 0.02). Thus, it appears that mortality may be significantly associated with increases in SO_2 and particulate matter at levels (190 - 520 $\mu g/m^3$ BS; 150 - 375 $\mu g/m^3$ SO_2) below those stated by Holland et al.[301] to be the lower limits where mortality occurs. Furthermore, such mortality effects appear to have occurred in the absence of any significant influence by temperature, which was always above freezing and averaged approximately 39°F (minimum) during the December period studied.

Similar thorough reevaluations are being carried out for mortality data from the 1975 London episode, when 100-200 excess deaths occurred and pollution peaked for only 2 days, and also from a 1975 Pittsburgh episode, when 20 excess deaths were reported. Apparently, Holland et al.[301] overlooked the possible mortality effect in Pittsburgh, Pennsylvania, which was noted at the end of a paper[82] cited by them (Holland et al.[301] reference 5-21). These mortality effects associated with the Pittsburgh episode were described by Riggan et al. (1976)[12] and were also reported in a companion paper presented at the 1977 Puerto Rico epidemiology symposium (Riggan et al., 1977)[341] attended by several of the authors of the Holland report.[301] It is not implausible that these excess deaths in Pittsburgh were related to the pollution levels, because these pollution levels were similar to those found in London from December 8-24, 1958. There exists another insidious similarity between the London episodes and the Pittsburgh episode in 1975. As Holland et al. (1979)[301] aptly pointed out on page 556 of their report, sulfuric acid might be a

component of crucial importance. The catalytic reaction of sulfur dioxide to sulfuric acid on moist particulate materials might have been occurring in London where iron is present as an impurity in coal (as noted by Holland et al.[310]), and also in Pittsburgh where ferric oxide is likely present as "an impurity" associated with steel making operations (see Sugden, 1967[342]). Consequently, more credence must be placed in the possibility that mortality in air pollution episodes can and has occurred even under present day air quality conditions in the United States and Britain.

Glasser and Greenburg[222] carried out an analysis of daily mortality in New York City during the 5 year period 1960 to 1964, using only data from the months October through March. Deaths were analyzed both as deviations from a 15-day moving average and as deviations from the 5-year average for each day. Results from the two analyses were said to be qualitatively similar. Twenty-four hour average pollution data were based on hourly SO_2 and bihourly smoke shade (CoH) readings. The results are adequately summarized by the unadjusted analysis, which is given in Table 14-14 and 14-15. This analysis suggests a mortality effect for smoke shade above 3.0-4.0 CoH (350-400 $\mu g/m^3$ TSP) and SO_2 above 786 $\mu g/m^3$ with very distinct increases above 5 CoH (568 $\mu g/m^3$ TSP) and 786 $\mu g/m^3$ SO_2. In cross-tabulation of daily mortality by SO_2 and smoke shade level, SO_2 appeared to be more strongly related to mortality and was used as an index of pollution in some analyses. In a multiple regression analysis with temperature and rainfall, SO_2 was more strongly associated with mortality than either weather variable. This association persisted in analyses of bimonthly periods. Although the observations are dependent, Glasser and Greenburg computed standard errors for the mean deviations by assuming independence. Most of these standard errors were near 2.0, though the entry 18.80 in Table 14-14 had a standard error of 4.3.

TABLE 14-14. AVERAGE DEVIATION OF DAILY MORTALITY FROM NORMAL,
BY LEVEL OF SMOKE SHADE (CoH), (NEW YORK, 1960 to 1964, OCTOBER THROUGH MARCH)

Smoke shade level, CoH	Number of days	Mean deviation
<1.0	26	-2.79
1.0-1.9	160	-1.55
2.0-2.9	318	-2.37
3.0-3.9	239	1.48
4.0-4.9	83	2.52
5.0-5.9	19	18.80
6.0+	9	17.18

TABLE 14-15. AVERAGE DEVIATION OF DAILY MORTALITY FROM NORMAL,
BY LEVEL OF SO_2 (NEW YORK, 1960 to 1964, OCTOBER THROUGH MARCH)

SO_2 level, $\mu g/m^3$	Number of days	Mean deviation
<262	112	-3.49
262-524	311	-3.08
524-786	172	1.78
786-1048	66	9.42
>1048	80	11.86

To analyze possible mortality effects of even lower levels of pollution, even the 15-day moving average method is not sufficiently sensitive. Some authors have argued that more sophisticated adjustment techniques are necessary to ensure that seasonal and temperature effects are eliminated in adjusted analyses.

Kevany et al.[15] used partial correlation analysis to develop a relationship between SO_2 and smoke pollution in Dublin, Ireland, and specific mortality data derived from death certificates between 1970 and 1973. Some forms of mortality were reported to be occasionally correlated with SO_2 levels of 100 to 150 $\mu g/m^3$. The findings, however, were internally inconsistant and based on truncated distributions of pollutant concentration estimates.

In summary, the results of the above studies of mortality associated with short-term variations in air pollution collectively provide further evidence for associations between excess mortality and marked elevations in atmospheric concentrations of SO_2 and particulate matter. Again, however, as in the case of the earlier discussion regarding acute pollution episode mortality effects, it must be noted that in assessing various published results or the data sets and analyses upon which the results are based, it is often difficult to differentiate precisely the relative contributions to the observed excess mortality rates of: (1) SO_2 or particulate matter, acting alone or in combination; and (2) the possible effects of covarying changes in temperature, other meteorological parameters or concurrent outbreaks of influenza or other diseases.

Nevertheless, based on several methodologically sound studies which have taken the latter factors into account, it appears to be possible to derive credible, albeit rough, quantitative estimates of particulate matter and SO_2 concentrations associated with the occurence of increased mortality in

disparate geographic areas. Thus, for example, the studies of Martin and Bradley[11] and Martin[6] strongly point toward notable increases in mortality in London having occurred in association with repeated short-term exposures to particulate matter levels exceeding approximately 500-600 $\mu g/m^3$ BS and SO_2 levels of 300 to 500 $\mu g/m^3$. Careful further analysis of their data, as detailed above, suggests possible significant mortality effects at even lower levels of BS and SO_2, in the absence of significant temperature effects. In addition, analysis of the Glasser and Greenburg[222] study points toward increased mortality in New York City, occurring in association with particulate matter levels rising above approximately 350-400 $\mu g/m^3$ TSP) and SO_2 above 524-786 $\mu g/m^3$.

14.3.4 Cross-Sectional Studies of Mortality

Numerous qualitative studies have been performed comparing mortality in areas of lowest-to-highest pollution concentrations. Most of these studies do not account for cigarette smoking, occupation, social status, and/or mobility differences between areas, thus making it difficult to define accurately any quantitative relationships between mortality and air pollution parameters. Many such studies are summarized in Table 14-16. These are followed by a discussion in more detail of other studies yielding better quantitative information bearing on the present discussion.

Buck and Brown[199] found a gradient of mortality from chronic respiratory illness from 1955 to 1959 that coincided with areas of lowest-to-highest pollution in 1962 in middle class areas. The pollution concentrations and mortality were from different years. This study did not find a significant relationship between smoking and mortality from lung cancer but the authors estimated that increased mortality occurred with levels of over 200 $\mu g/m^3$ BS and 200 $\mu g/m^3$ SO_2. Controlling for regional smoking and socio-economic

TABLE 14-16. QUALITATIVE ASSOCIATION OF GEOGRAPHIC DIFFERENCES IN MORTALITY
WITH RESEDENCE IN AREAS OF HEAVY AIR POLLUTION

Pemberton and Goldberg[223]	1950-1952 bronchitis mortality rates in men 45 years of age and older in county boroughs of England and Wales	Sulfur oxide concentrations (sulfation rates) were consistently correlated with bronchitis death rates in the 35 county boroughs analyzed
Stocks[138,164-167]	Bronchitis mortality, 1950-1953, in urban and rural areas of Britian, with adjustments for population density and social index	Significant correlation of mortality from bronchitis and pneumonia among men, and from bronchitis among females, with smoke density
Gorham[224-225]	1950-1954 deaths, 53 counties of England, Scotland, and Wales	Bronchitis mortality was strongly correlated with acidity of winter precipitation
Gore and Shaddick[8] and Hewitt[226]	Mortality in London, 1954-1958 and in 1950-1952, respectively	Duration of residence in London significantly correlated with bronchitis mortality, after adjusting for social class
Haastrom et al.[16] Zeidberg et al.[17] Sprague et al.[18]	1949-1960 deaths for each cause in Nashville, Tenn., categorized by census tract into 3 degrees of air pollution and 3 econimic classes (levels not accurately determined)	Within the middle social class, total respiratory disease mortality, but not bronchitis and emphysema mortality, were significantly assoicated with sulfation rates and social index. White infant mortality rates were significantly related to sulfation rates
Lepper et al.[227]	1964/1965 mortality rates in Chicago census tracts stratified by socioeconomic class and SO_2 concentration	Increased respiratory disease death rates in areas of intermediate and high SO_2 concentration, within a socioeconomic status, without a consistent mortality gradient between the areas of intermediate and high SO_2 concentration
Jacobs and Landoc[175]	1968/1970 mortality rates in Charleston, S.C., industrial vs. non-industrial areas	Higher total and heart disease mortality rates in industrial area

Morris et al.[24]	1960-72 mortality rates compared to 1959-60 air pollution levels	Mortality higher in smokers with lower air pollution exposures
Collins et al.[287]	Death rates in children 0-14 years of age, 1958-1964, in relation to social and air pollution indices in 83 county boroughs of England and Wales	Partial correlation analysis suggested that indices of domestic and industrial pollution account for a differences in mortality from bronchopneumonia and all respiratory diseases among children 0-1 year of age
Beaker et al.[323]	Thanksgiving 1966 Fog, New York	Complaints of cough, phlegm, wheezing, breathlessness, eye irritation increased with increasing air pollution
Toyama[330]	Mortality in districts of Tokyo	Bronchitis mortatliy associated with dustfall (but not cardio-vascular, pneumonia or cancer mortality)
Lindeberg[321]	Deaths in Oslo winters	Average deaths per week, 1958-65 winter, correlated with pollution

differences did not remove the high correlation between air pollution and bronchitis mortality.[307] That is, although Buck and Brown[199] did not find a relationship between smoking and lung cancer and bronchitis mortality,[301] the variation in smoking between regions was too small to differentiate the observed mortality differences.[247,307]

Wicken and Buck[19] compared deaths from lung cancer and bronchitis (1952 to 1962) in areas of contrasting air pollution (1963) in northeast England. Differences in death rates were associated with differences in exposure to pollutants with high areas having annual BS of 160 $\mu g/m^3$ (250 $\mu g/m^3$ TSP) and SO_2 of 115 $\mu g/m^3$. Because adjustments in analyses were made for smoking, age, and social class, this study is generally considered to be a methodologically sound study.[304]

Burn and Pemberton[20] studied total mortality and mortality from lung cancer and bronchitis in three areas of differing pollutant concentrations in Salford, England. Total mortality showed a gradient in the standardized mortality ratio of between 90 and 106 with gradients in winter and summer for SO_2 (340 to 715 and 450 to 680 $\mu g/m^3$, respectively) and British Smoke (145 to 255 and 170 to 270 $\mu g/m^3$, respectively). Since cigarette smoking, social status and mobility were not examined, questions have been raised regarding the validity of these reported associations.[248,301]

Watanabe and Kaneko[228] studied 1965/1966 mortality rates in the Osaka, area of Japan, stratified into 3 areas by degree of air pollution. Moving averages and lags in mortality were utilized. A stepwise increase in total mortality and deaths from circulatory disease was seen in areas of greater pollution independent of temperature effects. The levels in the highest area were 300 $\mu g/m^3$ TSP and 215 to 266 $\mu g/m^3$ SO_2 (0.08 to 0.10 ppm).

Winkelstein et al.,[21-23] studied total and cause-specific mortality in
Buffalo and Erie County, New York, for the years 1959 to 1961, in relation to
the air pollution levels. A network of 21 sampling stations provided data on
TSP, settleable solids, and oxides of sulfur for the period July 1961 to June
1963. Four areas were designated on the basis of the isopleth concentrations
of particulate matter, with the 2-year geometric mean concentrations of TSP in
the four areas being <80, 80 to 100, 100 to 135, and >135 $\mu g/m^3$. Each area
was also divided into five economic groups. Chronic respiratory disease
mortality for white males 50 to 69 years old was about three times higher in
the high-pollution areas than in the low-pollution areas. The positive association
between TSP concentrations and total or chronic respiratory disease mortality
persisted across all economic groups. There was a positive association between
stomach cancer and 2-year geometric mean TSP in excess of 80 $\mu g/m^3$. Deaths
from cirrhosis of the liver also showed a positive association with TSP con-
centration for both white men and white women 50 years and older. Average
annual death rates, as they related to TSP concentration and economic level,
are shown in Table 14-17. Multiple probit analysis indicates the independent
effect of particulate matter on mortality.

Questions have been raised[301,308] concerning the validity of the above
Winkelstein[21-23] findings, because the study did not include smoking, occupation
or mobility data. However, these variables correlate significantly with
economic levels, which were controlled for in the analyses, somewhat minimizing
such shortcomings.[313] In addition, Winkelstein[305] conducted a follow-up
survey of smoking in adult women in Buffalo in 1963. He attempted to determine
the potential influence of smoking by residence. Among non-smoking women over
age 44, productive cough was positively correlated with residential suspended
particulate concentrations. Smokers with 5 or more years residence also had

TABLE 14-17. AVERAGE ANNUAL DEATH RATES PER 1000 POPULATION
FROM ALL CAUSES ACCORDING TO ECONOMIC AND PARTICULATE LEVELS, AND
AGE: WHITE MALES, 50-69 YEARS OF AGE, BUFFALO AND ENVIRONS, 1959-1961

| Economic level | Particulate level | | | | |
	1 (low)	2	3	4 (high)	Total
1 (low)	--	36 (530)*	41 (5281)	52 (1954)	43 (7765)
2	24 (3663)	27 (9720)	30 (6968)	36 (3185)	29 (23536)
3	--	24 (7684)	26 (3954)	33 (1298)	25 (12936)
4	20 (6625)	22 (7881)	27 (2639)	--	22 (17145)
5 (high)	17 (6335)	21 (6394)	20 (574)	--	19 (13303)
Total	20 (16623)	24 (32209)	31 (19416)	40 (6437)	26 (74685)

Source: Winkelstein, et al.[21]

*Population sizes given in parentheses

ANALYSIS TABLE USING ASYMPTOTIC CHI-SQUARES ESTIMATED BY PROBIT ANALYSIS

Effect	Asymptotic chi-square	Degrees of freedom	P-value
Particulates	76.55	3	<.001
Linear effect	72.55	1	<.001
Nonlinear effect	4.00	2	.135
Economic effects	392.34	4	<.001
Interactions	4.23	8	.836

Source: V. Hasselblad (personal communication)

TABLE 14-18. AVERAGE ANNUAL DEATH RATES PER 1000 POPULATION
FROM ALL CAUSES ACCORDING TO ECONOMIC,
PARTICULATE AND SO_x LEVELS

Economic level	Pollution Levels			
	Part. low SO_x low	Part. low SO_x high	Part. high SO_x low	Part. high SO_x high
1 (low)	36 (530)*	--- (0)	46 (4,413)	41 (2,822)
2	26 (13,383)	--- (0)	33 (2,245)	32 (7,908)
3	24 (7,684)	--- (0)	28 (4,189)	26 (1,063)
4	21 (13,771)	19 (735)	27 (2,639)	--- (0)
5 (high)	19 (11,428)	16 (1,301)	20 (574)	--- (0)

Source: Winkelstein et al.[188]

*Population sizes given in parentheses

ANALYSIS TABLE USING ASYMPTOTIC CHI-SQUARES ESTIMATED BY PROBIT ANALYSIS

Effect	Asymptotic chi-square	Degrees of freedom	P-value
SO_x-particulate interaction	.55	1	.458
SO_x adjusted for particulates	3.26	1	.071
Particulates adjusted for SO_x	43.36	1	<.001
Economic	406.84	4	<.001
Other interactions	4.95	7	.666

Source: V. Hasselblad (personal communication)

positive correlations with residential TSP; both findings were independent of socio-economic factors.[305,307] This indicates the likely existence of effects on health of residential pollution independent of smoking. Nevertheless, the specific contribution of smoking to mortality effects observed in his early studies[21-23] could not be definitively determined, by this approach.

It has also been conjectured,[301] (without presentation of convincing supporting data), that Winkelstein's[21] original findings might be simply accounted for by higher mortality rates in high pollution areas being due to greater proportions of residents in the high pollution areas coincidentally also falling higher in the 50-69 age range studied than those in the low pollution areas. This would, however, have to be an extraordinary coincidence indeed for the same pattern of age bias to follow precisely the same dose-response relationship patterns observed for pollution-mortality relationships shown in Tables 14-17 and 14-18. Winkelstein also evaluated the possibility that census tract population size (and thus density) could be positively correlated with both air pollution levels and mortality rates. The total death rate for white men ages 50 to 69 were computed for each of the four air pollution levels in each group; it did not appear that the observed association of air pollution and mortality was related to population size.[305]

Winkelstein[188] reanalyzed the same mortality data using two particulate levels and two oxides of sulfur (SO_x)levels. The areas were split at 100 $\mu g/m^3$ for particulate matter and 0.45 mg/cm^2-30 days for SO_2. The mortality rates (Table 14-18) show increases for particulate matter independent of economic level; tests of significance calculated as in Table 14-17 show that particles explain a highly significant increase in mortality. Probit analysis indicates that SO_x adjusted for particulate matter had only borderline significance while particulate matter adjusted for SO_x was highly significant. The relative

risk ratio of the high-particulate areas to the low-particulate (and low SO_x) areas was between 1.15 and 1.29, for the economic levels (except for the highest economic level). Winkelstein[189] performed a similar analysis for women (similar to Table 14-17). The same pattern of increasing mortality rates across particulate categories was found. The number of occupationally exposed women can be assumed to be small at that time (1960) such that industrial exposure was not the primary cause of increased mortality.

Taking into account all of the above analyses and information concerning the Winklestein studies, it would appear that his finding on associations between variations in mortality and geographic areas in terms of relative levels of particulate matter or sulfur oxides are likely valid and cannot be explained away in terms of possible confounding or covarying factors alone. On the other hand, caution must be exercised in regard to uncritical, full acceptance of the specific quantitative dose-response relationships implied by the summarization of pertinent air quality data appearing in the published Winkelstein reports without closer examination and analysis of the original air quality data.

More specifically, conversion of Winkelsteins' air quality data from 2-year geometric means to annual arithmetic means is especially important in order to allow for more direct comparison of his findings with results which have more typically been reported in relation to annual average TSP concentrations expressed as arithmetic means. Conversion to arithmetic means of the specific geometric means that served as the basis for Winkelstein's original TSP pollution level groupings results in the values listed in the third vertical column of Table 14-19. Similarly, conversion to arithmetic means of the geometric means for pertinent SO_x air quality data reported by Winkelstein[21-23] yields results as indicated in the third column of Table 14-20.

TABLE 14-19. COMPARISON OF ARITHMETIC AND GEOMETRIC
MEANS OF TSP DATA - BUFFALO STUDY, 1961-1963

TSP Measurement Original Grouping	2-Year Geometric Mean	2-Year Arithmetic Mean*	With Flow Rate Correction
< 80 µg/m^3	75	87	
	76	83	≅ 100
	78	87	
	80**	91	
80-100	87	100	
	89	100	115-125
	89	102	
	90	103	
	93	105	
	95	109	
100-135	106	119	
	110	122	
	111	125	≅ 140-175
	124	146	
	125	146	
	132	156	
	135	154	
> 135	142	163	
	152	180	≅ 180-285
	178	203	
	205	249	

*Modified from Winkelstein (1967)[21] by E. Davis, personal communication to D. Mage
**In the original analysis, this station was included in the grouping
< 80 µg/m^3, 2-year geometric mean.

TABLE 14-20.   COMPARISON OF ARITHMETIC AND GEOMETRIC MEANS OF
OXIDES OF SULFUR DATA - BUFFALO STUDY, 1961-1963*

TSP Measurement Original Grouping 2-yr geometric mean	Oxides of Sulfur (mg/cm^2)** 2-Yr. Geometric Mean	Oxides of Sulfur (mg/cm^2) 2-Yr. Arithmetic Mean	Estimated SO_2 Level $(\mu g/m^3)$***
< 80 $\mu g/m^3$	0.198	0.237	19
	0.219	0.256	20
	0.257	0.290	23
	0.256	0.289	23
80-100	0.219	0.252	20
	0.278	0.299	24
	0.209	0.241	19
	0.237	0.259	21
	0.339	0.385	31
	0.262	0.297	24
100-135	0.242	0.359	29
	0.429	0.455	36
	0.326	0.423	34
	0.337	0.375	30
	0.359	0.421	34
	0.307	0.417	33
	0.461	0.509	41
> 135	0.328	0.349	28
	0.169	0.327	26
	0.530	0.566	45
	1.250	1.315	105

*Based on data from Winkelstein (1967).[21]

**Actually SO_x values shown here represent mg/cm^2 readings per 30 days.

***Values stated here are likely underestimations of actual SO_2 concentrations due to probable errors in measurement associated with use of "sulfation rate" analytical technique, as discussed briefly in accompanying text and in more detail in Chapter 3.

In addition to the above considerations, certain sources of measurement error that would likely have affected the precision of the quantitative estimates of TSP and SO_x levels employed by Winkelstein,[21-23] have come to light in recent years. For example (as also discussed in Chapter 3), underestimation of TSP concentrations likely occurred due to probable overestimation of flow rates during sampling periods. This arises from the standard procedure, employed by Americans, in taking an average of the flow rate readings obtained at the start and end of a sampling period, rather than obtaining continuous readings during the period and more accurately determining the flow rate by integrating the area under the curve defined by the decreasing flow rate readings over the sampling period. Precise estimation of the size of likely resulting errors associated with specific American hi-vol TSP estimates determined in the above manner is of course impossible but probably would not be more than about 15 percent (see Appendix A of Chapter 3). Applying a 15 percent maximum correction to the "arithmetic mean" TSP estimates in Table 14-19 results in annual average TSP values designated as being obtained "with flow rate correction" in that table.

Analogously, it must be noted that the "sulfation" method used in determining the oxides of sulfur SO_x data reported by Winkelstein[21-23] is not specific for sulfur dioxide (SO_2). Also only approximate estimates can be made of the proportion of SO_2 contributing to the reported SO_x data, as per the values shown in the fourth column of Table 14-20. The interpretation is further complicated because the basic SO_x and, therefore, these derived SO_2 estimates likely were affected by the sensitivity of the sulfation technique to variations in temperature and humidity. Thus, unless the latter were well controlled within the monitoring sites, the net outcome would likely be that

the values shown in Table 14-20 somewhat underestimate the actual oxides of sulfur air levels (see Chapters 2 and 3 for a more detailed discussion of the sulfation method). Regardless of the precise actual levels of either overall oxides of sulfur or SO_2 as a subset, however, the matter of their possible contribution to mortality (either alone or in combination with TSP) is more or less moot because no statistically significant SO_x effects or SO_x-particulates interactions are demonstrated by the probit analysis in Table 14-18.

Lave and Seskin,[25] in another often-quoted study, obtained a positive association for both men and women between bronchitis mortality in England and smoke (BS) measurements. The positive association persisted when socioeconomic factors were included in a multiple regression analysis. These investigators[26] then compared bi-weekly concentrations of air pollutants in 114 SMSAs in the United States during 1964 with deaths from bronchitis. Regression analyses showed significant positive relationships between mortality and suspended particulate matter, even after adjustment for climate and the type of home heating (both associated independently with mortality).

The bi-weekly high-volume TSP concentrations during the period covered by the analyses ranged from 45 to 268 $\mu g/m^3$, with a mean of 118 $\mu g/m^3$. This would suggest that biweekly mean TSP concentrations of 120 $\mu g/m^3$ or higher would be associated with excess bronchitis deaths. Lave and Seskin[27] subsequently published results of a time series analysis of air monitoring data from 25 SMSAs as they related to bronchitis mortality, lung cancer mortality, and infant mortality during the years 1960 and 1969. In this analysis, each type of mortality was related to air pollution concentration as indicated by the annual mean concentration of TSP or sulfate.

Again, TSP readings and suspended sulfate readings >120 >10 exceeded the mean pollutant concentrations and, on the regression scale, were associated with increased mortality. The time series analysis indicates that TSP has about three times the explanatory power in the regression than does sulfate and almost five times the explanatory power of SO_2. Nitrates and NO_2 were not significant in this analysis. The authors state that SO_2 and the nitrogen compounds may be important acting together with the particulate matter.

Many questions can be raised about these study results. Cigarette smoking was not considered in the analysis. There may also have been problems arising from nonuniform distributions of samples or from other variables not included in the analysis. Air pollution was measured only twice monthly at one or more monitoring stations in each of 114 metropolitan areas. The regressions also included some possible confounding by sex distributions, age distributions and socioeconomic levels. Although this was an attempt to specify effects of SO_x/TSP, effects of other pollutants cannot be subtracted. The greater effects of smoking were not included, nor were the effects of other exposures. Potentially confounding are the choice of residential area related to the co- and intervening variables and other community differences not measured. The method is unable to relate pollution levels in cities to actual exposure of individuals to air pollution attributed to the area of residence, especially given the mobility of the U.S. population.[251] Time series analysis also may have systematic biases. Seasonal variation was not controlled. Problems with geographic comparisons of mortality include: lack of information on covariables, intervening variables and confounding factors; lack of specific exposure histories and of specific causes of death; errors of omission and commission in assigning deaths to places; inability to pinpoint effects of specific

pollutants or to characterize dose-response relationships; inability to generalize. Considering all of the above problems with the Lave and Seskin analyses, their reported findings and conclusions cannot be accepted as being accurate or useful for present health criteria development purposes.

Four regression analyses are also reported by Lipfert.[252,253] The first of these arises from analysis of 1969 mortality data from 60 U.S. cities using a model much like one of Lave and Seskin's; very similar coefficients are obtained. The first two models differ only in that the first uses mortality data from 60 SMSAs while the second uses mortality data from 60 U.S. cities. The coefficient of sulfate (SO_4)is larger in the second regression using smaller geographic areas. The third model differs from the second in that more cities are included and age of housing and birth rate are added as independent variables, while smoking is added in the fourth. Though the coefficient of TSP changes very little, the coefficient of sulfate is negative in these regressions.

A regression analysis of 60 U.S. cities in 1970 was performed by Crocker et al.[254] In addition to variables used by other investigators, this model includes variables for climate, education, availability of medical care and nutritional habits. Although Crocker uses SO_2 and not SO_4 as a pollution variable, neither pollutant contributes significantly to the regression. They report a correlation between SO_2 and SO_4 of 0.74.

In evaluating regression analysis studies further, it should be noted that the contribution of air pollutants to mortality can be summarized by "elasticity". Elasticity is a dimensionless number that represents the expected percent change in the dependent variable, mortality, associated with a 100 percent increase from the mean value in each of the independent variables.

Elasticity is computed by multiplying each air pollutant regression coefficient by the average value of that pollutant in the data set, adding these quantities for all pollutants, and dividing by the average mortality over study units. So long as the set of pollution variables chosen contains variables expressing the association of air pollution with mortality, elasticity is relatively insensitive to subset selection from a set of highly colinear pollutant variables. Thus, elasticites can be viewed, at least approximately, as measuring the total mortality effect of all pollutants included.

Elasticities for the nine regression analyses summarized above are as follows. The simplest model used by Lave and Seskin[256] for the analysis of the 1960 data had the largest elasticity (0.09). As other variables were added, such as home heating fuel in the second regression, elasticity declined (0.03). When occupation was added to the model for the first regression, elasticity declined to 0.05. The first two Lipfert regressions use population density, percent above age 65, percent nonwhite and percent with income below $3000 as independent variables. Their elasticities were 0.10 and 0.09, respectively. When birth rate and age of homes are added to the third or cigarette smoking to the fourth, elasticity declines to 0.06 and 0.004, respectively. The effect of cigarette smoking is especially notable. Finally, in the analysis by Crocker et al.[254] using several other independent variables, the elasticity is nearly zero (0.004). These variables included measures of medical care, diet, climate and cigarette smoking and could easily be defended as critically important in any analysis controlling for other factors influencing mortality.

Though several authors have argued that the omission of smoking only adds to error, Crocker et al.[254] report a correlation of 0.23 between cigarette consumption and sulfur dioxide in the six cities in their study. Certainly

the two variables are not causally related, but both may reflect other characteristics of the population.

Schwing and McDonald[255] report on a study of 46 SMSAs (1959 to 1961) in which 23 explanatory variables were used, including climate, socioeconomic, occupational and smoking variables and eight air pollutants. This study differs from others in that the investigators included all 23 variables in their models. To counter the effects of severe colinearity, the authors used two methods of analysis: ridge regression and constrained least squares, as opposed to ordinary least squares. (The previously reported studies all used ordinary least squares.)

Ridge regression is a numerical method for stabilizing estimates from data that have several colinear variables. While the method does achieve stability, it does so by selecting an arbitrary constant that has the effect of shrinking each estimated coefficient toward zero. Though ridge regression leads to smaller standard errors for the estimated coefficients, these coefficients are no longer interpretable as partial regression coefficients, that is, measures of the effects of changes in a single variable while other variables are held fixed. As emphasized throughout this chapter, colinear data sets are fundamentally insufficient to allow assignment of mortality effects to individual members of a group of colinear independent variables.

Schwing and McDonald[255] also used constrained least squares, constraining the air pollution coefficients to positive values. This may be unreasonable when eight air pollutants are studied simultaneously; for instance, respirable sulfate as a fraction of total sulfate is not constant over different levels of air quality (see Chapter 5). Schwing and McDonald report an elasticity of 0.022 from ridge regression and an elasticity of 0.045 from constrained least

squares. These values are still an order of magnitude larger than that reported by Crocker et al. (0.004).[254] While Crocker et al. did not include data on occupation, Schwing and McDonald did not include medical care.

While Lave and Seskin[256] found associations between air quality and both cardiovascular and cancer mortality, Crocker et al.[254] found neither association. Crocker et al. found an association between particulate level and pneumonia mortality, while Lave and Seskin did not. In most analyses that can be compared, Crocker et al. estimated air pollution effects smaller than those of Lave and Seskin. This difference may be explained largely by the use of additional independent variables in the models of Crocker et al.

In general, the regression analyses of cause-specific mortality show inconsistencies across studies which highlight the sensitivities of these analyses to the selection of independent variables. The colinearity of air pollution variables, and other variables related to mortality, limits the information to be gained from observational studies on the mortality effects of pollutants at low concentrations.

In summary, many of the cross-sectional mortality studies reviewed above either yielded only qualitative findings concerning air pollution mortality relationships or, alternatively, suffer from methodological deficiencies which make it impossible to accept their published findings regarding pertinent quantitative dose-response relationships. Still, on the other hand, at least some of the studies, such as those by Buck and associates[19,199] and Winkelstein,[21-23] have yielded quantitative results not convincingly attributable to potentially confounding or covarying factors and appear to be of use, when appropriately interpreted in light of certain methodological considerations, in arriving at quantitative estimates of air concentrations of TSP or SO_x associated with increased mortality.

14.3.5 Lung Cancer Mortality

Exposure to materials found in the ambient air may be associated with increases in lung cancer under some circumstances. Cigarette smoking is the major known cause of lung cancer, and occupational studies indicate that significantly high risks of lung cancer are associated with exposure to ionizing radiation, fibers, or specific metals. The interactions between smoking, occupations, and ambient air exposure are not well understood.

A number of studies have reported on differences in lung cancer rates in urban and rural areas.[126-137] Higher rates are consistently found in urban areas even after removing the effects of cigarette smoking. Doll and Hill[118] found increased lung cancer deaths for urban dwellers that might have resulted from increased air pollution. They reported that the effect of living in an urban area was insignificant compared with the effect of smoking cigarettes. The assumption is that the major difference has to do with the ambient air pollutant exposures. This may not be the case, as there are many other factors that differentiate urban and rural areas, such as: number of pollutants; meteorological conditions; occupational and other exposures; and social and cultural backgrounds. Unless all the differences between urban and rural communities are controlled for, such comparisons run the risk of being fortuitous The relationships of community size or population density, as indicators of varying potential environmental stresses also show a consistent relationship to lung cancer rates.[137-141] Again, the impact is considerably less than is the effect of smoking, and may be related to other urban-rural differences.

Some investigators[142-144] have compared lung cancer rates for immigrants from a specific country with rates for native born living in both countries. Most of the data suggest that risk for the immigrant, controlling for smoking,

is intermediate to the risk in the native and adopted countries. Considering the long latent period for the development of many cancers, this suggests that in some immigrants the effect of early exposure may develop after emigrating. However, migration involves a time element, a change in place, and differential host characteristics. These studies assume that the populations in the native and adopted countries and factors other than pollutant exposures are similar. Such assumptions are difficult to appraise, but are more often incorrect than correct.

Waller,[126] after reviewing evidence from Britain, concluded that air pollution either alone or in combination with other factors, may contribute in a minor way to the development of lung cancer. He also pointed out the difficulties in assessing relationships between air pollution exposure and the development of any chronic condition during a period of rapidly changing concentrations of air pollution. For example, during the period 1954 to 1965, the annual mean and peak concentrations of smoke in London decreased significantly, as did the concentrations of potential carcinogens such as polycyclic aromatic hydrocarbons,[119] though no significant reduction in SO_2 was recorded.

Wynder and Gori[197] reviewed information relating cancer to environmental factors. They concluded that individuals were able to control many of the factors related to cancer risk and thus individual lifestyles were far more important risk factors for cancer than was air pollution.

Corn[161] estimated relative dose of toxic materials inhaled from various sources and concluded that the impact of the maximum quantity of air pollution permitted by the ambient air quality standard was insignificant compared with that of smoking one pack of cigarettes per day.

Benzo(a)pyrene is a known co-carcinogen and is the one constituent of particulate matter most commonly monitored in ambient air as an index of

potential carcinogenic hazard. Increases in total pollution exposure (dustfall, SO_2, trace elements, and polycyclic hydrocarbons) have been shown to be associated in Japan with increased lung cancer rates in smokers but not in non-smokers.[141] Smoking also has been shown to increase the risk of lung cancer among asbestos workers[145] and uranium miners.[146] There is, however, no evidence that the concentrations of materials in the ambient air are sufficient to stimulate similar smoking-associated increases.

A 1977 report from an international study group[125] concluded that, although data are not consistent and are affected by various types of indoor pollution, the products of fossil fuel combustion (probably acting together with cigarette smoke) are very likely responsible in large urban areas for approximately 5 to 10 cases of lung cancer per 100,000 males per year. On the other hand, from the above discussion, and as noted by other reviewers,[307,308,312] insufficient qualitative or quantitative epidemiologic data presently exists to define clear associations between cancer effects and exposures to atmospheric concentrations of either sulfur dioxide or particulate matter.

14.3.6 Summary for Mortality Studies

In the above discussion, numerous studies on associations between mortality and acute, short-term, or chronic exposures to particulate matter and sulfur oxides were critically evaluated. Many were evaluated as being flawed methodologically or their results likely explainable in terms of confounding or covarying factors to an extent that said findings are taken here as not being useful in helping to develop quantitative health criteria for the effects of atmospheric particulate matter and sulfur oxides. Several other studies, however, were evaluated as being useful for such a purpose and are briefly summarized in Tables 14-21 and 14-22. Note that the values listed in those tables for 24-hr and annual average air concentrations, respectively, at

TABLE 14.21.   SUMMARY OF EVIDENCE FOR MORTALITY EFFECTS OF ACUTE EXPOSURE TO PARTICULATE MATTER AND SO_2 (NON-EPISODIC)

| Type of study | Reference | Effects observed | 24 Hour average pollutant levels at which effects appear | |
			TSP ($\mu g/m^3$)	SO_2 ($\mu g/m^3$)
Daily Mortality	Martin and Bradley[11]	Increases in daily mortality	500-600 (300-500)*	300-400 (200-300)*
Daily Mortality	Martin[6]	Increases in daily total mortality above the 15-day moving average	500-600	400-500
Daily Mortality	Glasser and Greenburg[222]	Increases in daily mortality	350-400	524-786

*From supplemental analysis given in this chapter.

TABLE 14.22. SUMMARY OF EVIDENCE OF MORTALITY EFFECTS OF CHRONIC EXPOSURE TO PARTICULATE MATTER AND SO_2

Type of study	Reference	Effects observed	Annual average pollutant levels at which effects appear	
			TSP ($\mu g/m^3$)	SO_2 ($\mu g/m^3$)
Geographic Comparison	Watanabe and Kaneko[228]	Increased mortality	300	215-266
Geographic Comparison (214 areas)	Buck and Brown[199]	Increased mortality	200 BS (300 TSP)**	200
Geographic Comparison	Wicken and Buck[19]	Increased chronic bronchitis mortality	160 BS (260 TSP)**	115
Geographic Comparison	Winkelstein[188]	Increased mortality	125-140 TSP*	not significant
Geographic Comparison	Burn and Pemberton[20]	Increased chronic bronchitis and lung cancer	680 BS (winter) 270 BS (summer) (350 TSP)**	715 (winter) 270 (summer)

* Two-year arithmetic mean with maximum possible flow correction, from Table 14.19.
**Estimated TSP from 100 BS = 200 TSP and 250 BS = 333 TSP (Holland et al.[4]).

which effects appear represent the best estimate of TSP or SO_2 levels present

and associated with mortality effects demonstrated by particular studies,

taking into account various considerations discussed in the preceeding text

and Chapter 3. Thus, some of the estimates listed in the tables may differ

markedly from those appearing in the published versions of the listed studies.

14.4 MORBIDITY ASSOCIATED WITH SHORT-TERM POLLUTION EXPOSURES

14.4.1 Introduction

Morbidity studies of short-term air pollution exposures are much less

common in the epidemiologic literature than morbidity studies of long-term air

pollution exposures. This reflects the dual complications of the difficulty

of having adequate estimates of pollution exposure as well as the statistical

analytical problems of the health data being collected. For ease of discussion

the studies to be discussed in this section are divided into six categories:

- Episodic morbidity

- Chronic heart and lung symptoms and patients

- Acute respiratory disease

- Aggravation of asthmatic symptoms

- Hospitalization-clinic admissions

- Absences data

- Pulmonary function

Difficulties in either the analysis or interpretation of these classes of

studies will be addressed separately as they appear in this section. Qualita-

tive studies are described only in summary form (Table 14-23). The key con-

clusions derived from such studies are that: (1) clear relationships or

associations exist between various health effects and elevated levels of SO_2

and particulate matter, although the data in the studies do not allow for very

TABLE 14-23 QUALITATIVE STUDIES OF AIR POLLUTION AND ACUTE RESPIRATORY DISEASE

Study	Characteristics	Findings
Angel et al.[69]	Attack rates of minor respiratory illness among 85 London workers, examined every 3 weeks, October 1962-May 1963.	Attack rates were associated with weekly average smoke and SO_2 concentrations.
Levy et al.[70]	Hospital admissions for respiratory disease in Hamilton, Ontario, correlated with sulfur oxide/particulate air pollution index.	Increased hospital admissions on heavy pollution days, except at one hospital far removed from major pollution sources.
Schoettlin and Landau[288]	137 asthmatics reporting attacks on daily occurrence of asthma, September-December, 1956, in Los Angeles Basin.	Significantly more asthma on days of heavier oxidant pollution. No adjustment was made for variations in temperature or season
Zeidberg et al.[289]	Study during 1 year of 49 adults and 34 children with asthma in Nashville, Tenn.	Doubling of asthma attack rates in persons living in more polluted neighborhoods. No adjustment for demographic or social factors.
Cowan et al.[290]	History of asthma, and skin tests of University of Minnesota students, in relation to dust from nearby grain elevator.	Significant association between grain-dust exposure and asthma attacks.
Greenberg et al.[291]	New York City hospital emergency room visits for asthma in month of September.	Emergency room visits strongly associated with onset of cold weather but not with degrees of air pollution during the one month of study.
Weill et al.[292] Carroll[293]	Retrospective study of emergency room visits to New Orleans Charity Hospital.	Periodic "epidemics" of asthma in New Orleans could not be traced to any common pollutant exposure.

TABLE 14-23 (continued)

Study	Characteristics	Findings
Phelps[294] Meyer[295]	"Tokyo-Yokohama asthma" in American servicemen stationed in Japan after World War II.	Disease primarily in smokers attributed to allergic response to atmospheric substances that could not be characterized. Patients improved after leaving the area and were immediately affected on return. Some had long-term effects afterwards.
Glasser et al.[296]	Emergency room visits in seven New York city hospitals during the November 1966 air pollution episode.	Increased emergency room visits for asthma in three of seven hospitals studied.
Chiaramonte et al.[297]	Emergency room visits at a Brooklyn hospital during a November 1966 air pollution episode.	Statistically significant increase in emergency room visits for asthma and for all respiratory diseases, continuing to 3 days after the peak air pollution concentrations.
Derrick[57]	Nighttime emergency room visits for asthma in Brisbane, Australia.	Negative correlation between asthma visits with degrees of smoke shade.
Rao[298]	Pediatric emergency room visits for asthma at Kings County Hospital, Brooklyn, October 1970-March 1971.	Negative correlation of asthma visits with degrees of smoke shade. Lack of temperature adjustments. Considerable distance of hospital district from air monitoring stations.
Goldstein and Black[58]	Emergency room visits for asthma at a hospital in Harlem and in Brooklyn, September-December 1970 and September-December 1971.	Temperature adjusted asthma rates positively correlated with SO_2 values in Brooklyn but not in Harlem. In 1971 period, 50-90% increase in asthma visits on 12 days of heaviest pollution.

TABLE 14-23 (continued)

Study	Characteristics	Findings
Finklea et al.[117]	Incidence of acute respiratory disease, determined at 2-week intervals, in parents of nursery schoolchildren residing in Chicago, December 1969-November 1970.	Acute lower respiratory illness rates were significantly lower among families living in neighborhoods where air pollution had been substantially decreased. Rates were adjusted for social class, smoking, residential mobility, and season of year. Cannot quantitate pollutant exposures.
Finklea et al.[122] [123]	Daily diaries kept by 50 asthmatics in each of three New York City area communities, October 1970-May 1971.	Temperature-adjusted attack rates significantly correlated with total particulates in two of the communities. Increase in relative risk from days of light to heavy pollution was relatively small. High turnover in reporting panels.

*Reference 251

precise quantitation of the specific air concentrations at which the health

effects occur; (2) the particular health effects observed with elevated SO_2

and particulate matter air levels range from temporary pulmonary function

decrements and biochemical changes to rather serious acute respiratory diseases

and exacerbation of preexisting disease processes; and (3) particular population

subgroups (e.g., the elderly, infirm, and children) are at special risk for

manifestation of deleterious health effects associated with short-term SO_2 and

particulate matter exposures.

Included in the further discussion below of quantitative studies of morbidity

associated with short-term exposures to airborne sulfur oxides and particulate

matter is a series of studies conducted by the U.S. Environmental Protection

Agency, most of which were the result of research conducted under the Community

Health and Environmental Surveillance (CHESS) Program,* an integrated set of

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*The matter of misinterpretation or overinterpretation of data or results of
analyses of data collected as part of the CHESS Program contributed to
considerable controversy regarding the validity and accuracy of results
of early CHESS studies, as interpreted and reported in a 1974 EPA
monograph entitled "Health Consequences of Sulfur Oxides: A Report from
CHESS" 1970-71, U.S.EPA Document No. EPA-650/1-74-004 (May 1974). The
controversy eventually led to the 1974 "CHESS Monograph" becoming the subject
of U.S. Congressional oversight hearings in 1976. Subcommittees of the U.S.
House of Representatives Committee on Science and Technology produced a report
on the Monograph, other aspects of the CHESS Program, and EPA's air pollution
research programs generally--a report entitled "The Environmental Protection
Agency's Research Program with Primary Emphasis on the Community Health and
Surveillance System (CHESS): An Investigative Report." Of primary importance
for the present discussion, that report, widely referred to either as the
"Brown Committee Report" or the "Investigative Report" (IR), contained various
comments regarding sources of error in CHESS Program air quality and health
effects data and quality control problems associated with such data collection
and analysis. The I.R. also contained various recommendations to be imple-
mented by the Administrator of EPA pursuant to Section 10 of the Environmental
Research, Development, and Demonstration Authorization Act of 1978
("ERDDAA," P.L. 95-155, 91 Stat. 1257, November 8, 1977). ERDDAA also requires
that EPA and the Agency's Science Advisory Board report to Congress on the
implementation of the IR recommendations.

epidemiologic studies performed between 1969 and 1975. The health status of volunteer participants was either ascertained during single contacts or followed for time periods of up to nine months. These health measures were coordinated with air pollution observations from the residential neighborhoods of the study participants. Areas selected for study were chosen to represent pairs or larger groups exhibiting a substantial pollution exposure range.

Approximately ten CHESS Program studies are cited and discussed in the remainder of this chapter.[113,117,122,123,212,213,214,215,297,306] The rationale for inclusion here of these studies, and qualifications regarding their use, are set forth in Appendix A of this chapter. Generally the studies cited have been included on the same basis as other non-CHESS studies, ie. in light of their potential usefulness in yielding information on quantitative relation-ships between health effects and air concentrations of sulfur oxides and particulate matter. We have attempted to limit the discussion to studies which have undergone peer review and have been published in the open scientific literature apart from internal EPA reports.

Although the 1974 CHESS Monograph itself is not cited or relied upon in this chapter, these considerations reflect the spirit of recommendation 3(b)

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*(continued)

One recommendation of the IR was that an addendum to the 1974 sulfur oxides monograph be published, to be used in part to qualify the usefulness of the CHESS studies, and to apprise the public of the controversy surrounding CHESS. An addendum has been published, and is available from EPA, as announced in the Federal Register of April 2, 1980, 45 F.R. 21702. The addendum is incorporated by reference in this document in partial qualification of the CHESS studies cited herein, and is part of the public file (or docket) established for revision of this criteria document. The addendum contains the full text of the IR, reports to Congress by EPA on its implementation of the IR recommendations, and a report to Congress by EPA's Science Advisory Board on the same subject.

of the IR (1976) that the 1974 Monograph not be used as a source of specific quantitative data or interpretations thereof to serve as the basis for regulatory decisions without explicit qualifications being provided.

14.4.2 Episodes

Several British studies have been published on health effects associated with short-term exposures to sulfur oxides and particulate matter which appear to provide useful information on quantitative dose-effect relationships.

Waller and Lawther,[59] for example, reported that when smoke (BS) concentrations in London increased ten-fold during the course of 2 hours, there was a deterioration in the clinical condition of some patients with bronchitis or asthma. On this day, peak smoke (BS) concentration may have reached 6500 $\mu g/m^3$. SO_2 also increased [maximum about 2860 $\mu g/m^3$ (1.0 ppm)] but H_2SO_4 did not, on the basis of washings from impactor slides. Most of the mass of particulate matter was determined by microscopic studies to consist of particles less than 1 μm in diameter.

Lawther[52] studied associations between daily variations in smoke and SO_2 pollution and the self-indicated health status in 29 British patients with chronic bronchitis. Patients maintained diaries on which their daily condition was indicated in relation to their usual condition. The alternatives were "better," "same," "worse," and "much worse." During the month of January 1954, an episode of relatively high pollution resulted in a sharp increase in the number of patients whose condition worsened as 24-hour smoke (BS) increased to about 400 $\mu g/m^3$ (470 $\mu g/m^3$ TSP) and 24-hour SO_2 increased to about 450 $\mu g/m^3$ (0.15 ppm). Figure 14-4 shows graphically the effects of high pollution levels observed in the 29 bronchitic patients studied in January 1954.
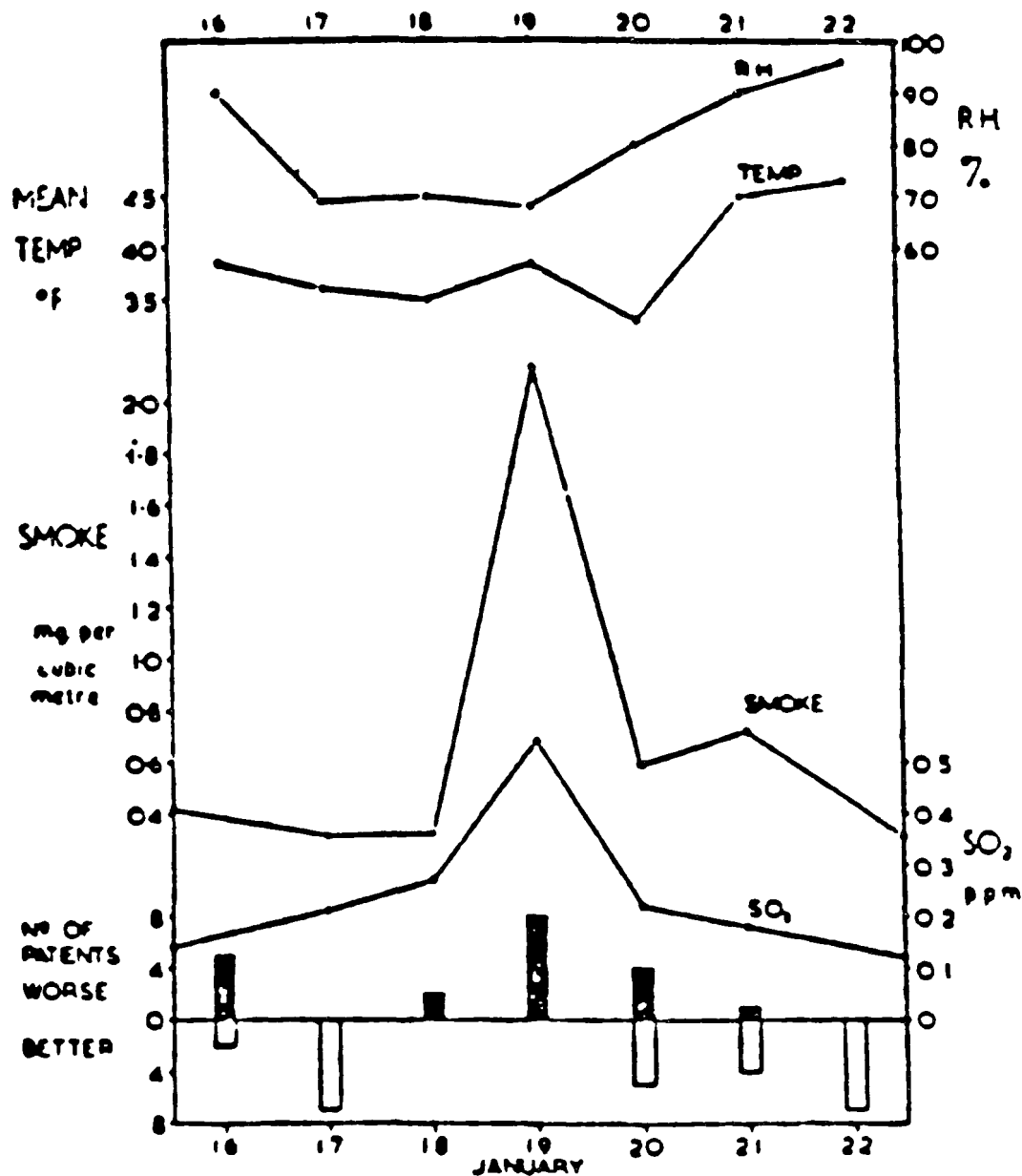
Figure 14-4. Effect on Bronchitic Patients of High Pollution Levels (January 1954).[52,55] (The figure represents the effect on bronchitic patients of increased pollution levels; patients stated whether they regarded their condition as "worse" or "better".)

In the winter of 1955, the study was extended to include 180 patients in the London area. The prevalence of illness was related more closely to pollution than to temperature or humidity during the winter months, and the relationship disappeared when the levels of pollution decreased in the spring. Actual numerical data are not given in the report, but inspection of the figures indicate that prevalence increased with increases in smoke (BS) to about 350 $\mu g/m^3$ (425 $\mu g/m^3$ TSP) and increases in SO_2 to about 300 $\mu g/m^3$. The data suggest that during the winter months, SO_2 was associated more closely with variations in health status; however, in the spring of the year, when pollution concentrations were no longer associated with health status, SO_2 continued to occur in intermittent peak concentrations as high as those associated with increased illness during the winter. However, the association between pollution and illness decreased when smoke (BS) concentrations fell to a fairly consistent 24-hour concentration of less than 250 $\mu g/m^3$ (325 $\mu g/m^3$ TSP). The few short higher peaks in smoke (BS) after this time had little effect on illness status. These investigators state that the results are not indicative of causal relationships, but suggest that the measurements of smoke (BS) and SO_2 are at least indicators of whatever is the cause.

A later report by Lawther et al.[53] gave the results of further extension of these studies into the winters of 1959-60 and 1964-65. The techniques used were similar except that the patients now reported on health status in relation to the previous day rather than in relation to usual conditions. These studies supported the results in previous years in that the worsening of health status was associated clearly with increases in air pollution. The author stated that, although exact relationships between the responses of patients and the concentrations of smoke and SO_2 could not be determined, the minimum pollution leading to any significant response was about 500 $\mu g/m^3$

(0.17 ppm) SO_2, together with about 250 $\mu g/m^3$ smoke (BS). Inspection of the information provided in the report, however, could lead to the conclusion that this is a conservative estimate. Some less consistent, but significant effect may have been occurring with SO_2 concentrations of 250 $\mu g/m^3$ or more.[247] As in the earlier studies, the results appear to relate more closely during the first part of the winter and, in some instances, there was little response to higher concentrations of pollution near the end of the winter. Although the concentrations of smoke and SO_2 closely correlate, examination of the data again suggests that often higher concentrations of SO_2 near the end of the winter, occurring with generally lower concentrations of smoke, produced less response in the study subjects than did the same concentrations of SO_2 earlier in the winter, when smoke was higher. There was some evidence for a loss of interest by participants. When the association between exacerbations and SO_2 pollution concentrations were compared in the two winters, the impression was of a slightly reduced and less consistent, but definite effect during the second winter. The declines in concentrations were from 342 $\mu g/m^3$ BS to 129 $\mu g/m^3$ BS (225 $\mu g/m^3$ TSP) and from 299 $\mu g/m^3$ to 264 $\mu g/m^3$ SO_2.[247] Lawther et al. also emphasized that these responses may reflect the effects of brief exposures to maximum concentrations several times greater than the 24-hour average.[259]

These studies among chronic bronchitis patients in London continued into the 1970s as the frequency of periods of high pollution declined. There were no sharp increases reported in illness scores in the winter of 1969-70,[260] nor in the winter of 1974-75.[261]

Fry et al.[51] reported that home visits for respiratory throat disorders increased from a normal level of about 85 to 150 per day for their clinic patients during the air pollution episode in 1962. However, this rate represented

only 2.4 illnesses per 1000 patients, with no deaths. In the 1952 episode of comparable length, the illness rate was 9.5 per 1000 patients, and there were two deaths. Perhaps their most significant of their observation was that their bronchitis patients were affected but their asthmatic patients were not.

Greenburg et al.[196] found during a New York episode that visits to emergency rooms for cardiac or respiratory illness increased as CoHs approached 3.0 (260 $\mu g/m^3$) and 24-hour SO_2 concentrations reached about 715 $\mu g/m^3$ (0.25 ppm) as air quality improved if the high levels of pollution had any immediate effect. However, lung function deteriorated slightly over the study period as air quality returned to more usual conditions, and therefore no immediate effect could clearly be attributed to the air pollution levels observed although it could not be ruled out the post-episode lung function deterioration might reflect prolonged continuing effects of the pollution episode.

Results also obtained at Rotterdam have shown that when the SO_2 concentration rose for 3 to 4 days from about 300 $\mu g/m^3$ to 500 $\mu g/m^3$ (0.11 ppm to 0.19 ppm), the number of admissions into hospitals for respiratory tract "irritation" rose, especially in older individuals.[302] In one episode in December 1962[312] p. 69, local hospital admissions increased for cardrovascular diseases for those 50 and older land mortality may have increased). Smoke was about 500 $\mu g/m^3$ (24 hour) and SO_2 was about 1000 $\mu g/m^3$.

Stebbings et al.[82] reported on the effects of an episode of high pollution in Pittsburgh on pulmonary function measurements in schoolchildren. Forced expiratory volume and forced vital capacity were measured in 270 fourth, fifth, and sixth grade children attending six schools. Four of the schools were in the high-pollution area in which 24-hour TSP levels had exceeded 700 $\mu g/m^3$ and SO_2 levels had exceeded 300 $\mu g/m^3$ (0.1 ppm). Measurements of air pollution and pulmonary function were not initiated until after the peak of

the episode had passed, but it was speculated that lung function would improve as air quality improved if the high levels of pollution had any immediate effect. However, lung function deteriorated slightly over the study period as air quality returned to more usual conditions, and therefore no immediate effect could clearly be attributed to the pollution levels observed, although it could not be ruled out the post-episode lung function deterioration might reflect prolonged continuing effects of the pollution episode.

Stebbings and Fogleman,[216] also reported on pulmonary function test results on 224 parochial schoolchildren during and after the Pittsburgh air pollution episode of November 1975, then reanalyzed to determine whether a small subgroup of susceptible children could be defined. Individual regressions of $FEV_{.75}$ and FVC on time over the six-day study period were calculated, and the distributions of individual slopes for the four exposed and two control schools were compared. Excesses of strong upward trends in the exposed areas would suggest effects of suspended particulate air pollution by indicating significant improvement following the episode. A highly statistically significant excess of strong upward trends in the FVC among exposed students was observed, and was consistent by sex and by school within sex. Approximately 10 to 15 percent of the students appear susceptible to an average impairment of about 20 percent of the FVC. The findings are limited by the small number of subjects with strong post-episode upward trends in the FVC, and by lack of validation or replication of the study design, but do suggest that episode levels of suspended particulates induce lung damage, and that this may occur only in a small susceptible subgroup. Children with low baseline pulmonary function values, a history of asthma, or with acute respiratory symptoms immediately following the episode were not found to be especially susceptible to these

effects of suspended particulates. No effect of day-of-week, learning, or other potential intervening effects (including regression toward the mean) were noted.

Carnow et al.[174] conducted a study specifically designed to investigate dose-effect relationships between air pollution and morbidity from respiratory disease in patients during the late 1960s with chronic bronchitis, as they related to air pollution exposure in Chicago. Patients, maintained daily calendars of symptoms, grading the severty of their illness from 0 to 4. SO_2 measurements were obtained from eight continuous monitors and from 20 additional stations where 24-hour mean measurements were obtained 3 days a week. From the data and the square mile grid covering the city, an index of exposure was developed for patients based on the locations in which they spent most of their daytime and nighttime hours. In patients over 55 years of age with grades 3 and 4 bronchitis, increases in symptoms were associated with higher SO_2 levels on the same day or on the previous day. Increased symptom rates were reported when the 24-hour SO_2 concentrations were 143 to 257 $\mu g/m^3$ (0.05 to 0.09 ppm). However, the failure to include data on TSP levels, on occupational exposures, or on smoking habits detracts from the value of this study.[307]

Burrows et al.[173] related the occurrence of symptoms recorded daily by patients with chronic bronchitis to continuous monitoring data for gaseous pollutants. No relationships were found, except for hydrocarbons, when data were adjusted for season and daily temperature. It was concluded that 24-hour concentrations of SO_2 played no major role in producing symptoms in people with CRD but temperature probably did. This study was performed in similar

patients in the same city and at about the same time as Carnow's, and the two appear to cancel each other.

Stebbings and Hayes[190] report on a study in New York during 1971-1972. The authors studied the relationship between daily fluctuations in air pollution levels and the aggravation of symptoms in over 300 elderly panelists in the New York City Metropolitan area in 1971-72. Candidates for the study were interviewed and questionnair information was used to classify them as well, heart, lung, or heart-lung panelists. Eligible candidates had to reside within 1.5 miles of a monitoring site and had to be 60 years of age or more. Panelists were included in one of four groups identified as "well"; "lung" (with respiratory symptoms); "heart" (with cardiac symptoms); and "heart-lung" (with both respiratory and cardiac symptoms). The study lasted 34 weeks during which time each panelist was asked to submit weekly diaries through the mail indicating the days on which their symptoms were worse or better than usual. Panelists who submitted diaries for fewer than 11 weeks were excluded from the analyses, of which there were many. Symptoms about which information was requested differed for each panel but together included the presence of angina or chest pain, wheezing, cough and phlegm, shortness of breath and feet swelling. Panelists also gave information on the presence of cough, colds or sore throat, doctor visits and hospitalizations.

Air monitoring consisted of measuring 24-hour mean levels of SO_2 (West-Gaeke), TSP, RSP, SS, SN, and NO_2 (Jacobs-Hochheiser method); the quantitative data for SO_2 and NO_2 for individual days may be less than reliable. Weather data used in the study included maximum and minimum daily temperatures and 24-hour relative humidity.

This report contained a discussion of the method then available for analyzing the data collected and the probable effect of its inadequacies. The authors concluded, however, that despite the qualification and limitations of the methodology, the proportion of the respondents suffering more symptoms on high pollution days than on low pollution days was sufficiently high that the relationships could be detected in the panels as a whole.

Exacerbation of symptoms in the "well" panel was associated with elevated levels of SO_2, RSP, SS, and SN; a similar but weaker pattern was found for the "lung" panel. Symptoms in the "heart" panel related only to SN and TSP. Temperature showed a positive relationship to symptom rates in the "heart" panel, but consistent relationships between temperature and symptoms were not found in the "well," "lung," or "heart-lung" panels. The data suggested no threshold for the effects, and no lesser susceptibility in the well panelist than in the elderly panelist with chronic illness. The high and low ranges of 24-hour pollution concentrations from which the observations were developed were TSP, <60 and >200 $\mu g/m^3$; RSP, <30 and >60 $\mu g/m^3$; SS, <6 and >12 $\mu g/m^3$; SN, <2 and >8 $\mu g/m^3$; and SO_2, <40 and >100 $\mu g/m^3$. The range for minimum temperatures was between <20 and >50°F.

14.4.4 Panel Studies of Acute Respiratory Disease (ARD)

In addition to methodological problems similar to those mentioned for chronic respiratory disease studies, lack of information on specific agents, and exposure to them, may pose a problem in correct classification of acute respiratory diseases. Respiratory tract illnesses, especially in childhood, are critical as both pathogenic and natural history events. Assessment by questionnaire alone is difficult to validate and such history may be inconsistent. On the other hand, definitions and criteria utilized in determining the presence

and nature of acute respiratory illness are important, but not as critical, in that any changes in symptomatology from a baseline (or lack of symptoms) may indicate an acute event, although this does not imply that criteria (symptom, duration and severity dependent) should not be utilized.

For acute conditions, the mode of assessment is more difficult than for chronic conditions in that almost continuous monitoring is required. The use of daily dairies is one mode of assessment, although not lacking in criticism. Symptom information in daily dairies often suffers from errors of omission and from the likelihood that the subjects would complete the dairy at the end of the period of requested recall, which is likely to produce errors of commission. Frequent interviews have been shown to minimize these errors. Gaps in information are the most difficult problem in evaluating acute respiratory illness occurrence in individuals. Meteorological factors are important, perhaps more important than the pollutants. Other covariables and intervening variables of importance include smoking, alcohol consumption, occupational exposures, housing, family size, and structure. Although acute respiratory illnesses may be better indicators of effects of pollutants, temporal analysis of such effects may produce conflicting findings related to covariables, intervening variables, the presence of endemic and epidemic infections, reporting biases, and the environmental interactions of pollutants and weather.[249]

McCarroll et al.[71] studied daily symptoms (from weekly interviews) of over 1800 individuals in three New York City housing projects between 1962 to 1965. This represents 35,400 person-weeks of data. They found that cough frequency was related to SO_2 concentration but not particulate matter. In a further report, McCarroll et al.[205] showed several period of increased SO_2 with associated increases in respiratory and irritation symptoms. One episode

(December 1962) saw a shart increase from 0.1 ppm to over 0.2 ppm in 2 days accompanied by increased symptoms. During another episode SO_2 increased slowly from 0.05 ppm to about 0.14 ppm over a 3-week period (October 1963) with increased symptoms. A third episode occurred in March 1964, with levels exceeding 0.3 ppm and increased symptoms (although there was some lag in symptoms), and corresponding increases in school absenteeism.

McCarroll and colleagues[206] also demonstrated increased prevalence rates for common colds and cough in children and adults in 6-month periods surrounding winter and summer controlling for smoking. However, these were often inconsistent with SO_2. Summer particulates (CoH) were positively correlated with respiratory symptoms with some increase in prevalence rates for days with CoH above 1.50 significant for children. With inclusion of meteorological variables in multiple regression,[207] the incidence rate of common colds was found significantly independently related to SO_2 in some seasons. The prevalence rate of the common cold was significantly related to CoH and meteorological variables, especially in the spring of 1964 (R = 0.93), and "epidemic period."[205]

Cassell et al.[208,209] showed two contrasting trends in the relationship of pollutants to acute respiratory illness in winters, storms and air pollution episodes, the former of which usually hiding the effect of the latter in most analyses.[207] Separated, the air pollutants (CO, COH, SO_2) measured within a quarter-mile of subjects correlated significantly with common cold incidence and prevalence rates in winter (after controlling for weather variables). The winters during this study had mean daily SO_2 levels of 0.17 ppm or greater, mean daily COH of 2.20 or greater, and mean daily CO of 2.94 ppm or greater.[207] Individuals sensitive to the effects of air pollution and weather were delineated.[210] The young (under 10) reacted the greatest to high air pollution combined with

low temperature. Reactions in sensitive individuals were also of greater duration and severity. The reporting of acute illness varied proportionately with social status but did not change the relationships mentioned; the different social status groups weing followed equivalently and simultaneously.

French et al.[306] conducted an ARD study in the New York communites of Bronx, Queens, and Riverhead in 1970-1971. Telephone interviewer made biweekly calls to mothers of families enrolled in the study to inquire whether any family member had developed upper or lower respiratory illness in the 2 weeks and, if so, whether a doctor had been consulted and on how many days activity was restricted. If an individual was reported to have both upper and lower respiratory symptoms, the illness was classified as lower respiratory disease. The major response variables were the number of respiratory illnesses per hundred person-weeks of observation (the attack rate) and an arbitrary severity score, which reflected physician visits, fever, and restricted activity. Selected interviews were repeated a few days after the initial call and concordant results were obtained in over 90 percent of those previously reporting ARD and 98 percent of those previously denying ARD; this shows reproducibility but not validity of reported illness. Total and lower respiratory illness attack rates in Riverhead tended to be lower than in either Queens or Bronx, is consistent with the pollution gradient. Based on NYC DAR levels in 1970, this would indicate more morbidity in areas with SO_2 of 160 $\mu g/m^3$ (Queens) or more and 82 $\mu g/m^3$ TSP or more (Queens) compared to 39 $\mu g/m^3$ TSP in (Riverhead). See Appendix A for further discussion regarding the results and their interpretation from this EPA CHESS Program study.

French et al.[306] also reported on an ARD study in families of nursery school children in Chicago for one year (12/69-11/70). A census was obtained

on families agreeing to participate using a standardized questionnaire. Migration, crowding and education were obtained and compared between areas. Telephone interviews by trained interviewers were made fortnightly to the mother or guardian concerning new respiratory illnesses and their symptoms, and any medical consultation. Lower respiratory illnesses (LRI's) were limited to chest colds with a persistant productive cough, croup, bronchiolitis, or pneumonia. A sample of replies were compared to physicians' records to validate reports. There were 2705 fathers, mothers and children (ages 112) participating. Areas of relative pollution were grouped into two categories (see Table 14-24). All families resided within 1 1/2 miles of an air monitoring station. There was an increased attack rate of ARD in all family members with 3 or more years residence in that area. Except for children under 3, all family members in the high pollution areas had an excess risk of acute LRI (Table 14-25). Upper respiratory illness (URI) rates were higher in all family member in the high pollution areas. These higher ARD rates were still significant after adjusting for family smoking (Table 14-26); The pollution effect was independently significant. See Appendix A for further discussion regarding the results of this EPA CHESS study and their interpretation.

TABLE 14-24. CHICAGO MEAN ANNUAL LEVELS OF POLLUTANTS IN AREAS, 12/69-11/70

	SO_2 ($\mu g/m^3$)	TSP ($\mu g/m^3$)	SS ($\mu g/m^3$)
LOW	57	111	14.5
HIGH	106	151	16.0

Family Segment	Community Pollution Exposure	Family Changed Address During Previous 3-5 yr	Involving Upper Tract	Involving Lower Tract	All Acute Respiratory Illness
Chicago Fathers	Intermediate	No	1.00(2.59)*	1.00(0.42)	1.00(3.01)
	Highest	No	1.21	2.29	1.36
	Intermediate	Yes	1.27	1.10	1.25
	Highest	Yes	1.20	0.90	1.14
Mothers	Intermediate	No	1.00(3.96)	1.00(0.64)	1.00(4.60)
	Highest	No	1.46	1.45	1.46
	Intermediate	Yes	1.14	1.53	1.19
	Highest	Yes	1.24	1.22	1.28
Older siblings	Intermediate	No	1.00(4.09)	1.00(0.63)	1.00(4.73)
	Highest	No	1.37	1.44	1.80
	Intermediate	Yes	1.14	0.81	1.09
	Highest	Yes	1.17	0.82	1.25
Nursery school children	Intermediate	No	1.00(7.57)	1.00(1.63)	1.00(9.20)
	Highest	No	1.12	1.30	1.15
	Intermediate	Yes	1.05	1.25	1.09
	Highest	Yes	1.21	1.53	1.24
Younger siblings	Intermediate	No	1.00(7.65)	1.00(2.84)	1.00(10.49)
	Highest	No	1.27	0.93	1.18
	Intermediate	Yes	1.16	0.90	1.09
	Highest	Yes	1.65	1.00	1.43
New York Fathers	Low	No	1.00(1.77)	1.00(1.66)	1.00(3.43)
	Intermediate (pooled)	No	0.95	1.39	1.16
	Low	Yes	0.85	1.27	0.95
	Intermediate (pooled)	Yes	0.65	1.35	0.89
Mothers	Low	No	1.00(2.51)	1.00(1.80)	1.00(4.31)
	Intermediate (pooled)	No	0.91	1.56	1.18
	Low	Yes	1.04	1.67	1.30
	Intermediate (pooled)	Yes	0.83	1.12	1.20
School children	Low	No	1.00(2.80)	1.00(3.25)	1.00(6.06)
	Intermediate (pooled)	No	1.09	1.23	1.16
	Low	Yes	0.93	1.08	1.00
	Intermediate (pooled)	Yes	0.94	1.21	1.18
Preschool children	Low	No	1.00(2.71)	1.00(5.47)	1.00(8.18)
	Intermediate (pooled)	No	1.26	1.25	1.25
	Low	Yes	1.48	0.73	0.98
	Intermediate (pooled)	Yes	1.19	1.21	1.15

TABLE 14-25—Acute Respiratory Illness Among Families Living in Two Metropolitan Areas

*Figures in parentheses indicate base rate per 100 person weeks of risk.

TABLE 14-26 — Smoking-adjusted, Acute Respiratory Disease Attack Rates*

Family Segment	Community Air Pollution Exposure	Relative Risk of Acute Respiratory Illness
Chicago		
Fathers	Intermediate	1.00 (2 80)
	Highest	1.33
Mothers	Intermediate	1.00 (4 76)
	Highest	1.25
Older siblings	Intermediate	1.00 (7.04)
	Highest	1.18
Nursery school students	Intermediate	1.00 (0.35)
	Highest	1.02
Younger siblings	Intermediate	1.00 (9 41)
	Highest	1.37
New York		
Fathers	Low	1 00 (1.58)
	Pooled Intermediate	1.41
Mothers	Low	1.00 (1.72)
	Pooled Intermediate	1.55
School children	Low	1.00 (3 97)
	Pooled Intermediate	1.09
Preschool children	Low	1.00 (6.12)
	Pooled Intermediate	1.10

*Families lived at least three years in these communities; differing air pollution exposures in metropolitan Chicago

All ARD diary studies experienced attrition over time and some methodological problems plagued them. It is likely, however, that families exposed to high levels of urban pollution experienced higher ARD attack rates than did those less exposed.

A couple of studies have investigated relationships between the incidence of acute respiratory disease and very high air pollution concentrations.

Kalpazanov et al.[63] studied by regression analyses the relationship between the daily number of newly reported cases of influenza during an epidemic in Sofia, Bulgaria, and specific meteorologic or air pollution factors. The number of new cases was taken from the official registration. Sundays and Mondays were eliminated since it was shown that many Sunday illnesses were not recorded until Monday. Aerometric samples were collected daily from 8:00 a.m. until noon in the city center. Correlation coefficients were developed for each factor for the day on which the illness was reported, for the previous day, and for 2 days prior to the reporting of the illnesses. Results indicated that the same-day measurements of air temperature, visibility, SO_2, oxidants, cloudiness, and wind velocity all related to the number of illnesses reported. Oxidants, however, showed a negative correlation. On the day prior to the reporting of illnesses, only SO_2 was related significantly ($r = 0.6$); 2 days prior to the reporting, nitric oxides, formaldehyde, and oxidants were associated, oxidants again with a negative correlation. The authors compared these results with those of an earlier 1972 influenza epidemic also in Sofia[64] in which almost the same protocol was followed. In 1972, but not in 1974-75, dust was associated with illness reporting; a possible explanation of this was the much lower dust measurements in 1974-75. Nitric oxides were also lower in 1974-75, while SO_2 was about three times higher.

14.4.4 Aggravation of Asthmatic Symptoms

Cohen et al.[55] studied attack rates in 20 asthmatics over a period of 7 months and showed significant correlations between reported attack rates and temperature as well as between reported attack rates and 24-hour mean air pollution levels after the effect of temperature had been removed from the analysis. Temperature showed by far the strongest association with attack rates in multiple regression analyses. However, SO_2, TSP, SS, SN, and soiling index (CoHs) each explained a significant portion of the residual after the effect of temperature had been removed. After temperature and any one pollutant had been removed, none of the other pollutants explained a significant amount of the variation in attack rates. Thus, the overall effect of air pollution can be attributed to no specific pollutant. Significant 24-hour concentrations were assessed as: TSP, 150 $\mu g/m^3$; SO_2, 200 $\mu g/m^3$ (0.07 ppm); suspended sulfates 20 $\mu g/m^3$; or suspended nitrates, 2.0 $\mu g/m^3$.

Kurata et al.[56] found no associations between weekly mean concentrations of SO_2, NO_2, O_3, or CO and asthma symptoms. In this multifactorial study, weekly mean concentrations of SO_2 averaged less than 280 $\mu g/m^3$ (0.10 ppm), but occasional weekly highs reached 500 $\mu g/m^3$ (0.17 ppm). It may be, however, that asthma attacks would relate much more closely with daily means or daily peaks than with weekly mean concentrations of pollution.

Many studies of asthma failed to evaluate many relevant factors, including medication (steroids), humidity, exercise, daily temperature changes, other pollutants, pollen, emotional factors, and exposure to smokers at home or work.

14.4.5 Hospital/Clinical Admission Studies and Absence Studies

Visits to the emergency room provide a health outcome measure of a more severe type than is generally provided by physician visits. Emergency room records are frequently more complete, especially as to the acute episode, than

are physician records. For these reasons, such disease outcomes have been utilized in several studies of the acute health effects of air pollution. Frequently, these studies have examined cause-specific reasons for the visits, such as asthma. Most of these studies have been temporal in nature, although some have compared of visits to hospitals in different regions of the city. Data organization and analyses are usually similar to analyses of daily mortality.

Unfortunately, emergency room visits have the same problems with denominators and reference populations as do other types of visits or medical records. Also, it is difficult to relate spatio-temporal exposures to specific health events or to the perceptions of those who come into the emergency room. Finally, with the increased use of the emergency room as a family practice center, fewer visits are associated with any acute exposure or attack.

Although hospital admissions have some of the same problems associated with emergency room visits, more information is generally available from the records. Hospital studies are limited, however, in terms of the finite number of people that can be admitted.

During the winter of 1972 or 1973, Kevany[15] studied 2364 admissions to study hospitals. Data for cardiovascular disease and respiratory disease admission rates showed very low (r <.30) but significant correlations for both sexes between heart diseases and smoke or SO_2. Insufficient exposure data were provided.

Heimann[54] studied the effect of short-term variations in pollutant levels on the frequency of clinic visits for Boston patients with chronic respiratory disease. These studies were conducted during periods of higher pollution in 1965 and 1966. Although indicated associations were less than in New York during episodes, there was a positive association between pollution levels and

clinic visits even though the maximum 24-hour geometric means from 20 stations were 226 μg/m^3 for high-volume TSP, 350 μg/m^3 (0.12 ppm) for SO$_2$, and 2.2 for CoHs.

Sterling et al.[72,73] used data from a medical insurance group to obtain information on relationships between air pollution and hospital admission for "relevant diseases" among about 10,000 individuals in California. Daily pollution concentrations were given as the mean of the maximum and minimum values of measurements taken at eight stations, 5 to 10 weeks apart, from March to October. After allowing for the confounding effects of day-of-week, deviation of stay, higher relevant admission rates occurred on those days among the highest third of sulfur dioxide pollution than on those days among the lowest third. The sulfur dioxide concentration mean for was about 45 μg/m^3 (0.015 ppm); concentrations on the highest pollution day were not reported) They also correlated with NO$_2$, OX, TSP, but not with temperature or humidity. Correlations were low and SO$_2$/TSP concentrations were low. Consequently, one of the other pollutants with which illness rates were associated (CO, NO$_2$, or O$_3$) may have been more significant. The indicated association for SO$_2$ may have been caused by the interrelationships between pollutants. It is difficult to state to what extent either SO$_x$ or TSP were causally involved in producing the health effects observed.[307]

Illness data were obtained in many of the early severe pollution episodes.[2,] This information did little more than confirm the mortality results, though there was some evidence that the increase in illness was not as large in percentage terms as the increase in deaths, and the effects were not so sudden. Martin[6] examined hospital admissions for the winters of 1958 to 1959 and 1959 to 1960 and found, after adjustment for day of the week and correction for 15-day moving average, significant correlations for both

cardiovascular and respiratory conditions with smoke and sulfur dioxide. The average deviations by group are shown in Tables 14-27 and 14-28 and show more irregularity than the mortality data.

Fletcher et al.[274] and Angel et al.[69] followed 1,136 working men aged 30 to 59 in West London by surveys at 6-month intervals. The surveys included collection and measurement of morning sputum volume and FEV,as well as data from respiratory symptom questionnaires. Expected patterns of decline in lung function with age occurred, and this was most rapid in cigarette smokers with low lung function to start with. Another finding was a decrease in sputum volume in men with constant smoking habits most consistently in the winter samples. During six years of study, there was a decrease in mean sputum volume during the first morning hour from about 1.5 ml to about 0.75 ml, associated with a decrease in smoke (annual) from 140 $\mu g/m^3$ (234 $\mu g/m^3$ TSP) to 60 $\mu g/m^3$. Possible changes in cigarette tars, and in methods of smoking could have influenced this result.[251] During the winter of 1962 to 1963, they intensively monitored a subsample of 87 men. The incidence and prevalence of respiratory illnesses were associated with both BS and SO_2, though the prevalence was more related to smoke. Weekly concentrations were about 300 $\mu g/m^3$ BS (370 $\mu g/m^3$ TSP) and 400 $\mu g/m^3$ SO_2.

Studies of the acute effects of air pollutants and exacerbations in chronic respiratory disease related to pollutant exposures have been conducted by various investigators using absenteeism records. The use of these records is complicated by the lack of shorter illnesses, the specific diseases (if really present), the nature of the population under study, the absence of weekend information, the absence of co-morbidity information, the absence of covariable information (including smoking). and by such variables as day-of-week

TABLE 14-27. AVERAGE DEVIATION OF RESPIRATORY AND
CARDIAC MORBIDITY FROM 15-DAY MOVING AVERAGE,
BY SO_2 LEVEL (LONDON, 1958-1960)

SO_2 Level ($\mu g/m^3$)	Number of days	Mean Deviation
400-499	9	2.2
500-599	6	5.1
600-799	9	6.9
800-899	6	12.8
900+	5	12.8

TABLE 14-28. AVERAGE DEVIATION OF RESPIRATORY AND CARDIAC
MORBIDITY FROM 15-DAY MOVING AVERAGE,
BY SMOKE LEVEL (BS) (LONDON, 1958-1960)

Smoke Level ($\mu g/m^3$, BS)	Number of days	Mean Deviation
500-599	9	3.2
600-699	6	-0.7
700-799	9	2.4
800-1099	8	4.9
1100+	7	12.9

effects, season, holidays, etc. Nevertheless, these studies have been meaningful, when appropriately done and when some of the shortcomings have been overcome.

Dohan and Taylor[66] and Dohan[67] studied relationships between 24-hour air pollution concentrations (measured biweekly) and respiratory illnesses lasting more than 7 days in female workers in five United States cities. The workers, all with one company, received insurance payments after the seventh day of illness when a physician attested to the illness. Over a period of 3 years (1957-1960), illness absence rates were related to measured concentration of suspended particulate sulfate but not to TSP (range 100 to 190 $\mu g/m^3$), benzene-soluble organics or specific trace metals. Among the five cities the lowest case rate was associated with mean 24-hour sulfate concentration of 7 $\mu g/m^3$ and the highest rate was associated with mean 24-hour sulfate concentrations of 20 $\mu g/m^3$.

Ipsen et al.[68] studied employees from the same company but restricted their investigations to one city and approximately 20,000 employees. As an indication of illness frequency, the sum of dispensary visits during a particular week was divided by the average working population. Air monitoring data were obtained from the Department of Community Health Services of the City of Philadelphia, Air Pollution Control Section. Data obtained included daily measurements of TSP, suspended sulfates, and soiling index (CoHs), but not SO_2. Results indicated that periods of high particulate sulfate levels and low temperatures were associated with high morbidity and that low sulfate levels and high temperature were associated with low morbidity. No pollutant had a notable effect over those of weather variables, but the sum of the air pollutants, although actual concentrations were not reported, were said to be positively correlated with prevalence measured on the same day, or with a lag

of 7 days. This study did not consider the significant age differences, smoking habits, or differences in weather and climate among these cities.

Gregory[60] found that in the 1950's, sickness absences at a Sheffield steelworks increased as monthly mean concentrations of smoke (BS) and SO_2 increased. The monthly data provide little information relative to the actual effective air pollution values. These original data were reviewed by Holland et al.[4] who concluded that rough judgment estimates of the concentrations associated with increases in sickness absences were 24-hour means above 1,000 $\mu g/m^3$ for smoke (BS) and above 850 $\mu g/m^3$ (0.3 ppm) for SO_2.

Gervois et al.[61] made a comparison of sickness absence records of French employees, with daily variations in smoke, SO_2, and temperature, for 89 days during a winter season. Although pollution concentrations were similar in each of two towns involved in the study, positive associations between pollution and illness were obtained in only one. In this town, some association was found after adjusting for temperature. Although the daily pollution data were not given, the highest 24-hour mean values in the town with the positive association were about 200 $\mu g/m^3$ for both smoke and SO_2. The mean values for the 3-month period were 53 $\mu g/m^3$ for smoke and 37 $\mu g/m^3$ for SO_2; therefore, an estimate of higher values associated with increased illness could be between 100 and 200 $\mu g/m^3$ for both smoke and SO_2.

Verma et al.[65] reported that in a multiracial population of males and females 16 to 64 years of age who worked for an insurance company in New York, minimum respiratory disease absences occurred on hot days (maximum temperature >76°F) when the 24-hour mean SO_2 levels were low (29 to 143 $\mu g/m^3$; 0.01 to 0.05 ppm). Higher SO_2 levels increased absence rates. On cooler days (maximum temperature <50°F), when SO_2 and suspended sulfates both were high, respiratory

illness absence rates were highest. Air pollution data for this study were provided by the Department of Air Pollution Control of the City of New York but information for particulates was not reported.

Burn and Pemberton[20] found that incapacity for work due to bronchitis among Salford, England, workers exceeded the expected number by a factor of two when 24-hour mean smoke concentrations exceeded 1000 $\mu g/m^3$ for 2 consecutive days, thus relating bronchitis morbidity to smoke. It is possible, however, that the episode conditions indicated by smoke concentrations above 1000 $\mu g/m^3$ may have included sufficient SO_2 or derivatives (H_2SO_4 or sulfates) to produce the increased morbidity.

Additional information on the relationships between air pollution concentrations and absences from work has been reported from the British Ministry of Pensions and National Insurance[62]. This information indicates that sickness absences (October 1961 to March 1962) for bronchitis, influenza, arthritis, and rheumatism all occurred more frequently in high-pollution areas. Daily pollution measurements were not provided, but data from five areas in Scotland and around London showed correlations between bronchitis and pollution that were stronger for SO_2 than for smoke. In these areas, the lowest bronchitis inception rate appeared to be related to smoke levels between 100 and 200 $\mu g/m^3$ and SO_2 between 150 and 250 $\mu g/m^3$ (0.053 and 0.081 ppm). In South Wales, however, more bronchitis appeared to be associated with lower pollutant concentration, and lowest inception levels appeared to be less than the values stated for the other study areas. The cause of the higher bronchitis rates in South Wales is not clear.

14.4.6 Pulmonary Function Studies

Lawther et al.[78-81] have reported on relationships between ventilatory function measurements in four subjects and daily concentrations of smoke and

SO$_2$ from 1960 to 1971. The tests performed daily included forced vital capacity, forced expiratory volume, maximum midexpiratory flow, and peak expiratory flow rates. During the period of study, 24-hour smoke concentrations ranged from 10 to 650 μg/m^3, and 24-hour SO$_2$ ranged from 50 to 1500 μg/m3. Increases in SO$_2$ were most consistently associated with poorer test results. However, small decreases in function were associated with large increases in SO$_2$. Peak flow rates in all subjects were related significantly with either smoke or SO$_2$ (p < 0.05), but were reduced by only 4 percent.

Emerson[37] conducted weekly spirometric measurements on 18 patients with chronic airway obstructions during 1969-1971 in London. They found them (FEV$_1$ and MEFR) to correlate with changes in atmospheric conditions and with air pollution. FEV$_1$ was more correlated with temperature. Average smoke (BS) concentrations were 45 μg/m^3 together with average SO$_2$ concentrations of 190 μg/m^3 (0.07 ppm) pollution figures were averaged for 5-day periods while operometric measures were made on specific days. Only one subject had significant responses. This is a weak study[312,314b] although some authors[308] consider it to demonstrate levels of no effect.

Ramsey[83] studied bronchoconstricting tendencies and pulmonary function on a daily basis over a 3-month period in seven male, non-smoking asthmatics 19 to 21 years old. Three spirograms were produced each day at hourly intervals. A Warren & Collins 13.5 liter respirometer was used. The three values were averaged for FEV$_{1.0}$, MEFR, MMFR, and flow rate. No information was provided on the method and techniques for calibrating the instrument. Results were analyzed by multiple regression, and values were considered significant only when p < 0.001 (r > 0.42). Results showed that in three of the seven subjects, one or more of the pulmonary function tests (MEFR, MMFR, flow rate, 10 to 25

or 50 percent volume) was correlated with mean air temperature on the day of the tests or on the previous day. Two subjects also showed correlation, each in a single test parameter, with barometric pressure on the previous day, and two showed positive, not negative, correlations between specific test results and daily mean ozone concentrations. None of the test results showed significant correlation with 24-hour TSP measurements that averaged 82.5 ± 35.5 $\mu g/m^3$ (maximum, 175 $\mu g/m^3$), or 24-hour sulfate concentrations that averaged 3.2 ± 1.8 $\mu g/m^3$ (maximum, 7.5 $\mu g/m^3$). Protein (daily mean, 1.28 ± 0.7 $\mu g/m^3$) and total organics (average, 22.1 ± 9.8 $\mu g/m^3$) also showed no significant correlations with test results. The investigator concluded that temperature and barometric pressure appear to be more instrumental in promoting tendencies to asthmatics' dyspnea than do exposures to ambient air pollutants even when levels of the pollutants exceed Federal air quality standards.

Shepherd et al.[327,328] studied 10 respiratory patients for 3 months. Several function measurements were negatively correlated with relative humidity and CoH of 8 or more per day (1140 $\mu g/m^3$). Lebowitz et al.[180] tested pre- and post exercise lung function in children 6 to 12 years of age in a smelter town on 4 days with high temperature and varying SO_2/TSP (measured near the test site), and in children 10 to 12 in an urban area on 4 days with high temperature and varying TSP (measured nearby). A portable pneumotachygraph was used in the latter study to measure FVC and $FEV_{1.0}$ and MMEF in the former study. The two instruments were compared in a group of subjects and differences were less than one percent. Results controlled for time of day, smoking, and respiratory medical history, showed that exposures to high temperatures produced post exercise decreases in FVC and $FEV_{1.0}$ that were related to the relative level of pollution and temperature. In comparison, a nonexercise (cross-over)

control group showed nonsignificant declines on high air pollution days. During testing, outdoor temperatures were always above 86°F and relative humidity was less than 30 percent. SO_2 ranged from <1 ppm to 5 ppm and absolute TSP was unknown during testing in the smelter town. In the urban area, TSP on high days averaged 106.7 $\mu g/m^3$ and on low days averaged 98.3 $\mu g/m^3$; suspended sulfate was low and photo-oxidant levels were not known in absolute terms but were considered equivalent. A control group who remained indoors in an air conditioned building where pollution was low showed no significant differences in pulmonary function (measured with the Collins 13.5 liter spirometer) that could be related to the type or degree of exercise, day of week, or time of day.

Summarized in Table 14-29 are the results of quantitative studies reviewed above as providing information on associations between morbidity effects and elevated levels of sulfur oxides and particulate matter. Examination of the table reveals that several studies have shown worsening of health status among bronchitic patients and increased hospital admissions to be associated with acute exposures to TSP and SO_2 levels as low as 200-350 and 300-500 $\mu g/m^3$, respectively. Also, other study results suggest that decreased pulmonary function and increased respiratory symptoms in normal populations, as well as increased symptomatology in asthmatic patients, may all be associated with somewhat lower levels of TSP and SO_2 (between 150 to 250 $\mu g/m^3$ and 250 to 300 $\mu g/m^3$, respectively.)

TABLE 14-29. SUMMARY OF EVIDENCE FOR MORBIDITY EFFECTS OF ACUTE EXPOSURE TO SO_2 AND PARTICULATES

Type of Study	Reference	Effects observed	24-hour average pollutant levels at which effects appear	
			TSP ($\mu g/m^3$)	SO_2 ($\mu g/m^3$)
Morbidity Acute-hospital	Martin[16]	Increases in hospital admissions for cardiac or respiratory illness	500	400
Acute-clinical	Lawther et al.[53]	Worsening of health status among 195 bronchitics	250 BS (344 TSP)	300-500
Acute-long. (Daily - 3 yrs)	McCarroll et al.[205 206]	Increased ARI daily inc/prev	100 BS (200 TSP)	372
Acute-long.	Cassell et al.[208 209]	Increased ARI average daily inc/prev	145 BS (245 TSP)	452
ER visits	Greenberg et al.[196]	Increased cardio-respiratory visits	260 BS (340 TSP)	715
Acute - children	Stebbings et al.[216]	Decreased $FEV_{.75}$	700	300
Acute-clinical CB/AS	Waller and Lawther[59]	Increased symptoms in patients in 2 hours	6500 BS (1° resp.)	2860
Acute-clinical CB	Lawther et al.[52]	Decreased condition	400 BS 250-350 BS	450 300
Acute-clinical CB	Stebbings and Hayes[190]	Increased symptoms	200 (60 RSP) 12SS (8SN)	100
Acute-AS	Cohen et al.[55]	Increased asthma attacks	150 (20SS)	200

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TABLE 14-29 (continued).

Type of Study	Reference	Effects observed	24-hour average pollutant levels at which effects appear	
			TSP ($\mu g/m^3$)	SO_2 ($\mu g/m^3$)
Acute-clinical visits	Heimann[54]	Increased visits by CRD patients	226	350
Absenteeism	Gervois et al.[61]	Increased, male workers	100-200 BS	100-200
Absenteeism	British Ministry Pension[62]	Increased, male workers	100-200 BS	150-250

14.5 MORBIDITY ASSOCIATED WITH LONG-TERM POLLUTION EXPOSURES

14.5.1 Introduction

Morbidity means the presence of any state of illness or disease. It may represent acute disease or chronic disease. It may represent symptoms in one organ system or in many. It may even represent temporal variations in symptoms of a specific or a general nature. The incidence of morbidity represents the new onset of morbidity, while the prevalence represents the presence of morbidity. The incidence rate is usually the number of new cases over the number of persons at risk in a given place during a given time. Prevalence rate is the number of present cases over the number at risk in a given place for a given period of time. Incidence and prevalence are usually obtained by questionnarie. In general, morbidity is harder to ascertain than mortality, but is usually a more sensitive indicator of health effects of ambient air pollutants. (Goldsmith, 1977: Lebowitz, 1973a, Speizer, 1969).

Studies of morbidity associated with long-term pollution exposures represent the largest portion of epidemiologic air pollution studies. This is true in part because it is easier to characterize long-term exposure (one or more years) than short-term exposure (24 hours or less). For convenience the studies are divided into six subcategories, based on the health end point: (1) chronic bronchitis prevalence studies, (2) other respiratory disease/symptom prevalence studies, (3) panel studies of acute respiratory disease, (4) pulmonary function studies, (5) studies combining respiratory disease symptoms with pulmonary function, and (6) hospitalization-clinic admission-absence studies.

Emergency room visits, hospital admissions, and physician visits represent one measure of morbidity. They have been used frequently in examining the

health effects of different levels of ambient air pollutants. Unfortunately, appropriate denominators (the number of those at risk) are not generally available in studies that use these measurements, and the populations so described may be very specific sub-populations, presenting difficulties of definition and preventing generalizations from the results.

Absenteeism from work or school due to specific morbidity is sometimes used to determine the effects of pollutants. This method presents difficulties in ascertaining of cases and of causes. Even more than hospital and physician visits, absenteeism is directly related to the day of the week, the season, and other social and behavioral factors. Absenteeism is also dependent on interpretation by health or administrative personnel. Very often, absenteeism is not examined unless it exceeds a certain number of days, and this seriously limits it as a sensitive indicator of pollutant effects.

In the various types of epidemiologic studies, changes in some biological function over time may be a good indicator of the effects of pollutants. Such changes may include altered pulmonary function, alterated immunologic responses, or altered biochemical activities or functions. These are usually quite sensitive measures of biological activity, although they do not necessarily represent meaningful stages of morbidity. Such measurements usually require an expenditure of greater resources and greater cooperation on the part of subjects or patients. Changes in function are measured in terms of percent change over time or change in absolute function in individuals over time.

Morbidity studies typically employ one of three experimental design strategies: spatial, temporal, or spatiotemporal. Spatial studies examine health end point differences between communities (geographic areas) with

differences in pollution exposure. Since it is impossible to find communities with characteristics that are identical except for pollution exposure, it is necessary to account for these differences. This can be done either by sub-dividing the communities into similar subgroups or by adjusting for the differences in the analysis. These differences typically include age, race or ethnic group, sex, socioeconomic status, smoking habits, and general health care. A critical examination of any spatial study must consider all factors exerting an effect on the health end point. A study's credibility depends on the adequacy with which it considers these factors.

Temporal studies associated with long-term pollution exposure are less common than spatial studies. A temporal study compares the changes of the health end point through time with the changes in pollution. Each community acts as its own control, making the factors critical to the spatial studies much less important. Temporal factors such as temperature, season, other meteorologic factors, and influenza cycles become critical. The appropriate statistical analyses for such studies often have not been available at the time of analysis. Studies should be judged on their ability to cope with these factors and problems. Many long-term temporal studies are also spatial studies, and thus offer a comparison of the two designs.

Common to both spatial and temporal designs is the problem of estimating pollution exposure. The specificity of exposure assessment ranges from crude indices such as coal combustion to sophisticated continuous monitors at several locations. Unfortunately, even the most sophisticated devices have a history of problems such as gross inaccuracies and non-specificity. More difficult is the extrapolation from the measurements at a monitoring site to individual

exposure levels. A major improvement in this characterization would be the use of personal monitors. Although studies have been undertaken using these, none have yet been published. Qualitative studies of morbidity associated with long-term exposures to particulate matter or sulfur oxides are summarized in Table 14-30. Studies yielding more quantitative information on the same subject are discussed in more detail in the next several sections.

14.5.2 Chronic Respiratory Disease Prevalance Studies

Studies of the relationships between air pollution concentration and the prevalence of chronic bronchitis have been reported from several countries. Among the studies of morbidity, the chronic bronchitis indicator has most consistently given positive associations. Nevertheless, there are a number of problems encountered in attempts to interpret the data reported. These arise from the fact that criteria for diagnosing chronic bronchitis are not consistent around the world.

Historically, chronic bronchitis has been the most commonly utilized representation of obstructive lung diseases and has most often been defined or quantified in terms of answers to the British Medical Research Council's Respiratory Questionnaire (BMRC), in one of its several versions. This definition generally implies that the subject has a persistent cough and/or phlegm, meaning cough and/or phlegm that occurs on most days for as many as 3 months of the year; in addition, the definition may require that the subject has had these symptoms for at least 2 years. Although labelled "chronic bronchitis," this illness differs from clinically diagnosed chronic bronchitis in several respects. The clinical diagnosis may be made on the basis of the presence of one or more criteria, including not only responses to that question in a clinical setting, but also responses to questions about wheeze,

TABLE 14-30. QUALITATIVE STUDIES OF AIR POLLUTION AND PREVALENCE OF CHRONIC
RESPIRATORY SYMPTOMS AND PULMONARY FUNCTION DECLINES

Study	Characteristics	Findings
Fairbairn and Reid[265]	Comparison of respiratory illness among British postmen living in areas of heavy and light pollution	Sick leave, premature retirement, and death due to bronchitis or pneumonia were closely related to pollution index based on visibility
Mork[266]	Questionnaire and ventilatory function tests of male transport workers 40-59 years of age in Bergen, Norway and London, England	Greater frequency of symptoms and lower average peak flow rates in London. Differences were not explained by smoking habits or socioeconomic factors
Deane et al.[267]	Questionnaire and ventilatory function survey of outdoor telephone workers 40-59 years of age on the west coast of U.S.	Increased prevalence of respiratory symptoms, adjusted for smoking and age, a larger volume of morning sputum and a lower average ventilatory function in London workers, and in the English compared with American workers. No differences in symptom prevalence between San Francisco and Los Angeles workers, although particulate concentrations were approximately twice as high in Los Angeles
Cederlöf,[39] Hrubec et al.[40]	Chronic respiratory symptom prevalence in large panels of twins in Sweden and in the U.S. Index of air pollution based on estimated residential and occupational exposures to SO_2, particulates, and CO	Increased prevalence of respiratory symptoms in twins related to smoking, alcohol consumption, socioeconomic characteristics, and urban residence, but not to indices of air pollution

TABLE 14-30   QUALITATIVE STUDIES OF AIR POLLUTION AND PREVALENCE OF CHRONIC
RESPIRATORY SYMPTOMS AND PULMONARY FUNCTION DECLINES

Study	Characteristics	Findings
Bates et al.[268-270]	Comparison of symptom prevalence, work absences, and ventilatory function in Canadian veterans residing in 4 Canadian cities	Lower prevalence of symptoms and work absences and better ventilatory function in veterans living in the lest polluted city
Bates[271]	10-year follow-up study of Canadian veterans initially evaluated in 1960, and followed at yearly intervals with pulmonary function tests and clinical evaluations	Least decline in pulmonary function with age in veterans from least polluted city
Yashizo[272]	Bronchitis survey of 7 areas of Osaka, Japan, 1966, among adults 40 years of age and over	Bronchitis rates, standardized for sex, age, and smoking were greater among men and women in the more polluted areas. Bronchitis rates followed the air pollution gradient.
Winkelstein and Kantor[273]	Survey of respiratory symptoms in a random sample of white women in Buffalo, New York	In nonsmokers 45 years of age and over, and among smokers who did not change residence, respiratory symptoms were correlated with particulate concentrations obtained in the neighborhood of residence. No association of symptom prevalence with SO_2 concentrations
Ishikawa et al.[275]	Comparison of lungs obtained at autopsy from residents of St. Louis and Winnipeg	Autopsy sets, matched for age, sex and race, showed more emphysema in the more polluted city. Autopsied groups may not reflect prevalence of disease in general population
Fujita et al.[276]	Prevalence survey (Medical Research Council questionnaire) of post office employees in Tokyo and adjacent areas, 1962 and re-surveyed in 1967	Two-fold increase over time in prevalence of cough and sputum production in same persons, irrespective of smoking habits. Change was attributed to increasing degrees of air pollution

TABLE 14-30. QUALITATIVE STUDIES OF AIR POLLUTION AND PREVALENCE OF CHRONIC
RESPIRATORY SYMPTOMS AND PULMONARY FUNCTION DECLINES

Study	Characteristics	Findings
Reichel,[277] Ulmer et al.[278]	Respiratory morbidity prevalence surveys of random samples of population in 3 areas of West Germany with different degrees of air pollution	No differences in respiratory morbidity, standardized for age, sex, smoking habits, and social conditions, between populations living in the different areas
Nobuhiro et al.[279]	Chronic respiratory symptom survey of high and low exposure areas of Osaka and Ako City, Japan	Higher prevalence of chronic respiratory symptoms in more polluted areas
Comstock et al.[280]	Repeat survey in 1968/1969 of east coast telephone workers and of telephone workers in Tokyo	After adjustment for age and smoking, no significant association of respiratory symptom prevalence with place of residence
Speizer and Ferris[281-282]	Comparison of respiratory symptoms and ventilatory function in central city and suburban Boston traffic pollicemen	Slight but insignificant increase in symptoms prevalence among non-smokers and smokers, but not exsmokers, from the central city group. No group differences in ventilatory function
Linn et al.[283]	Respiratory symptoms and function in office working population in Los Angeles and San Francisco, 1973	No significant difference in chronic respiratory symptom prevalence between cities; women in the more polluted community more often reported nonpersistent (<2 years) production of cough and sputum
Prindle et al.[284]	Comparison of respiratory disease and lung function in residents of Seward and New Florence, PA	Increased airway resistance in inhabitants of more polluted community. Differences in occupation, smoking, and socioeconomic level could account for these differences

TABLE 14-30. QUALITATIVE STUDIES OF AIR POLLUTION AND PREVALENCE OF CHRONIC RESPIRATORY SYMPTOMS AND PULMONARY FUNCTION DECLINES

Study	Characteristics	Findings
Watanabe[285]	Peak flow rates in Japanese school children residing in Osaka	Lower peak flow rates in children from more polluted communities. Improved peak flow rates when air pollution levels decreased
Anderson and Larsen[286]	Peak flow rates and school absence rates in children 6-7 years of age from 3 towns in British Columbia	Significant decrease in peak flow rates in 2 towns affected by Kraft pulp mill emissions. No effect on school absences. Ethnic differences were not studied
Collins et al.[287]	Death rates in children 0-14 years of age, 1958-1964, in relation to social and air pollution indices in 83 county boroughs of England and Wales	Partial correlation analysis suggested that indices of domestic and industrial pollution account for a greater part of the area differences in mortality from bronchopneumonia and all respiratory diseases among children 0-1 year of age

shortness of breath, and attacks of wheeze with shortness of breath. The

clinician is also likely to use chest radiography results and/or pulmonary

function test abnormalities, as well as the results of physical examination,

in making a diagnosis. Although there is some correlation of persistent cough

and/or phlegm with these other symptoms, it is far from perfect, and may even

be quite disparate.[236,243,248,249] Also, although chronic bronchitis may be a

disease marked by mucus gland hyperplasia and other morphological changes, the

relationship of the morphological change with the symptoms and/or the

physiological changes are quite imperfect.

Criteria for inclusion and exclusion are pertinent in chronic bronchitis.

They are specifically relevant in studies of the incidence of disease, since

respiratory diseases have slow onsets in most cases (except possibly for

childhood asthma and bronchiectasis associated with childhood lower respiratory

tract illness). Chronic bronchitis often occurs in conjunction with emphysema

and/or asthma and must be differentiated from these other illnesses.

Methodological problems encountered in studies of chronic bronchitis

relate not only to difficulties of definition, but to perceptual differences

between observer and observed, sensitivity and specificity of measurements,

the lack of long-term exposure information, and the frequent lack of infor-

mation on other important variables. The occurrence of chronic bronchitis

has been related to occupation, smoking, socioeconomic status, and other

demographic characteristics as well as to ambient air pollution levels. Many

studies have failed to consider one or more of these factors, making inter-

pretation of results more difficult.

Several extensive studies on associations between air pollution and

chronic respiratory disease have been conducted on European populations.

Lambert and Reid,[28] for example, surveyed nearly 10,000 British postal workers (age 35 to 59) for respiratory symptoms indicated by response to a self-administered MRC questionnaire. Current air pollution data were used to determine associations with symptoms where possible. However, the areas from which such data were available included only about 30 percent of the study group. Consequently, an index of pollution developed by Douglas and Waller in 1952, from domestic coal consumption, was used as well. The areas covered by the index included 88 percent of the study group.

The results, adjusted for age and smoking habits but not socioeconomic status (Table 14-31) show relationships for both males and females by both pollution indices. One reasonable conclusion from the study may be that a greater prevalence of cough and phlegm occurred in areas in which annual mean smoke concentrations were 150 $\mu g/m^3$ or more than in areas in which smoke concentrations were 100 $\mu g/m^3$ or less. These investigators also developed data showing that smoking was an important factor in acquiring chronic bronchitis and that the combined effect of smoking and pollution exceeded the sum of the individual effects. Failure to consider socioeconomic status might have affected the results,[301] but this is not very likely since the entire population consisted of a single occupational group.[248,312]

Holland and Reid[263] surveyed respiratory symptoms, sputum production, and lung function levels in post office employees in both central London and peripheral towns. Over the age of 50, London men had more frequent and more severe respiratory symptoms, produced more sputum, and had significantly lower lung function tests. Socioeconomic factors were presumed the same, the occupational exposures were homogeneous, and corrections were applied for smoking. There were some physique differences in the rural areas and

TABLE 14-31. PREVALENCE RATIOS FOR PERSISTENT COUGH AND PHLEGM STANDARDIZED FOR AGE AND SMOKING, BY AIR POLLUTION INDICES

Smoke (BS) annual mean, μg/m³	SMOKE		SO$_2$		Douglas and Waller Index	Males	Females
	Males	Females	Males	Females			
<100	97	93	87	103	Very low	88	95
100-150	112	120	96	110	Low	91	94
150-200	116	116	120	115	Moderate	117	97
200+	134	129	118	120	High	118	115

Source: Lambert and Reid, 1970[28]

allowances were made for these in the statistical evaluation. Unfortunately, no quantitative air quality determinations accompanied these results. However, Brasser et al.[302] have furnished some applicable 24-hour average SO_2 values for London (St. Pancres), ie. 100 $\mu g/m^3$ in summer and 500 $\mu g/m^3$ in winter, and Gloucester, Petersborough and Norwich, England, ie. 75 $\mu g/m^3$ SO_2 and 200 $\mu g/m^3$ SO_2, respectively, for summer and winter.[247] Holland and Reid[263] concluded that the most likely cause of their observed difference in respiratory morbidity between the men working in Central London and those in the three rural areas was related to the differences in the local air pollution. These and other studies[86,162,263] by Holland and coworkers demonstrate this gradient between respiratory disease and air pollution as well as a gradient between such disease and smoking. Lung function gradients were also seen[86,162] indicating effects above 75 $\mu g/m^3$ SO_2 and 200 $\mu g/m^3$ TSP.[247]

Holland et al.[89] studied the occurrence of chronic bronchitis in 2365 families in two areas of a London suburb that had different air pollution concentrations. Area 1 was reported to have had far worse pollution than area 2 during the previous 10 years. Between 1962 and 1965, the particulate matter (BS) dropped in area 1 from 108 to 72 $\mu g/m^3$, and the SO_2 first increased from 210 to 260 $\mu g/m^2$ (0.08 to 0.10 ppm) and then decreased to 238 $\mu g/m^3$ (0.08 ppm). In area 2, smoke decreased from 175 to 73 $\mu g/m^3$ and SO_2 decreased from 279 to 193 $\mu g/m^3$ (0.10 to 0.07 ppm). Trained health visitors conducted personal interviews, obtaining information on present and past respiratory symptoms in parents and children, on social and environmental conditions of the family, and on the parents' occupation and smoking habits.

Morning cough or phlegm was strongly associated with smoking in both fathers and mothers. There was a weak social class gradient for symptoms within smoking categories.[301] There were no differences between area 1 and area 2 in

the occurrence of symptoms in fathers. However, mothers and male and female siblings all reported significantly more symptoms in area 1, the area with presumed higher past BS and SO_2 (no specific data confirmed past levels) and known higher present SO_2.

Colley and Holland[334] studied the symptoms in all the members of the 2365 families in the London suburb. They attempted to assess the influence of various factors: smoking, area of residence, place of work, overcrowding, family size, social class and genetic factors. They showed that area of residence was not as important for the prevalence of cough when compared to home and occupational hazards, smoking and social class. In mothers, smoking and area of residence were important; but social class was not. In children, an effect of area of residence was demonstrated.

In addition to the above British studies, there exist several reports concerning a long-term study on the effects of air pollutants on British schoolchildren. Because the findings of this study appear to be important but controversial, it is discussed in some detail here, since not all of the results have yet appeared in the peer reviewed open scientific literature. Considering that two authors of the report by Holland et al. (1979)[301] are also coauthors of these studies, Holland et al.'s own descriptions are used where available. Holland et al. (1979) described these studies in a lengthy paragraph on page 613 of their report:

> One study in the United Kingdom concerned with exposure/response has been presented in a preliminary communication (10).* It consisted of data for primary schoolchildren aged 6-11 years in 10 areas in England. The parents were asked about respiratory illnesses in the

past year. The air pollution data, obtained from smoke (BS) and
sulfur dioxide samplers, were collected either at or within 0.8 km
(0.5 mi) of the schools. The results indicated a statistically
significant relationship between the frequency of colds going to the
chest during 1972-1973 and pollution measurements taken in November,
1973, after allowing for differences in the distributions of age,
sex, and social class between the areas. Although it was stated
that the relationship could be found for smoke (BS) levels from 10
to 130 µg/m³, four factors cast doubt on so precise an interpre-
tation. First, smoking in the home was not considered; second,the
pollution measurements were taken after the period to which the
questionnaire related and in some areas smoke abatement orders
were being put into effect; third, the 10 areas in the analysis
were a non-randon sample of the set of 28 areas in the whole study;
and fourth, the findings were not replicated in the same study
using data collected two years later. A second report from this
longitudinal study using data collected in 1975 indicated no relation-
ship between symptoms and either smoke (BS) or sulfur dioxide
levels in the 19 areas with substantial pollution data for the period
to which the questionnaire related (28).*

After the (November 15, 1979) preliminary draft of this chapter 14 was

reviewed by Holland et al.,³⁰¹ their letter to the Administrator of the U.S.

Environmental Protection Agency dated January 11, 1980 stated:

> The discussion of the study by Irwig and his colleagues (ref. 98)
> (14-92) is incomplete as it fails to identify the fact that what is
> quoted is a preliminary communication and the later definitive
> .communication failed to substantiate the earlier results.¹/
> The preliminary report presented data for primary schoolchildren
> aged 6 to 11 years in ten areas in England. The parents were asked
> about respiratory illnesses in the past year. The air pollution data,
> obtained from British standard smoke and sulphur dioxide samplers,
> were collected either at or within half a mile of the schools. The
> results indicated a statistically significant relationship between
> the frequency of colds going to the chest during 1972-73 and pollution
> measurements taken in November 1973, after allowing for differences
> in the distributions of age, sex, and social class between the areas.

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*The above references (10) and (28) in the Holland et al. (1979) text refer to:
(10) Irwig L, Altman DG, Gibson RJW, Florey CduV. Air pollution: Methods to
study its relationship to respiratory disease in British schoolchildren. Pro-
ceedings of the International Symposium on Recent Advances in the Assessment of
the Health Effects of Environmental Pollution. Volume I. Luxembourg, Com-
mission of the European Communities, 1975, pp. 289-300; and reference
(28) Melia RJW, Florey CduV, Swan AV: The effect of atmospheric smoke and sul-
fur dioxide on respiratory illness among British schoolchildren: A prelimi-
nary report. Paper given at the VIIth International Scientific Meeting of the
International Epidemiological Association, Puerto Rico, 1977.

Although it was stated that the relationship could be found for smoke (BS) levels from 10 to 130 µg/m³, four factors cast doubt on such an interpretation. First, smoking in the home was not considered; secondly, the pollution measurements were taken _after_ the period to which the questionnaire related, and in some areas smoke abatement orders were being put into effect; thirdly, the ten areas in the analysis were a non-random sample of the set of 28 areas in the whole study; and fourth, the findings were not replicated in the later study discussed below.

A second report from this longitudinal study of data collected in 1975 indicated no relationship between symptoms and either smoke or sulphur dioxide levels in the 19 areas with substantial pollution data for the period to which the questionnaire related.[1] (Note: Reference 1 in the above quotation refers to the Melia, Florey and Swan, 1977, paper read at the 1977 Puerto Rico meeting footnoted on the prior page).

Some of the implications of these above-quoted descriptive passages are that:

1. The Irwig paper was a "preliminary communication", and the Melia paper was the "definitive communication" on the subject.

2. In the Irwig report, "smoking in the home was not considered", but it was in the Melia report.

3. The Melia report "indicated no relationship between symptoms and either smoke (BS) or sulfur dioxide levels".

However, the facts of these studies may be interpreted quite differently.

First, the Melia paper was perhaps just as "preliminary" as the Irwig paper. In their own title of their paper cited in Holland et al. (1979),

Melia et al. described it as "A preliminary report". Further, the pre-meeting abstract of the paper states: "The results of Irwig in 1973 will be compared with those from 1974 and 1975"... However, when the paper was presented in September 1977, it stated at the end of the introduction: "Due to a problem arising in the data processing, information collected in 1974 was not available at the time of writing".

Consequently, it is hard to understand how the 1977 paper is definitive, since the 1974 data have not been reported yet even in draft form, and neither the 1975 paper nor the 1977 paper have passed the intense scrutiny of a peer reviewed scientific journal.

Secondly, smoking was <u>not</u> considered in either the Melia paper or the Irwig paper as confirmed by the authors' description of their "Method of Data Collection". Melia, Florey, and Swan (1977) state:

> No information on the smoking habits of members of the household or of the children themselves was obtained in the study.

Consequently, the possibility that the children themselves were already smoking was not considered. The possible importance of smoking as a confounding factor in these studies, however, is clouded by Holland et al. (1979) in pointing out (page 604):

> Since 1969, there have been many more surveys in children. Increasing numbers of investigators have realized that the young have special advantages as subjects for the study of air pollution. Under the age of nine years, they are unlikely to smoke cigarettes.

That is, since the Irwig and Melia studies were of schoolchildren "aged 6-11 years", perhaps a small proportion of the children over nine years old may have begun smoking cigarettes, but probably the vast majority of those studied did not; and this would lessen tremendously the likelihood that smoking may have been an important confounder affecting the outcomes of the two studies. If it were an important factor, however, then it would not be any more appropriate

to assert that the later Melia findings somehow contradict the earlier Irwig findings than to accept the initial Irwig findings for 1973 without hesitation. The matter would simply remain an open question and, since it is possible that more "smokers" were included among the low pollution area "control" populations, smoking may have actually obscured even more significant results than those reported in the two papers. Apropos to the latter point, it is interesting that the Melia report actually did indicate a possible statistically significant relationship between symptoms and air pollution, but the authors apparently "corrected away" such significant differences.

Tables 14-32 and 14-33 from Melia, Florey, and Swan report the summary of seven questions on respiratory disease and its symptoms for boys and girls in areas of low and high smoke and SO_2 pollution. If there is no association of air pollution with health, we would expect that out of the 28 comparisons listed that 14 will show a positive association and 14 will show a negative association . Instances of positive associations are indicated in the table by (+) and cases of negative or inverse associations by (-). Because there were equal numbers of boys reporting day or night cough independent of smoke (BS) level a zero is placed in Tables 14-32 and 14-33 to indicate that it is neither plus or minus within the significant figures reported by Melia, Florey, and Swan (5.9 vs 5.9). The positive and negative associations seen are summarized in Table 14-34.

Since Melia, Florey and Swan (1977) do not report the detailed results of their regression analysis to allow for independent evaluation of the "effect of the interfering factors" that they corrected for, it is difficult to understand and reconcile their statement:

TABLE 14-32

THE PREVALENCE (%) OF RESPIRATORY SYMPTOMS AND DISEASES BY LOW AND HIGH SMOKE POLLUTION IN BOYS AND GIRLS.   FROM MELIA ET AL. (1977)

Respiratory symptom or disease	Boys		Girls	
	Low smoke pollution	High smoke pollution	Low smoke pollution	High smoke pollution
Morning cough	3.0	4.0 (+)	1.4	5.7 (+)
Day or night cough	5.9	5.9 (o)	3.2	8.7 (+)
Wheeze	9.6	10.0 (+)	6.5	7.8 (+)
Colds to Chest	24.5	21.9 (-)	18.7	19.7 (+)
Asthma	2.5	1.6 (-)	1.1	0.5 (-)
Bronchitis	4.6	4.2 (-)	3.3	3.8 (+)
Respiratory illness	28.4	25.7 (-)	22.5	24.1 (+)
No. of children	1064	867	1050	873

*Low smoke pollution: 12.0 - 34.9 $\mu g/m^3$

 High smoke pollution: 35.0 - 73.0 $\mu g/m^3$

(+) Positive association of symptom with air pollution increase

(-) Negative association of symptom with air pollution increase

(o) No association of symptom with air pollution increase

TABLE 14-33

THE PREVALENCE (%) OF RESPIRATORY SYMPTOMS AND DISEASES BY LOW AND
HIGH SO_2 POLLUTION* IN BOYS AND GIRLS.   FROM MELIA ET AL. (1977)

Respiratory symptom or disease	Boys		Girls	
	Low SO_2 pollution	High SO_2 pollution	Low SO_2 pollution	High SO_2 pollution
Morning cough	3.3	3.8 (+)	2.1	5.4 (+)
Day or night cough	6.2	5.5 (−)	4.2	8.1 (+)
Wheeze	8.6	11.8 (+)	6.5	8.0 (+)
Colds to Chest	21.7	26.1 (+)	17.8	21.3 (+)
Asthma	2.6	1.4 (−)	0.8	0.9 (+)
Bronchitis	4.0	5.1 (+)	2.8	4.7 (+)
Respiratory illness	25.6	29.8 (+)	21.8	25.5 (+)
No. of children	1199	732	1181	742

*Low SO_2 pollution: 19.0 - 49.9 μg/m^3

 High SO_2 pollution: 50.0 - 145.0 μg/m^3

(+) Positive association of symptom with air pollution increase

(−) Negative association of symptom with air pollution increase

(o) No association of symptom with air pollution increase

TABLE 14-34. SUMMARY OF ASSOCIATIONS (±) OF POLLUTION WITH HEALTH
DATA FROM MELIA, FLOREY AND SWAN (1977)

Respiratory symptom or disease	Smoke (BS)		Sulphur dioxide (SO_2)	
	Boys	Girls	Boys	Girls
Morning cough	+	+	+	+
Day or night cough	0	+	-	+
Wheeze	+	+	+	+
Colds to Chest	-	+	+	+
Asthma	-	-	-	+
Bronchitis	-	+	+	+
Respiratory illness	-	+	+	+
TOTAL (+)	2	6	5	7

(+) Positive association of symptom with air pollution increase

(-) Negative association of symptom with air pollution increase

(o) No association of symptom with air pollution increase

The prevalence in boys tended to decrease and that for girls to increase with increasing levels of smoke pollution, but conversely, the prevalence in boys tended to increase and that for girls to decrease with increasing levels of SO_2.

Since all health question categories for girls showed an "uncorrected" association with SO_2 (including asthma) and these associations were larger than the associations with BS in 5 out of 7 cases it is hard to understand, without carefully reviewing the regression analysis in it's entirety, how the correction to the questionnaire responses could have been so overwhelming to wipe out any associations for the girls.

The results for the boys in both cases, however, do not appear to be significant, since we expect 3.5 plus and 3.5 minus in each case and the chi-square with one-degree of freedom is $2 (1.5)^2/3.5 = 1.28$; $P > 0.25$.

The chi-square with one-degree of freedom for the girls in regard to smoke is computed as: $2 (2.5)^2/3.5 = 3.57$; $P = 0.06$. An alternate test of the probability of obtaining 6 or more "heads" out of a total of 7 flips of an honest coin (P of "heads" = P of "tails") is 1/16 or 0.0625. These values, "on the edge of statistical significance," indicate that the association with BS may not be unreasonable. However, for sulphur dioxide, the probability of obtaining 7 out of 7 positive responses when no underlying association is present is $(1/2)^7$ or 1/128 (P = .008) which is clearly statistically significant.

If we combine the data for boys and girls, we expect a total of fourteen positive and fourteen negative signs for the associations, if no association exists between health and air pollution. If we assume that the null association for Boys and day or night cough with smoke is negative, then we have a total of 20 positive responses and 8 negative responses.

The chi-square sum with one-degree of freedom is $2 (6)^2/14 = 5.14$ ($P = 0.025$) so the overall test for the children shows a statistically significant association of air pollution and health.

Perhaps, if boys start smoking at an earlier age than girls, this might explain the absence of observed associations of health effects for the boys with atmospheric levels of BS. The lack of positive associations for the boys, however, would in no way negate the finding of positive results for the girls. Nor would any failure to find positive associations for one or another of the groups studied by Melia in any way negate positive findings obtained by Irwig at an earlier time and with different subjects.

Approaching the evaluation of the Irwig and Melia studies in the above manner would be consistent with recommendations made by Holland et al. (1979)[301] which essentially hold that, when any study is performed with a group of individuals at a certain period in their life while they are exposed to an atmosphere of variable pollution levels, the results of the study must stand or fall on its own merits. It is obviously impossible to repeat the study precisely. Even if we go back to the same location at a later time and recapture the same individuals, they will all be older and the pollution levels will be different. Such changes of course were occurring between the time of the Irwig and Melia studies and Holland et al. even noted that "smoke abatement orders were being put into effect."

Holland et al. (1980) also point out, in a discussion of the Van der Lende study, that

> Hypotheses are not strengthened or weakened, they are accepted or rejected on the basis of available evidence.

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It is difficult for this statement to be reconciled with the statement quoted previously from Holland et al. (1979) that doubt is cast on the 1973 findings of Irwig because

> the findings were not replicated in the same study using data collected two years later.

In fact, contrary to that assertion, we find that a careful examination of results from Melia et al. (1977) suggests that there were likely observed positive associations of respiratory symptoms-disease with air pollution, which would make their findings consistent with Irwig et al. (1975).

A series of studies from Poland by Sawicki[29-31] reported higher prevalence rates of chronic bronchitis in males (all smoking categories) and females (smokers and nonsmokers but not ex-smokers) in a high-pollution community. Rates were adjusted for age, sex, and smoking habits. The annual mean concentration of particulate matter in the high-pollution area was 170 $\mu g/m^3$ (BS) compared with 90 $\mu g/m^3$ (BS) in the low-pollution area. SO_2 concentrations were 125 and 45 $\mu g/m^3$, respectively. During the heating season when more smoke was emitted, the average concentrations of smoke for the high- and low-pollution areas were 240 and 120 $\mu g/m^3$ (BS) and, for SO_2, 200 and 65 $\mu g/m^3$, respectively. No consistent relationship was found between the chronic bronchitis prevalence rate and length of residence in the high-pollution community. Some reviewers[301] have taken this as being evidence indicating that Sawicki's findings do not show a relationship between air pollution and bronchitis, but other reviewers[304,308,312,313,314a] have indicated that a positive association appears to exist, and the present authors concur with this latter conclusion.

A repetition of this study in 1973[181] also tended to confirm further the relationship between the prevalence of chronic bronchitis and air pollution levels. By 1973, annual smoke concentrations in the high pollution area averaged 190 $\mu g/m^3$ (BS) compared with 86 $\mu g/m^3$ (BS) for the low-pollution area. SO_2 average annual concentrations were 114 and 46 $\mu g/m^3$, respectively, for the high and low pollution areas. Both chronic bronchitis and asthma were more prevalent in the high pollution area in males and females aged 31 to 50 and in smokers. Chronic bronchitis was also more prevalent in female non-smokers in the high pollution area in both 1968 and 1973. The investigator demonstrated an interaction between air pollution and smoking. Between the earlier study and 1973, the persistence of asthma and chronic bronchitis was greater in males ages 31 to 50 in each smoking group in the high pollution area. The incidence of asthma/chronic bronchitis was also greater in females in several age groups in the high-pollution area.

Petrilli et al.[32] studied chronic respiratory illness, rhinitis, influenza, and bronchopneumonia in several areas of Genoa, Italy, in relation to air pollution concentrations, between 1954 and 1964. Respiratory illness rates in non-smoking women over age 64 with a long residential history and no industrial exposure history was strongly correlated with SO_2 concentrations.[307] These investigators found that all illness rates were higher in industrial districts where annual mean pollution concentrations were >210 $\mu g/m^3$ (0.008 ppm) for SO_2 and >190 $\mu g/m^3$ for high volume mean TSP concentrations. Illness rates rose in Genoa from 1954-1961 to 1962-1964 by 207 percent. Illness rates were high also in a nonindustrial area where mean SO_2 was 100 $\mu g/m^3$ (0.035 ppm) and TSP was 180 $\mu g/m^3$.

In addition to the above European studies, several analogous investigations have been reported for Japanese population study groups. For instance, Tsunetoshi et al.[38] performed a prevalence survey (MRC questionnaire) in nine areas of Osaka and Hyogo prefectures, Japan. They studied about 30,000 Japanese over 40 years of age. Pulmonary function was measured by a spirometer; maximum values were used. Multiple regression analysis indicated increasing prevalence of chronic bronchitis (adjusted for sex and smoking) related to the gradient of air pollution (sulfation rates and dustfall) in the different areas. The prevalence ranged from 4 percent where the sulfation rate was close to 1 mg/100 cm^2/day (about 80 $\mu g/m^3$ SO_2) to 10 percent in areas where the sulfation rate was about 3 mg/100 cm^2/day (240 $\mu g/m^3$ SO_2). TSP levels were not given.

Suzuki et al.[183] reported on data collected in each of six study areas in Japan. Information was obtained from about 400 housewives over 30 years of age. The BMRC respiratory symptom questionnaire was administered once each year between 1970 and 1974. The air pollutants monitored in each area included SO_2, sulfur oxides, NO and NO_2, CO, TSP (high volume), and dustfall. The prevalence of respiratory symptoms was associated with the annual arithmetic means measured. The incidence of cough, phlegm, or persistent cough and phlegm was higher among smokers and in the over-60 age group. These respiratory symptoms were related to the concentrations of TSP (p <0.05) and SO_2 (p <0.01) through 1972. SO_2 levels in 1971 were 94-97 $\mu g/m^3$ (.036 to .037 ppm) in the high areas. They decreased to 58-69 $\mu g/m^3$ (.022 to .024 ppm) in 1974. TSP levels in 1971 in the high areas were between 206 and 434 $\mu g/m^3$ decreasing between 122 and 374 $\mu g/m^3$ in 1974.

Toyama et al.[312,317] studied the prevalence of respiratory symptoms in relation to SO_2. Prevalence rates from 2.8 to 3.7 percent in males ages 40 to 59, after adjusting for age and smoking, were found in areas of a non-industrialized rural town with SO_2 concentrations of less than 30 $\mu g/m^3$ (0.01 ppm) and TSP concentrations of 106-341 $\mu g/m^3$ (mean of 197). Tani[312,318] performed a study around a pulp mill and in controlled areas in Japan. A consistent relationship was demonstrated between the prevalence of bronchitis and sulfation rates (candle method). A prevalence of about 3 percent in both sexes, ages 40 to 59, were found in areas where the sulfation rate was around 0.6 $mg/100$ cm^2 per day (approximately 48 $\mu g/m^3$ SO_2) compared to about 8 percent in areas where the sulfation rate was 1.2 $mg/100$ cm^2 per day (approximately 96 $\mu g/m^3$ SO_2). No data were provided on TSP.

Yoshii[312,319] noted an association between chronic pharyngitis accompanied by histopathological changes at biopsy in Yokkaichi, Japan, in sixth grade children. In heavily polluted districts, sulfation rates were much more than 1 $mg/100$ cm^2 per day (>80 $\mu g/m^3$ SO_2); in moderately polluted districts, they ranged from 0.25 to 1.0 $mg/100$ cm^2 per day (20 to 80 $\mu g/m^3$ SO_2); in the control area it was less than 0.25 $mg/100$ cm^2 per day (<20 $\mu g/m^3$ SO_2).

An EPA CHESS study on chronic respiratory disease (CRD) was reported on by Chapman et al[212] for populations studied in 1970 in four communities in Utah (Salt Lake City, Ogden, Kearns, Magna) to assess the effects of smelter emissions of sulfur oxides (SO_2 and suspended sulfates). Other pollutants (TSP and nitrates) were estimated to be low to moderate; but concurrent trace metal data were not collected. Questionnaire distribution to parents was through elementary school children and by mail for high school students.

Response rates of 85 percent and 35 percent were found for child-carried and mailed questionnaires, respectively. Although the 65 percent nonresponse

rate to mailed questionnaires may have increased the possibility of serious reporting bias, the authors indicated that similar inter-community CRD differences were observed for both sets of parents. Respondents were excluded if they had incomplete questionnaires, a residential change within the previous two years, or occupational exposure to irritants such as coal dust, cutting oils, asbestos, mine dust, smelter fumes, cotton dust and foundry dust. Subsequent analysis showed that exclusion for occupational reasons results in a conservative estimate of effects attributable to pollution. All races were included, but the proportion of black respondents was trivial. No covariate measurements were made to assess possible effects of religion or ethnic composition on response patterns, although Salt Lake City has proportionately fewer Mormons and Magna more Spanish Americans. Educational attainment was comparable, however, in the four communities. CRD prevalence rates reflected pollution levels faithfully in the different communities; and differences (2 to 7%) in CRD rates between high and low areas were statistically significant within sex and smoking status groups (Table 14-35). Relative risks were also different statistically and air pollution had one-third the risk of smoking in mothers and fathers (Table 14-35). Effects were additive.

Because of potential biasing factors, such as "CHESS" network air quality measurement problems discussed in Chapter 3 and the IR (1976)[107] and problems in the use of dispersion modeling to make certain pollution estimates, several reviews[107,301,312,338] have questioned the validity of the reported findings of the Utah CRD study, although one critique[107] ultimately judged the reported health effects differences between the study communities to be sound (see Appendix A for this chapter). With regard to the CHESS air quality measurements, however, the same report[107] found that detected deficiencies in analyses were

TABLE 14-35 *Chronic Prevalence Rates and Pollution Levels in Four Utah Communities, 1970*

Area & Smoking	Prevalence Rate[212]		Relative Risk Ratios[212a]		1970 Local Levels	
Low 3 areas	Mothers	Fathers	Mothers	Fathers	TSP($\mu g/m^3$)	$SO_2(\mu g/m^2$.
Non-Smokers	4.16	3.00	1.00(4.16)	1.00(3.00)	69-84	2.6-15.7
Smokers	15.80	19.60	3.80	6.53		
Magna					70	107.4
Non-Smokers	5.20	6.81	1.25	2.27		
Smokers	22.25	26.80	5.35	8.93		
Source of Risk[212aa]			0.33	0.35		

a *Relative Prevalence= Prevalence in specific group/Prevalence in non-smokers in low pollution area (baseline rates in parenthesis).*

aa *Ratio of Relative Prevalence due to air pollution/Relative Prevalence due to smoking.*

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sufficient, especially for suspended sulfate estimates, such that the published "CHESS" estimates were unacceptable as a basis for quantifying pollutant health effects relationships. Fortunately, local air monitoring by the Utah State Department of Health was available for some pertinent years and was judged[107] to be more accurate than "CHESS" estimates. Based on such local data Magna was highest in SO_2, Ogden had the lowest SO_2 levels. Kearns and Salt Lake City had exposures midway between Ogden and Magna. The 1970-71 local monitoring data for Magna can be contrasted to the other three "low" pollution areas as shown in Table 14-35. Since the TSP levels were nearly constant over time and similar across the four communities, they were unlikely (alone) to be producing the differential health effects reported. Therefore, observed differences in prevalence between the study communities appear to be more likely associated with higher Magna SO_2 levels, acting either alone or in combination with concurrently observed TSP levels. Precise quantitation of the past or then current CHESS TSP or SO_2 levels associated with the health effects observed in the Utah study, however, may not be possible, as concluded elsewhere.[107,312] On the other hand, to the extent that the 1970-71 local air monitoring data may be representative of fairly stable SO_2 and TSP levels in the study communities over many years, then the local monitoring values, or more accurately, the corrected estimate values shown in Table 14-35 for Magna might serve as rough pollution indices associated with CRD effects in smelter areas similar to Magna.

Chapman et al.[212] also reported on another CHESS study, involving military recruits at the Chicago Induction Center from June 24, 1969, to February 20, 1970. Adult chronic respiratory disease (CRD) prevalence was determined by means of a measured modified BMRC self-administered questionnaire that inquired

whether the subject usually coughed and produced phlegm for at least 3 months of the year.

A similar questionnaire had been validated for self-administration in a 1971 Japanese study,[38] but validating data were not available for this survey; still, it probably gave a reasonable good indication of the difference in ranking of communities based on CRD prevalence. The questionnaire located the subjects by their current residence, which was used to categorize recruits into three groups: (1) Chicago proper, Gary, Hammond, Whiting, and East Chicago, (2) other Chicago suburbs, and (3) other Illinois and Indiana areas. All recruits living outside Illinois and Indiana were excluded, as were those not living at their current address for at least 3 years. Symptom prevalence rates for Chicago and its immediate suburbs were almost identical and were consistently higher than the rates for other Illinois and Indiana areas for both blacks and whites (Table 14-36). These differences persisted even after adjustments were made for educational level of the recruits.

Questions have been raised[107,312] regarding the ability to associate the above reported "urban" health differences with specific air pollutants, especially in view of problems associated with estimation of the air quality data upon which published[212] quantitative conclusions concerning study results were based. Concerning the latter point, other applicable (NASN) aerometric data for the greater Chicago area during the time of the study exists and is summarized along with CRD prevalence results in Table 14-36. The annual average arithmetic means for the 1969 NASN aerometric data suggest that Chicago proper, East Chicago, and Hammond were highest in particulates, but the suburbs may have been somewhat higher in SO_2. For both pollutants it appears that the other Illinois and Indiana areas were generally distinctly lower, although the

TABLE 14-36. CRD PREVALENCE RATES FOR CHICAGO RECRUITS*

| Community | Chronic bronchitis prevalence, percent | | | | Annual Average 1969 NASN Levels | |
| | Blacks | | Whites | | TSP ($\mu g/m^3$) | SO_2 |
	Nonsmokers	Smokers	Nonsmokers	Smokers		
Other Illinois, Indiana	9.0	9.3	4.3	16.7	42-95	14-32
Suburbs	9.4	12.6	5.5	19.8	72-150	94-292
Chicago	9.4	12.9	5.2	18.3	129-172	85-138

*Based on 1969-70 Chicago Inductee "CHESS" study reported by Chapman et al.[212]

available data were quite sparse. Based on these limited aerometric data, increased symptom rates would appear to be associated with both increased particulates and increased SO_2, but the data provide no basis to distinguish the relative effects of the two pollutants. Use of these data as estimates of SO_x or TSP chronic exposures associated with increased morbidity effects reported by Chapman et al.[212] for the Chicago CRD study must be qualified somewhat, however, in view of the lack of more precise information on how representative such data are for actual long-term exposures of the study populations.[107]

Placing the studies by Chapman et al.[212] on United States "urban" and "smelter-exposed" populations into a broader perspective also encompassing other studies evaluated above, one finds that numerous studies have demonstrated that higher chronic respiratory disease prevalence rates are associated with elevated pollution levels in a number of locations around the world. These not only include sites in the United States, but also in Great Britain, continental European countries, and Japan. In addition, efforts have been made to utilize reported air quality data available for the various study areas in order to derive at least approximate estimates of ranges of ambient SO_2 and particulate matter air concentrations likely associated with the occurence of the chronic respiratory disease effects documented by the various studies.

14.5.3 Other Respiratory Disease/Symptom Prevalence Studies

Yoshida et al.[176] investigated the prevalence of bronchial asthma in relation to the SO_2 air pollution exposure among Japanese school children. Precise data were not included in the published report, but inspection of the figures indicates that in general the prevalence rate was between two and three percent when SO_2 monitored by the lead candle sulfation rate method was

between 0.5 and 1.0 mg 100 cm^2/day (40-80 µg/m^3). For the most polluted area, more than 1.5 mg SO$_2$/100 cm^2/day (110 to 120 µg/m^3), the prevalence rate exceeded five percent. In other respects (frequency of exacerbations of illness, school absence record, and reaction to allergies), patients in the high pollution area did not differ significantly from those in the low pollution area.

Rudnick,[182] as part of a well-designed and methodologically-sound study, collected information by a self-administered questionnaire on respiratory symptoms and disease in 3805 children, 8 to 10 years old, living in three communities in Poland with differing air pollution concentrations. The question-naire sought information on respiratory symptoms and symptoms of asthma during the previous 12 months. Mean SO$_2$ concentrations in the higher pollution area for the years 1974 and 1975 were 108 to 148 µg/m^3 for SO$_2$ and 150 to 227 µg/m^3 for smoke. The low pollution areas had SO$_2$ concentrations of 42 to 67 µg/m^3 and smoke concentrations of 53 to 82 µg/m^3. Most symptoms of respiratory illness in both boys and girls occurred more frequently in the high pollution area but the differences were, in general, nonsignificant. There was a higher prevalence of breathlessness, sinusitis and asthma attacks in boys living in the high pollution area but only "runny nose in the last 12 months" occurred more frequently in girls in the same area. There were no significant differ-ences between the frequencies of nonchronic cough, attacks of breathlessness, shortness of breath, or multiple cases of pneumonia associated with the differ-ent pollution levels. While the above results are highly suggestive of at least some SO$_2$ and TSP related health effects, difficulties in being able to fully evaluate the statistical analyses upon which the reported findings are based argue for caution in utilization of the reported findings.

Douglas and Waller[90] studied a cohort of a national sample of children born in the United Kingdom during the first week in March 1946. They prospectively examined the occurrence of respiratory illness in the children in relation to the estimated intensity of air pollution in the area of their residence. The areas in which the children lived were assigned to one of four pollution groups on the basis of estimates derived from domestic coal consumption in 1951-52. An effort to validate the index later, on the basis of measured smoke (BS) and SO_2 measurements in 1962 and 1963, indicated that the estimates were reasonably good. At the time of the measurements, SO_2 varied from about 90 $\mu g/m^3$ (0.03 ppm) in the low-pollution areas to about 250 $\mu g/m^3$ (0.09 ppm) in the high-pollution areas as shown in Table 14-37. Information on respiratory illness and symptoms was obtained from the children when they were 6, 7, and 11 and, if they had lived the first 11 years of their lives in the same area, similar information was gathered when they were 15, 20, and 25 years of age. No significant relationship was observed between upper respiratory tract infections and increasing air pollution levels, in contrast to a high significant and close correlation between lower respiratory tract infection prevalence rates and increasing air pollution level as seen in Table 14-37. In fact, these relationships are very consistent for all of the measures listed.

The lowest concentration of smoke and sulfur dioxide were 67 $\mu g/m^3$ and 90 $\mu g/m^3$, respectively. "Higher illness rates were noted in all higher pollution classes;"[307] and "Socio-economic status was important in the study but a relationship...still existed within spearate social classes."[312] Douglas and Waller[90] suggested that these children probably were exposed to higher pollution concentrations in their early lives than suggested by the measurements made in 1962-63 because of the improvement that followed the 1956 United Kingdom Clean

TABLE 14-37   Frequency of Lower Respiratory Tract Infections of
            Children in Britain by Pollution Levels, %[a]

Lower respiratory tract infections		Mean annual Pollution levels, $\mu g/m^3$			
		Very Low	Low	Moderate	High
	Smoke:	67	132	190	205
	SO$_2$:	90	133	190	251
First attack in first 9 months		7.2	11.4	16.5	17.1
At least one attack in first two years		19.4	24.2	30.0	34.1
More than one attack in first two years:		4.3	7.9	11.2	12.9
Boys		5.7	8.1	10.9	16.2
Girls		2.9	7.7	12.1	9.7
Middle class		3.0	4.0	7.7	9.3
Manual working class		5.1	10.8	13.9	15.4
Admission to hospital in first five years:					
Lower respiratory infection		1.1	2.3	2.6	3.1
Bronchitis		0.0	0.9	1.0	1.4
Pneumonia		1.1	1.4	1.6	1.8

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[a]From Douglas and Waller, 1966.[90]

Air Act.[301] However, the children in areas with lower concentrations actually probably experienced little change in exposure while those in higher polluted areas probably experienced much higher levels previously.

Further study of this population at 20 years of age indicated that in these now young adults, cigarette smoking had the greatest effect on respiratory symptom prevalence, followed by a history of lower respiratory tract illness under 2 years of age. At this time of their lives, social class and air pollution had little effect. The standardized prevalence rate (percent), however, was higher among the group who had lived in high-pollution areas (11.51) than in those who had lived in the low-pollution area (10.20) but the difference was not significant.

This study would appear to indicate that the effects of exposure to air pollutants in high concentrations during the first 11 years of life had disappeared by age 20, unless there was a history of lower respiratory illness before age 2. However, no information is provided in the report to indicate the concentration of pollution to which the children were exposed after 1957 when they were 11 years old. Nevertheless, various reviewers have consistently accepted this as a valid study although they have disagreed somewhat regarding the specific SO_2 and particulate levels associated with the observed effects.

A final survey, when the study population was 25 years old, confirmed the observation made 5 years earlier. At this time, Kiernan et al.[92] reported that smoking continued to have the greatest effect on respiratory symptoms and lower respiratory illness. The association with air pollution was again a positive one and stronger than had been observed 5 years earlier, but was not statistically significant.

The lasting impact of respiratory illness during the early years of life was confirmed by Burrows et al.[93,94] These investigators observed more than 2600 adults over 20 years of age and found that histories of pediatric respiratory illness were associated with the current prevalence of respiratory symptoms, obstructive airway disease, and ventilatory impairment. The authors concluded that childhood respiratory illnesses cause the adult lung to be unusually susceptible to the adverse effects of a variety of bronchial irritants and infectious agents.

Taussig[95] also produced evidence that effects of respiratory illnesses in childhood persist into later years. This investigator concluded from studies of children that a past history of croup or bronchiolitis, whether or not asthma was present, was associated with an increased prevalence of abnormalities in lung function. The predominant alterations were found in those tests believed to evaluate small airway function (V_{max} 25; V_{iso} V). In addition, these high risk children showed exercise-induced bronchospasm that also was independent of an allergic history.

The association between air pollution and lower respiratory tract illness was observed also by Lunn et al.[96] These investigators studied respiratory illness in 5- and 6-year-old schoolchildren living in four areas of Sheffield, England. Air pollution concentrations showed a gradient in 1964 across four study areas for mean 24-hour smoke (BS) concentrations from 97 $\mu g/m^3$ to 301 $\mu g/m^3$ and the same gradient for mean 24-hour SO_2 concentrations from 123 $\mu g/m^3$ to 275 $\mu g/m^3$. The following year, the concentrations of smoke were about 20 percent lower and SO_2 about 10 percent higher, but the gradient was preserved for each pollutant. In high-pollution areas, the 24-hour mean smoke concentration exceeded 500 $\mu g/m^3$ 30 to 45 times in 1964 and 8 to 15 times in 1965.

SO_2 exceeded 500 $\mu g/m^3$ 11 to 32 times in 1964 and 5 to 23 times in 1965. Information on respiratory symptoms and illness was obtained by questionnaires completed by the parents, by physical examination, and by tests of pulmonary function ($FEV_{0.75}$ and FVC). Socioeconomic factors (SES) were considered in the analyses, but home heating systems were not. Although certain differences in SES between areas were noted, the gradients between areas would exist even when the groups were divided into social class, number of children in house, and so on.[247] Positive associations were found between air pollution concentrations and both upper and lower respiratory illness. Lower respiratory illness was 33 to 56 percent more frequent in the higher pollution areas than in the low-pollution area (p <0.005).

In a second report, Lunn et al.[97] gave results for 11-year-old children studied in 1963-64 that were similar to those provided earlier for the younger group. Upper and lower respiratory illness occurred more frequently in children exposed to 24-hour mean smoke (BS) concentrations of 230 to 300 $\mu g/m^3$ and 24-hour mean SO_2 concentrations of 181-275 $\mu g/m^3$ than in children exposed to smoke (BS) at 97 $\mu g/m^3$ and SO_2 at 123 $\mu g/m^3$. This report also provided additional information obtained in 1968 on 68 percent of the children who were 5 and 6 years in 1963-64. By 1968, the concentrations of smoke (BS) were only about one-half of those measured in 1964, and SO_2 concentrations were about 10 to 15 percent below those measured in 1964. By 1968 the pollution gradient no longer existed, so the combined three higher pollution areas were compared with the single original low-pollution area. Lower respiratory illness prevalence measured as "colds going to chest" was 27.9 percent in the low-pollution area and 33.3 percent in the combined high-pollution areas, but the difference was not statistically significant (p >0.05). (Ventilatory function

results were similar.) Also, the 9-year-old children had less respiratory illness than the 11-year-old group seen previously. Since 11-year-old children generally have less respiratory illness than do 9-year-olds, this represented an anomaly that the authors suggested may have been the result of improved air quality. It should be noted that these Lunn et al.[96,97] findings have been widely accepted[245,248,301,307,308,312] as being valid, and, on the basis of changes observed between the two surveys, the NAS report on particulate matter concluded that levels of effect were 100 $\mu g/m^3$ BS and 120 $\mu g/m^3$ SO_2.[307]

Hammer et al.[214] and French et al.[306] reported on two studies, conducted as part of the EPA CHESS Program which investigated the occurrence of lower respiratory disease (LRD) in United States children less than 12 years of age New York City.[214,306] In the two studies, data were obtained from questionnaires asking mothers to recall how many times each of their children under age 12 had had pneumonia, croup, or bronchitis during the previous 3 years. Data were gathered also on related hospitalizations and physician visits. Validation studies of the questionnarie yielded highly significant correlations between the illnesses reported on the questionnaire and confirmatory hospital and physician records.[257]

Hammer et al.[214] reported on a study of historical acute lower respiratory disease in children aged 1 to 12 years surveyed retrospectively by questionnaire among parents in four New York metropolitan communities representing different exposures to sulfur dioxide, particulate matter and suspended sulfates. Morbidity patterns were similar with regard to age for blacks and whites, but pneumonia was more frequent and bronchitis and other chest infections were less frequent among blacks than whites in each community. Rates of "any lower respiratory disease" (a combined category), croup, bronchitis, and "other"

chest infections were significantly higher among black and white children residing in the communities with exposure to higher pollution. Pneumonia and hospitalization were significantly higher only among white children in the low exposure community but the absolute rates were low for both conditions in all communities. Differences in family size and composition, crowding, parental cigarette smoking or indoor air pollution due to gas stoves or gas space heaters could not explain the morbidity excesses in the high exposure communities. Significant differences in LRD in the previous 3 years were found for all ages (1-12) after adjusting for sex and education of head of household. Estimates of the average annual pollutant concentrations associated with excess childhood respiratory morbidity in this study were 160 to 260 $\mu g/m^3$ of sulfur dioxide, 82 to 96 $\mu g/m^3$ of total suspended particulates, and 13 to 14 $\mu g/m^3$ of suspended sulfates as measured by the New York City Department of Air Resources (NYC DAR). As reported by French et al.,[306] there was an increased relative risk of acute lower respiratory disease in all family members in the high pollution areas, especially for those with 3 or more years residence in the areas, and after adjusting for parents' smoking habits.

French et al.[306] conducted a similar study in the children (ages 1-12) in the families studied by Chapman et al.[212] in the four Utah communities. The prevalence rates of reported past lower respiratory diseases (LRD) were similar for those residing in the communities less than 3 years. For those with three or more years of residence, the rates were similar for the three low pollution communities Magna's prevalence rates, in those with the 3+ years residence, were significantly higher: age-, sex-, and SES-adjusted attack rates for one or more LRDs were 38.2 in Magna vs. 26.5 to 29.0 in the other three areas; age-, sex-, and SES-adjusted attack rates for two or more LRDs were 23.4 in

Magna vs 14.6 to 17.2 in the other three areas. Again, local monitoring indicated similar TSP averages for the four areas (about 70 $\mu g/m^3$), but higher SO_2 readings in Magna (107 mg/m^3 or more).

Some of the comments discussed for other EPA CHESS Program studies (see also Appendix A) may also apply to the above studies by Hammer et al[214] and French,[306] to the extent that similar methodological tools or procedures were used as in the other studies. Especially applicable, then, are questions raised[107] concerning: (1) air quality measurements obtained by "CHESS" monitoring in the study locations at the time immediately proceeding and during the collection of health effects data and (2) the estimation of historical exposures for the study populations from limited past local air monitoring data. Caution must, therefore, similarly be applied in regard to full acceptance of the published "CHESS" air pollution values for these studies. As judged by IR,[107] the local values (shown above) are more accurate, and they have been used to estimate exposures. Since these studies[214,306] are in children, prior exposures are likely similar to those presented.

Another retrospective survey conducted by Hammer[113,257] regarding the frequency of lower respiratory illness in children was undertaken in 1971 in the south east, using similar questionnaire sampling as employed in the above New York studies.[214,306] Data were obtained by questionnaire from parents of about 10,000 children aged 1 to 12 years. The two communities represent intermediate and high particulate exposures with low SO_2 exposures. The analysis of data indicated that in the high exposure community (Birmingham) there was significantly increased respiratory disease over that for the lower exposure community (Charlotte), based on statistically significant results obtained on 10 of 17 measures of respiratory morbidity. This included more

pneumonia and croup among blacks and more lower respiratory disease, bronchitis and croup among whites in Birmingham than in Charlotte, as shown in Table 14-38. There was also a consistent trend for the association of more illness and hospitalization with higher pollution to become stronger in older children. This suggests that the effect increased with extended exposure. The investigators assumed that cigarette-smoking for children under age 13 in the South was minimal, equally distributed, and did not affect their results. The investigators concluded that differences in parental recall, questionnaire reliability, family size, crowding, or parental smoking habits were not likely explanations for the excess morbidity in the high-pollution areas, since these factors did not differ significantly between communities. Therefore, the results were taken to be indicative of associations between increased lower respiratory disease rates in children and exposure to moderately elevated particulate matter levels in the presence of low SO_2 levels. Asthma rates clustered in families, were higher in male children and female parents, and were comparable to other studies. Significant increases of lower respiratory disease were also reported for asthmatic children in the high exposure community.

The above Hammer[214,257] study, peer-reviewed and published as a Harvard University doctoral dissertation, would appear to provide important and meaningful findings demonstrating significant respiratory effects in children associated with elevated particulate matter air concentrations in the presence of low levels of SO_2, suspended sulfates, and suspended nitrates. The response rates were excellent in both communities, though significantly lower in Charlotte (88 percent) than in Birmingham (95 percent) and significantly lower for Blacks (84 percent) than for Whites (89 percent) within Charlotte. The small differences in response rates in absolute terms, however, appear unlikely to

TABLE 14-38. FOUR-YEAR REPORTED RATES OF ONE OR MORE EPISODES
OF LRD AMONG WHITE AND BLACK CHILDREN, BY COMMUNITY EXPOSURE
SOUTHEASTERN U.S. 1971

		Adjusted age-specific rates, (%)						Air Pollution Levels - 1971[257] (annual averages in $\mu g/m^3$)						
	Pollution	White age			Black age									
Type of LRD	Exposure	1-4	5-8	9-12	1-4	5-8	9-12	City	Year	TSP[a]	RSP	SS[d]	SN[d]	SO$_2$[d]
Any LRD	Charlotte	35.0	29.9	22.0	27.8	16.4	12.7	Charlotte	1971	74	40.7[b]	9.6	1.7	16.3[e]
	Birmingham	38.9	36.3	26.4	24.0	20.6	15.9	Birmingham	1971	133	57.2[c]	11.8	2.5	12.1
								1960-1971 avg.		TSP		SS		SO$_2$
Croup	Charlotte	17.5	14.2	9.3	10.8	7.0	4.7	Charlotte		93 (74-112)[f]		8 (4-10)		17 (13-20)
	Birmingham	16.3	16.3	12.2	8.6	7.9	5.9	Birmingham		155 (133-169)		10 (9-16)		15 (6 <25)
Bronchitis	Charlotte	23.1	20.4	14.9	13.7	7.8	6.3							
	Birmingham	28.7	26.2	18.6	10.6	7.9	6.9							
Pneumonia	Charlotte	9.0	6.3	5.2	14.0	8.3	8.9							
	Birmingham	10.3	8.5	6.3	15.1	13.7	10.2							
Hospitalization	Charlotte	5.5	2.7	0.9	4.0	1.8	1.3							
	Birmingham	5.8	6.1	2.4	5.7	2.9	2.5							

[a] Values obtained from trend lines.
[b] TSP x .55.
[c] TSP x .43.
[d] CHESS data.
[e] County data.
[f] (range).

have affected the overall study results in view of excellent internal consistency in lower respiratory disease morbidity patterns among blacks and whites within both study communities, with morbidity patterns being similar in relation to age, sex, parental education, and history of asthma in each of the communities. The fact that many of the most likely potential confounding or covarying factors were adequately controlled for in terms of the particular multivariate age-, sex-, race-, and socioeconomic level - specific statistical analyses employed is another strength of the study. In addition, smoking does not appear to be a credible factor accounting for the observed results, especially those for the children in the 1 to 4 and 5 to 8 year old age groups. Lastly, the 1960-71, 1964-71, and 1968-71 air quality estimated shown in Table 14-39 respectively index lifetime exposures for the 9-12, 5-8, and 1-4 year old children constituting the present study populations. Thus, if those air quality data are accurate and adequately representative of the respective study population exposures, it would seem to be possible to define a relatively narrow range of annual average TSP concentrations likely associated with the childhood respiratory disease effects observed in the study.

In regard to further critical assessment of the Hammer[113,257] study, it should be noted that it was not specifically discussed in the Congressional Investigative Report,[107] which evaluated other EPA CHESS Program studies completed earlier. On the other hand, the present Hammer study appears to have avoided well most all of the methodological shortcomings of the types noted for various other specific CHESS Program studies in the IR[107] review. Only in a recently published review by Holland et al[301] has there appeared any specific critical comments regarding the study, and those were directed to an earlier unpublished draft report on the study. Referring to the draft report, Holland et al[301] noted:

TABLE 14-39. ESTIMATED[a] POLLUTANT EXPOSURE LEVELS IN CHARLOTTE, NORTH CAROLINA[113,257] (INTERMEDIATE EXPOSURE) AND BIRMINGHAM, ALABAMA (HIGH EXPOSURE): 1960-1971

Pollutant	Community	Estimated Pollutant Concentrations, $\mu g/m^3$			
		1960-63 Average	1964-67 Average	1968-71 Average	1960-71 Average
Total Suspended Particulates	Charlotte	107	93	79	93(74-112)[b]
	Birmingham	168	159	139	155(133-169)
Sulfur Dioxide	Charlotte	17	16	17	17(13-20)
	Birmingham	<25	11	13	15(6-<25)
Suspended Sulfates	Charlotte	6	9	10	8(4-10)
	Birmingham	10	11	14	10(9-16)
Suspended Nitrates	Charlotte	2	2	1	2(1-3)
	Birmingham	2	3	3	2(2-3)

[a]All values obtained from reference 257 and based on both measured and estimated values. Twenty-four hour integrated estimates of concentrations were measured expressed in micrograms per cubic meter. For each year, the average of all daily estimates was computed. For periods of several years, the average of the individual years is tabulated. For the period 1960 to 1971, the average for the 12-year period is shown together with the range of the 12 individual years.

[b]Range in parentheses

Rates of illnesses in the two cities were compared in three age groups and by race after adjusting for sex and education of head of household. The rates were higher in Birmingham except for blacks (sic) 1-4 years of age. However, in another analysis, consistent differences were only found for whites (sic). Although parental smoking was considered, it was not included in the analyses. No discussion was given of the validity of the data or consistency of results in different sectors of the cities, as had been provided by Love et al. In light of the results of the prospective study (ie. by Love et al),* this retrospective study, with its inherently less reliable data,requires more detailed analysis than is provided in the draft paper before the observed effects can reasonably be ascribed to differences in levels of total suspended particulates (HV).

Reference to the Love et al prospective study concerns a different CHESS Program study of acute respiratory disease during fall, winter and spring of 1970-71 and 1971-72 in preschool and schoolchildren in Birmingham and Charlotte a study which failed to demonstrate higher acute respiratory disease rates in Birmingham and, for which, internal inconsistencies existed with regard to social class, race, and smoking.

All told, the above Holland et al[301] comments do not seem to provide any compelling reasons for rejecting the findings or conclusions contained in the later, more thorough and complete, published analyses[113,257] of the Hammer study, judged by prominent American epidemiologists and statisticians (on Hammer's doctoral committee) to be methodologically sound and appropriately interpreted. Thus, for example, the failure to find higher rates of respiratory disease for Blacks age 1-4 in Birmingham, does not negate the finding of other statistically significant, internally consistent, and biologically plausible increases in respiratory disease rates in Birmingham for other Black age groups and all White age groups. Nor are the Hammer findings negated by the failure of the Love et al prospective study to find analogous effects at a

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*Editors' insertion.

later time when available air quality data indicates that lower TSP and SO_2 levels existed in both study communities along with smaller intercommunity differences than at the time of the Hammer study. Also, perhaps more importantly, the Love et al study used markedly different data collection procedures (telephone survey versus questionnaires in the Hammer study, etc.) and health endpoint measurements.

Also in his later report,[257] Hammer does demonstrates the validity of the data and the consistency of results (see above). In addition, Hammer[257] demonstrated that parental smoking was not important in his findings, which confirms the findings of other epidemiological studies.[338,339,340]

Two key issues that remain and must be considered before accepting the specific quantitative dose-effect relationships implied by Hammers' published analyses[113,257] are: (1) the representativeness of the reported air quality data as reflections of the respective exposures of the different study populations; and (2) the validity and accuracy of Hammers' published quantitative estimates for air levels of TSP, SO_2, and other pollutants in Birmingham and Charlotte during the 1960-71 period (as shown in Table 14-38 and 14-39).

With regard to the first issue, it should be noted that annual average TSP and SO_2 estimates for years before 1964 are based on data obtained from a single monitoring site in Charlotte and Birmingham each, and the published estimates for those years (1960-64) shown in Table 14-39 are thusly likely to be the most tenuous in reflecting actual exposures in comparison to data obtained with multiple monitoring sites in later years. The estimates listed in Table 14-39 for 1964-1968 are derived from results obtained via multiple county, NASN, or other Federal monitoring sites situated as depicted in Figures 14-5 and 14-6. The estimates listed in Table 14-38 and 14-39 for 1968-71 are
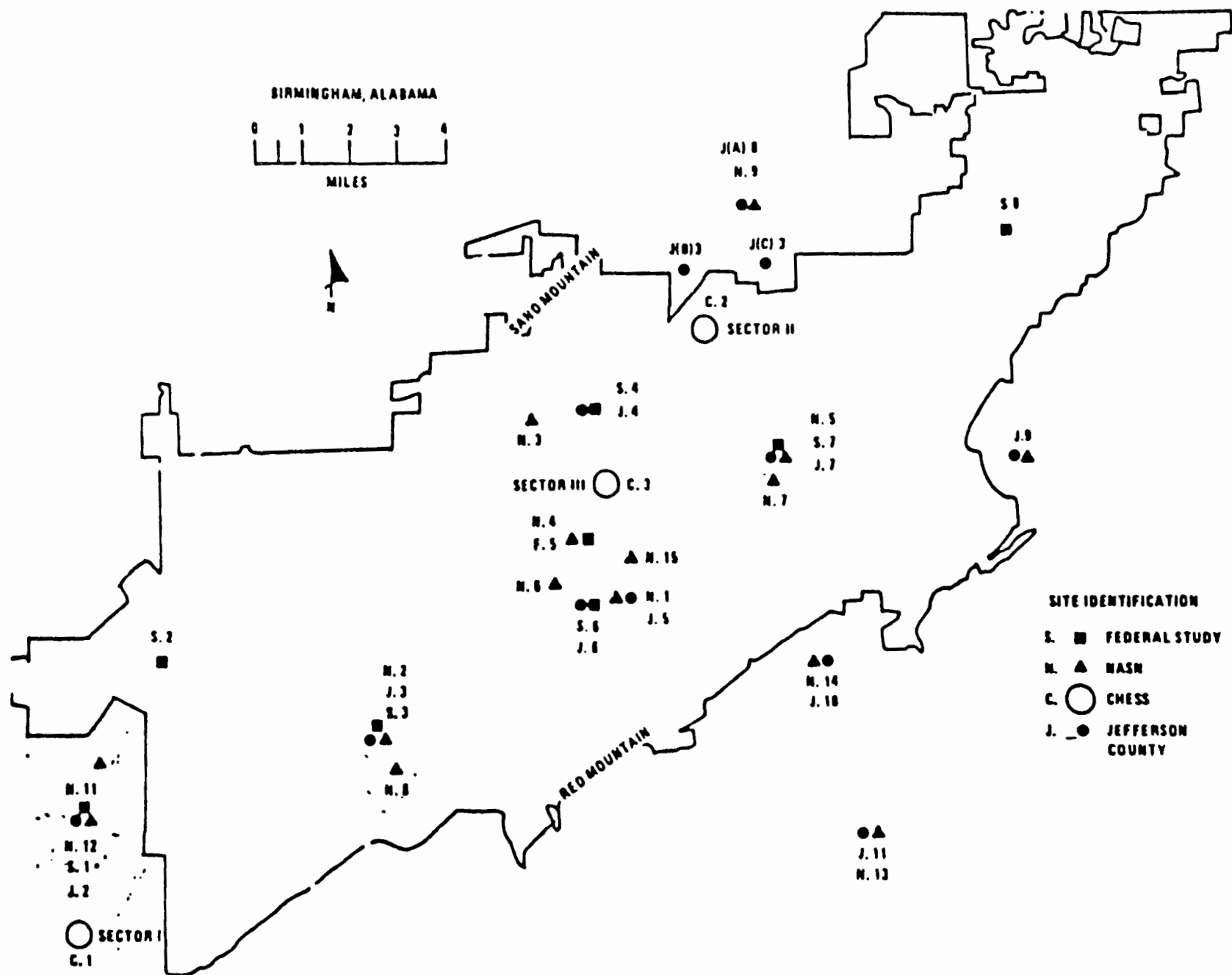
Figure 14-5   Locations of air monitoring stations in Birmingham, Alabama, from which air quality data employed in Hammer study were obtained.
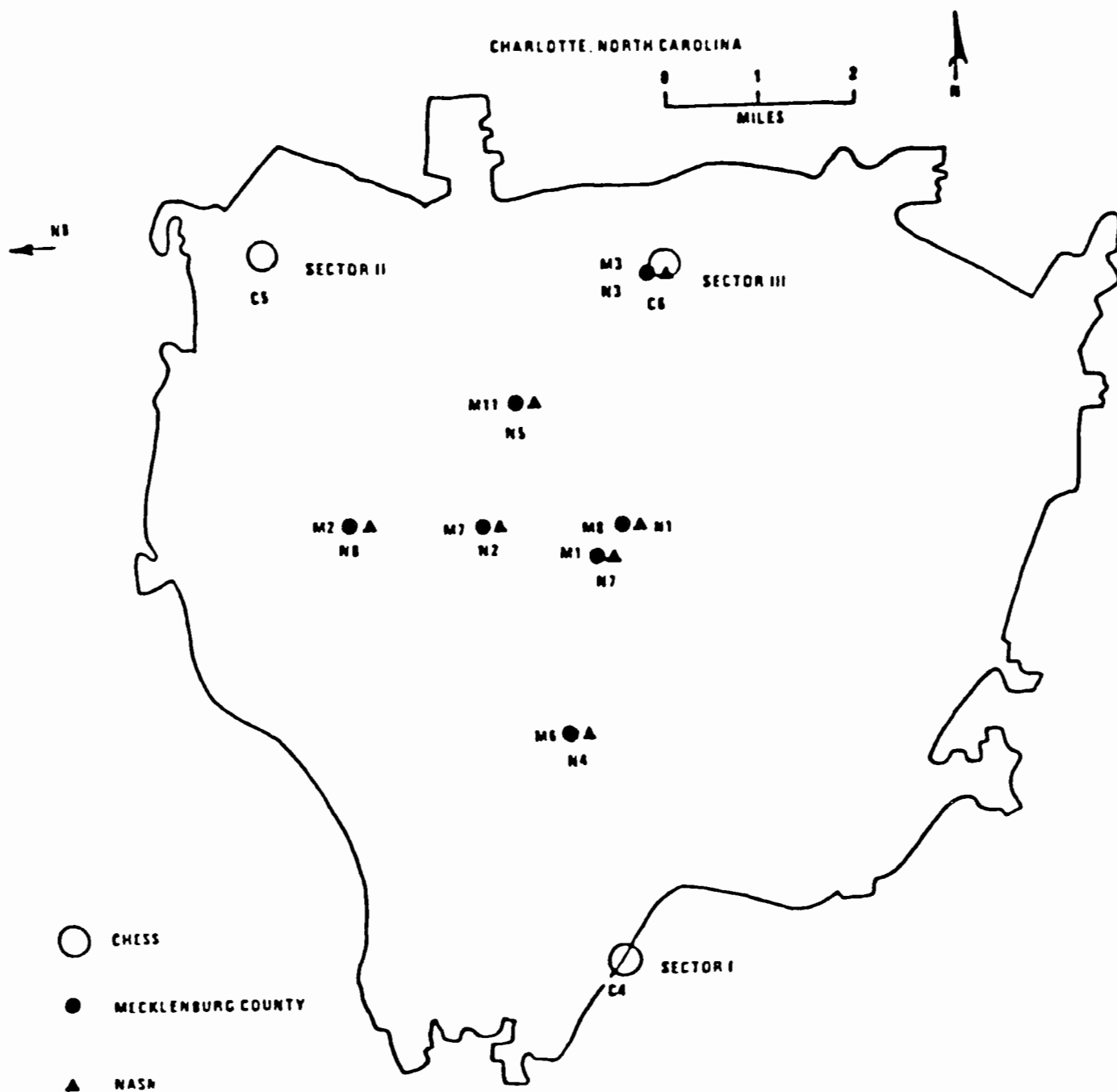
Figure 14-6 Locations of air monitoring stations in Charlotte, N. C. from which air quality data employed in Hammer study were obtained.

also derived from the same multiple county, NASN, and other Federal monitoring sites dispersed at points shown in Figures 14-3 and 14-4 so as, in general, to cluster around major air pollution emission point sources within Charlotte and Birmingham metropolitan areas.

Additional "CHESS" monitoring sites were set up in late 1969 at locations indicated in Figures 14-3 and 14-4, with one site (o) being situated in each of three residential neighborhoods (sectors) in each city and generally further distant from any of the high emission point sources than the other monitoring sites; the CHESS sites were also within 1½ to 2 miles of the residences of each of the study population families living in the respective sectors and were situated, except for one, at approximately six feet off the ground on flat, relatively open terrain. Thus such sites would appear to be likely to yield data well representative of exposures of the various study populations, exposures likely to be less than the air levels of pollutants monitored at the other sites closer to known pollution sources: and, consistent with this, "CHESS" estimates of TSP and SO_2 levels for 1969-71 are distinctly lower than the estimates based on the other monitoring data for the same period. Thus, the available "non-CHESS" monitoring data shown in Table 14-39 for TSP and SO_2 levels would seem to clearly represent the maximum estimates of the highest possible annual average (arithmetic mean) exposure levels likely to be associated with the respiratory disease effects demonstrated by the Hammer study.[113,257]

Turning to the second issue noted above, that concerning the validity and accuracy of the Hammer study air quality measurements, it should be noted that the Investigative Report[107] concluded that the TSP measurements obtained for other CHESS Program studies by means of procedures yielding the CHESS estimates

alluded to above were among the most consistent and reliable of the CHESS air quality estimates obtained and likely errored toward underestimation of actual TSP levels by, at most, 10 to 30 percent. Increasing the reported[113,257] Hammer study CHESS estimates by 30 percent, to allow for the maximum likely error associated with them, results in their approaching analogous estimates from the other monitoring networks more closely, but still remaining distinctly lower (being about 80-90 $\mu g/m^3$ for Charlotte sectors and 110-120 $\mu g/m^3$ for Birmingham sectors). As for the SO_2 air quality data, the IR[107] concluded that errors in SO_2 measurements in other CHESS studies may have resulted in underestimations of SO_2 levels by 50 to 100 percent or more, which means that published Hammer study SO_2 levels (being similar to the other monitoring estimates) might, theoretically, range up to still very low levels of 25 to 35 $\mu g/m^3$. On the hand, as discussed in the IR[107] the sensitivity of the SO_2 analytical methods employed in "CHESS" monitoring is such that SO_2 values under 25 to 50 $\mu g/m^3$ cannot be considered to be significantly different from zero. In other words, regardless of the precise SO_2 values actually present, there appears to be no question that they were equally low (nearly zero) in both Charlotte and Birmingham.

14.5.4 Pulmonary Function Studies

Impairment of pulmonary function is likely to be one of the effects of exposure to air pollution since the pulmonary system includes the tissues that receive the initial impact when toxic materials are inhaled. Acute and chronic changes in function may be significant biological responses to air pollution exposure. A number of studies have been conducted in an effort to relate pulmonary function changes to the presence of air pollutants in various European, Japanese, and American communities.

Studies in the Netherlands reported by van der Lende and colleagues[74-77] compared lung function in a large population group in 1969 and again in 1972. In a more polluted area, age-, health-, and smoking-adjusted $FEV_{1.0}$ values in men increased from the first to the second survey rather than decreasing with age as expected. This was associated with a concurrent decrease in air pollution concentrations. The highest 24-hour values for SO_2 during the time of the surveys in the high-pollution area were 160 and 300 $\mu g/m^3$, respectively, in 1969 and 1972; the highest 24-hour smoke values were 40 and 100 $\mu g/m^3$. Again, neither pollutant can be implicated individually. The investigators considered other possible causes of the improved pulmonary function but concluded that the most plausible was the effect of reduced air pollution. Expected decreases were seen in a rural area. The authors explored possible sources of bias in the study but were unable to explain their results on that basis. A third survey of this population, conducted in 1977, found that, under the improved air quality condition, expected decreases in pulmonary function values in the aging population was observed. This strengthens the possibility that the former pollution concentrations were related causally to the pulmonary status.[4]

Becklake et al.[33] used pulmonary spirometric and closing volume function tests (and symptom reporting) in three areas of Montreal Canada and did not find significant differences in children or adults that were associated with TSP levels. In the three areas studied, ambient SO_2 was reported to be 15, 123, and 59, and annual mean high-volume TSP values were 84, 95, and 131 $\mu g/m^3$, respectively, for the low-, intermediate-, and high-pollution areas, but there was a large overlap between areas. In a later report (Aubry et al.[300]) discriminant analysis was utilized to control for smoking, after which differences in health variables were not significant.

Manfreda et al.[85] studied pulmonary function in one rural and one urban population (25 to 54 years old) residing in the Winnepeg area of Canada in order to determine the effect of any urban factor. Pulmonary function was assessed by single breath N_2 tests and by force vital capacity using a dry rolling Seal Spirometer. Tests were repeated until three gave results within 10 percent of each other or a maximum of five determinations was reached. Annual mean concentrations of SO_2 were about 15 $\mu g/m^3$ (0.005 ppm) in both areas, although the authors stated that subjects in the urban area may have been exposed part of the time to the 30 $\mu g/m^3$ (0.01 ppm) that is measured in the more polluted part of Winnipeg. Annual mean TSP concentrations were reported to be no more than 56 $\mu g/m^3$ in either study area, although those in Winnipeg were 73 to 78 $\mu g/m^3$. The study results indicated that total lung capacity, vital capacity on expiration, residual volume, and closing volume in men and women were very significantly related to height, age, and smoking status ($p < 0.05$). However, there were no differences associated with the place of residence. Thus an urban factor was not apparent in a low-pollution urban area.

Kagawa et al.[218,264] investigated the effects of photochemical air pollution (oxidants, ozone, hydrocarbons, NO, NO_2, SO_2, suspended particulate matter), temperature, and humidity on respiratory functions of Tokyo schoolchildren. Ventilatory function was measured weekly for 29 weeks, June-December 1972, in 21 schoolchildren and again from November 1972-March 1973. Of seven measures of respiratory function, maximum expiratory flow rate showed the highest correlation ($p < 0.05$) with the greatest number of environmental variables. Among environmental variables, temperature significantly affected a number of respiratory functions, being positively correlated with R_{aw} in

particular. Partial correlations showed, however, that regardless of temperature, ozone, sulfur dioxide, and NO_2 alone also played significant roles in affecting individual respiratory functions.

Zapletal et al.[87] studied pulmonary function in 111 healthy 10- to 11-year-old children who had lived for at least 5 years in highly polluted areas of Czechoslovakia. Only 19 (17 percent) of the children demonstrated baseline abnormalities in FEV_1. They were studied further; 6 of the 19 showed significant reductions in maximal flow rates at low volumes. The investigators concluded the FEV_1 and flow abnormalities might be related to air pollution. Air concentrations of SO_2 and TSP were in excess of 240 $\mu g/m^3$ (daily averages) on more than 7 days a month during winter.

Holland et al.[101,102] and Bennett et al.[103] reported the results of studies of pulmonary function in schoolchildren, aged 5, 11, and 14 years, living in two urban and two rural areas of Kent, England. Peak expiratory flow rate (PEFR) was measured with a Wright Peak Flow Meter. Approximately 10,000 children were included in the study populations. Mean smoke concentrations in the two urban areas for the period from November 1966 to March 1967 were 69 and 50 $\mu g/m^3$ (BS). Smoke measurements were available from only one of the rural areas, and these averaged 34 $\mu g/m^3$. The other rural area was said to be at least as clean. Mean peak expiratory flow rates, adjusted for differences in age, height, and weight as well as for a history of bronchitis or pneumonia, social class, and the number of siblings in the family showed significant area differences. In the highest area (Rochester), the lowest levels of PEFR were found to be independent of parents' social class, family size, and past history of respiratory illness. The four factors operate independently and additively. Differences between other areas did not correspond to differences in air pollution concentrations. Thus, mean values of BS

of 70 μg/m^3 in winter (123 μg/m^3 TSP) were associated with reduced PEFR, but 30 to 50 μg/m^3 BS were not. Smoking in the home and other pollution were not considered in this study. Also details on instrument calibration and number of trials for each child were not given.

Colley and Reid[112] reported results of respiratory symptoms and lung function (PEFR) in approximately 10,000 children ages 6-10 in different parts of England. They examined relationships with SO_2 specifically. Mean values were found in the different areas from 33 μg/m^3 to 150 μg/m^3 of SO_2 (converted lead peroxide sulfation rates). Smoke levels were not provided. The biggest gradient they found was between respiratory symptoms and social class by area; the biggest differences occurred in social classes IV and V. They found an association of lower respiratory tract infections with the air pollution gradients, but no association for upper respiratory tract infections. Differences were not explained by domestic circumstances (persons per dwelling, rooms per dwelling, crowding). (The trends followed similar trends in the frequency of killing and disabling bronchitis among adults in the same areas.[248])

Turning to American studies on morbidity effects associated with long-term exposures, Ferris[195] conducted a carefully executed study of absence rates and pulmonary function in first and second grade schoolchildren in seven schools in areas of Berlin, N. H. with different concentrations of air pollution. Pollution measurements included sulfation rates in μg of SO_3/100 cm^2/day and average dustfall in tons/mile^2/30 days. Indications were that SO_2 was about four times more concentrated in the area of highest than lowest pollution (619 ± 246 vs. 130 ± 101 μg of SO_3/100 cm^2/day) and that particulates were nearly five times more concentrated in the area of highest pollution (62 ± 16 vs. 13 ± 7 tons/mile^2/30 days). Maximum particulate and SO_2 levels did not occur in

the same area. In spite of the differences in pollution, school absences for respiratory illnesses were not significantly different between schools; nor was their any relationship between social class and absence rates. Pulmonary function tests (peak flow with Wright Peak Flow Meter and forced vital capacity and 1-second forced expiratory volume from a Stead-Wells spirometer) during the winter (January) showed no significant relationship to school. However, such measurements taken in summer significantly related to particulate air pollution, as shown by individual comparison T-tests following an overall analysis of variance (ANOVA) comparing results obtained with children from different schools in high, medium, and low pollution areas.

Holland et al. (1979)[301] evaluated the Ferris[195] Berlin study results as follows:

> The children in the school in the most polluted area tended to have lower peak expiratory flow rates (both sexes), forced vital capacity and forced expiratory volume (girls only) than in one or two schools from areas with intermediate levels of dustfall. However, no differences were found between children in the most and least polluted areas. The method of carrying out individual t tests between so many schools is an unwise statistical practice: the analysis of variance is more appropriate as it indicates to what extent the variation between all the schools could have occurred by chance, given the hypothesis that there were no real differences. Since the result of the analysis of variance was not reported it is probable that no significant differences between the schools could be found.

Of course exactly the opposite inference should be drawn from the one stated by Holland et al.[301] on the basis of the above information; that is, one must assure that the individual t-test comparisons between shcools would not have been carried out unless significant overall differences were first obtained by means of the ANOVA in keeping with standard statistical procedures associated with ANOVA usage. It is difficult to understand how Holland et al.[301] missed information clearly stated in the Ferris publication[195] confirming that, in fact, this was done (as quoted below):

The results of the tests of pulmonary function were tested for significant differences among the schools by a one-way analysis of variance. If significant difference was noted, a two-tailed t test was done (table 12). Pulmonary function in pupils of School A was significantly lower than that in pupils of several other schools, particularly in the June 1967 study.

Furthermore, use of one-tailed t-test may have been more appropriate in this case, to test the hypothesis that air pollution was causing the observed health effects differences and may have identified even more statistically significant differences due to particulate pollution.

Mostardi and Leonard[177] compared measurements of pulmonary function (VC, FEV_1, MMF, and VO_2^{max}) in 42 volunteer male high school students from a polluted area with similar measurements for 50 male students from a rural area. The subjects in this 1973 study had all participated in a 1970 study in which measurements were limited to VC and FEV_{75}. Air pollution concentrations in both study areas declined somewhat between 1970 and 1973 but results of the two studies were similar. In 1970 the group in the polluted area had a mean VC (3.27 ± SE 0.07) lower than the group in the cleaner area (3.54 ± SE 0.10) p <0.05. In 1970, means were higher (4.65 ± SE 0.11 for the polluted area and 5.04 ± SE 0.10 for the rural pollution area) but the difference remained (p <0.01). The mean $FEV_{.75}$ in 1970 also was lower in the polluted area (2.57 ± SE 0.10) than in the low-pollution area (2.90 ±SE 0.08, p <0.01) but the mean FEV_1 values in 1973 (4.09 ± 0.09 and 4.20 ± 0.08) were not significantly different. Annual mean SO_2 concentrations measured as mg SO_2/100 cm^2/day by the lead peroxide candle method ranged in the high pollution area from 1.014 in 1970 to 1.020 in 1972 (81.1 to 81.6 $\mu g/m^3$) and in the low pollution area from 0.763 to 0.36 (61 to 28.8 $\mu g/m^3$). Comparable data were not collected in 1973. Annual mean suspended particulate matter concentrations ranged in the

high pollution area from 77 to 110 $\mu g/m^3$, and in the low-pollution area from 71 to 83 $\mu g/m^3$. The investigators suggested that the differences in test results may have related to the differences in pollution. The inclusion of blacks did not affect the results, although smoking may have. SES (apart from race) may have also had some effect. The area in which the study was done is heavily industrialized and the differences in the measured pollution levels may have been adequate indices of difference in risk experienced in the high pollution area.

Mostardi and Martell[258] reported on 173 and 161 students, respectively, from the same urban and rural areas. They tested FVC and $FEV_{.75}$ on subjects residing in the areas for 4 or more years. The groups were analyzed separately by sex and males were analyzed separately by whether or not they smoked cigarettes. The two groups were comparable in anthropometric characteristics. Higher values for pulmonary function were reported in the rural area for all males, females, and smoking males. While a higher proportion of smokers were found in the urban area (12 percent versus 6 percent in the rural area), the authors stated that this did not influence their results. They did not analyze by race in this study, because they found that the lung function differences persisted in their previous study after exclusion of the three black students in the urban area.

Pulmonary function was also studied in Cincinnati schoolchildren in 1967-1968 by Shy et al.[215]. Children from schools in an industrial valley of Cincinnati were compared with children from schools in a non-industrial river valley on the east side of the metropolitan area. Two each upper-middle white, lower-middle white, and lower-middle black schools were selected from each valley. Air monitoring stations within three blocks of the schools

showed that 7-month average TSP values were from 18 to 32 $\mu g/m^3$ higher in the industrial valley than in the non-industrial valley, but corresponding differences for suspended sulfates, suspended nitrates, and SO_2 ranged from 0.1 to 1.1, 0.1 to 0.8, and 0.6 to 10.4, respectively. Thus, the industrial valley had more TSP than the non-industrial valley, but its levels of SS, SN, and SO_2 exceeded those in the non-industrial valley by very small margins. Arithmetic averages over the 7 months of the study ranged for TSP from 96 to 114 $\mu g/m^3$ in the more polluted industrial area and from 77 to 82 $\mu g/m^3$ in the cleaner areas. SO_2 for the 7-month average ranged from 39 to 51 $\mu g/m^3$ in the polluted areas and from 40 to 45 $\mu g/m^3$ in the clean areas. Ventilatory function was measured as the forced expiratory volume at .75 second ($FEV_{.75}$) on a Stead-Wells water-filled spirometer once weekly on each child during each of the study months. The better of two satisfactory forced expiratory maneuvers obtained on each test day was used for all computations. Height, sex, and race were used to make adjusted $FEV_{.75}$ comparisons. The study was confined to 394 second graders who participated in weekly measurements during November 1967, February 1968, and May 1968. These students represented 93 percent of second graders in the classrooms selected. Mothers were interviewed to obtain socio-economic data. The educational attainment of fathers was similar for corresponding schools in the industrial and non-industrial valleys.

The Shy et al.[215] data showed that average height adjusted $FEV_{.75}$ in "clean" schools exceeded that in "polluted" schools in all 3 months for lower-middle class whites and in 2 of 3 months for upper-middle whites. Blacks consistently had lower $FEV_{.75}$ values, and a pollution effect was seen among blacks during only one of three study periods. The absolute differences in average $FEV_{.75}$ were roughly 40-120 ml (< 10 percent) in most cases. A

multivariate analysis of variance was applied which allowed for testing of community effects adjusted for a possible month effect and for the covariates height, sex, race, and social class. The dependent variable for each child was his vector of three monthly average $FEV_{.75}$ values. They concluded from this analysis that suspended sulfates had the strongest association with $FEV_{.75}$. These studies support the notion that $FEV_{.75}$ was 3 to 10 percent less among white second graders in the industrial valley than among those in the non-industrial valley.

In 1970 to 1971, a ventilatory function study was conducted by Shy et al.[215] in New York as part of the EPA CHESS Program. It included children ages 5 to 13 who attended schools situated within 1.5 miles of air monitors. Riverhead, Bronx, and Queens were represented by three schools each. Only white children were included in the analysis. Unfortunately, the electronic spirometer used to assess pulmonary function exhibited drift (≤ 350 ml). This could bias the study results only if one community was systematically studied with a spirometer with extreme drift or if the drift varied in phase with the rotation of spirometers through communities. The variability of the observations is increased by random distribution of drift, since the community effects (60 ml or less) are much smaller than the drift.[107] However, during testing periods, the instruments were calibrated against a Stead-Wells volume spirometer. They also were tested for reproducibility by obtaining six or seven successive $FEV_{.75}$ measurements with trained subjects and comparing them with the results obtained with the Stead-Wells spirometer connected in series. Percent differences in pulmonary function ranged from -7.0 to +6.6, about the same as the accuracy of any spirometer.

Families of children studied in Riverhead, Queens, and Bronx, were similar in regard to age distribution and parental smoking habits. Income and educational attainment decreased in the order Queens, Riverhead, and Bronx. No comparison of children's smoking habits is reported, although this may have been crucial in interpreting the results in view of statistically significant differences in pulmonary function being found only for older children.[107]

Male $FEV_{.75}$ values, adjusted for height and age, from Riverhead (the low pollution community) were intermediate between Queens and Bronx (the two higher pollution communities) for three of four test periods. For females, the Riverhead values exceeded Bronx and Queens values in each test period, but the differences usually were less than 50 ml. Riverhead height-adjusted $FEV_{.75}$ values were largest during one of four test periods for young males and females, and during three of four for older males and females. The average differences were inconsistent. However, the analyses for individual test periods do show statistically significant differences for older males and females. Shy et al.[215] speculate that lack of differences in 5- to 8-year olds may be due to improved air quality in years since the early childhood period of the older subjects studied. As noted above, local monitoring levels were judged accurate,[107] and were used to assess area differences in this study.

Chapman et al.[213] performed an EPA CHESS Program survey of the ventilatory function of 7997 black and white elementary schoolchildren in Charlotte, North Carolina and Birmingham, Alabama, during the 1971-1972 school year. These cities had been selected for study because they exhibited a gradient of exposure to suspended particulates, and had low levels of other pollutants. Birmingham had an average RSP of 45 g/m³ compared with 33.4 in Charlotte. The ventilatory

function test employed was the three-quarter second forced expiratory volume ($FEV_{0.75}$). Two instruments were utilized in each area sequentially (a hot wire anerometer in the first two surveys and a dry-seal spirometer thereafter).

In all eight age-, sex-, and race-specific subgroups, mean age- and height-adjusted $FEV_{.75}$ readings were consistently lower in the more polluted city, Birmingham. This finding strongly indicated that exposure to particulate pollution had exerted a deleterious effect on the $FEV_{0.75}$ of children in Birmingham. The results may be consistent with either of two alternate hypotheses: first, that exposure to TSP (high RSP and suspended sulfates) from the beginning of life onward promotes impairments in $FEV_{.75}$ in later childhood; or second, that such particulate exposure for the past several years promotes such impairments. The authors assumed, possibly wrongly,[107] that children ages 12 and under do not smoke appreciably nor differently in the two areas. See Appendix A for more discussion of this point.

Intercity differences in mean $FEV_{0.75}$ were smallest in fall, greater in winter, and greatest in spring. Intercity differences in TSP, RSP, suspended sulfates, and suspended nitrates parallelled this pattern. Because ventilatory function testing was performed on only three occasions, and the first two used a different instrument than used in the third, it was not possible to test the seasonal differences in $FEV_{.75}$ as a function of changes in particulate concentrations. Sulfur dioxide and suspended nitrates were present in low concentrations in both cities, both during the year of study and throughout the lives of the children under study. Thus, it was unlikely that either of these pollutants had exerted important deleterious effects on $FEV_{0.75}$ in either city. Beyond this point, it was not possible to determine which specific particulate fraction or fractions had exerted the strongest effects of $FEV_{0.75}$.

14.5.5 Studies Combining Respiratory Disease Symptoms with Pulmonary Function

Neri et al.[34] compared the prevalence of chronic bronchitis and results from respiratory function tests in Ottawa and in Sudbury, a Canadian smelter town. The authors reported that the smelting operation in Sudbury emitted large quantities of SO_2 at the time of the study, but that they were far lower than quantities emitted in former years. The operation shut down when 24-hour mean concentrations of SO_2 reached 850 $\mu g/m^3$ (0.3 ppm) or the TSP reached 500 $\mu g/m^3$. Twenty-two shutdowns occurred during the 2-year study period. Three-year mean values for high-volume TSP and SO_2 were 93.0 $\mu g/m^3$ and 52.1 $\mu g/m^3$, respectively in Sudbury. In Ottawa, there were 45.8 $\mu g/m^3$ and 90.5 $\mu g/m^3$, respectively.

In Ottawa, the prevalence of chronic respiratory disease and reduced pulmonary function values were associated with smoking and age but showed no relationship to duration of residence. However, in Sudbury, length of residence was associated with increased rates of chronic respiratory illness, and living in Sudbury for any period of time was associated with reduced pulmonary function. In Sudbury, smoking, occupation, and age were associated with the prevalence of chronic respiratory illness and impaired pulmonary function. After adjusting for smoking, age, and occupation, residence in Sudbury was associated with excess respiratory disease and diminished ventilatory function. Neri et al.[35] found that the mean ratio of FVC to FEV for 3280 Ottawa residents in 1969 to 1971 was higher than the mean for 2208 Sudbury residents in 1972-73. The difference was significant for both males and females and held true even after considering age and smoking habits ($p < 0.001$). The prevalence of chronic bronchitis also was higher in Sudbury males ($p \sim 0.03$), but no difference was found for females. Holland et al.[301] discussed the effects of the short-term high exposures in Sudbury, but did not negate the study.

Cohen et al.[36] made a comparison of respiratory symptoms and pulmonary function tests in two similar groups of nearly 2000 nonsmoking adults each. They found no indication that either increased symptoms of chronic lung disease or impairment of lung function as reflected by spirometry or flow volume loops was caused by a twofold difference in peak values of oxidant air pollution, or differences between 78 and 124 $\mu g/m^3$ annual average TSP (annual mean SO_2 concentrations were about 43 $\mu g/m^3$).

Ramaciotti et al.[179] determined rates for the occurrence of bronchitis symptoms in 1182 men in Geneva in relation to the ambient SO_2 concentration at the site of residence, the number of cigarettes smoked per day, and age. Because the prevalence of chronic bronchitis among non-smokers was very low, these were excluded from the study. Information on illness symptoms and demographic factors was collected by means of the BMRC questionnaire and the aerometric data were collected by the Institut d'Hygiène, Geneva. The study covered the period 1972 to 1976 and found 98 cases classified as chronic bronchitis, 477 classified as having intermediate symptoms, and 637 subjects were asymptomatic. Regression analysis (Linder-Berchtold method) was used to determine associations. The adjusted incidence of chronic bronchitis within the group increased from 2 percent to approximately 20 percent as the consumption of cigarettes increased from 1 to 50 per day; from 2 percent to about 16 percent as age increased from 18 to 65 years; and from 4 percent to about 12 percent as annual mean SO_2 pollution levels increased from 10 to 60 $\mu g/m^3$. Similar adjusted rates showed no significant slopes for the group with less severe symptoms (intermediate group). Peak respiratory flow (PFR) decreased from 500 to 470 liters/min on the average as cigarette consumption increased from 1 to 50 cigarettes per day; from 530 to 40 liters/min as age increased

from 18 to 65 years; and from 500 to 475 liters/min as annual SO_2 pollution
levels increased from 20 to 65 $\mu g/m^3$. Similar relationships were observed in
the intermediate group. The levels of SO_2 smoke and NO_2 observed in the study
were positively associated with the prevalence of chronic bronchitis.

A series of studies, reported on from the early 60s to the mid-70s,[41-50]
have been conducted by Ferris, Anderson, and others. The initial study involved
comparison of three areas within a pulp-mill town in northern New Hampshire.
In the original prevalence study,[41,47] no association was found between question·
naire-determined symptoms and lung function tests in the three areas with
differing pollution levels after standardizing for cigarette smoking. The
authors discuss why residence is a limited indicator for exposure.[47] The
study was extended to compare Berlin, New Hampshire, with the cleaner city of
Chilliwack, British Columbia in Canada.[50] Sulfation rates (lead candle method)
and dustfall rates were higher in Berlin than in Chilliwack. The prevalence
of chronic respiratory disease was greater in Berlin, but the authors conclude
that this difference is due to the interaction between age and smoking habits
within the respective populations. Higher levels of respiratory function in
some cigarette-smoking groups in the cleaner area were observed, but this
difference could be due to socioeconomic and ethnic differences as well as air
pollution. Ethnic differences could have been a confounding factor.[248] The
SO_2 level in Berlin, NH, in 1961, may also be in doubt since it is based on a
2 month period at a single site.[312]

The Berlin, New Hampshire, population was followed up in 1967 and again
in 1973.[42,46] During the period between 1961 and 1976, all measured indicators
of air pollution fell. In the 1973 follow-up, sulfation rates nearly doubled
from the 1967 level (0.469 to 0.901 mg $SO_3/100$ cm^2/day) while TSP values fell
from 131 to 80 $\mu g/m^3$. Only limited data on SO_2 was available (the mean of a
series of 8-hr. samples for selected weeks).[312]

TABLE 14-40. POLLUTION LEVELS, BERLIN, NEW HAMPSHIRE,
DURING THREE STUDY PERIODS

	Total dustfall gm/m^2/30-day	TSP (HV) $\mu g/m^3$	Sulfation (lead peroxide) mg SO_3/100 cm^2/day	Sulfation* converted to SO_2 $\mu g/m^3$
1961	18.4	180	0.731	55
1966-1967	14.3	~131	0.469	37
% decline	22%	28%	36%	28%
1961-1966/67	--	--	--	--
1973	--	80	0.901	66

*Assuming all sulfur in the form of SO_2.

During the 1961 to 1967 period, standardized respiratory symptoms rates decreased and there was an indication that lung function also improved. Between the period 1967 to 1973, age-sex standardized respiratory symptom rates and age-sex-height standardized pulmonary function levels were unchanged. The authors conclude that either the air pollution change was not associated with a change in respiratory health or that the study was not sensitive enough to detect an effect. However, the type of cigarette smoking may have changed.[314b] Internal migration may have been an additional factor. For these various reasons, these studies are difficult to interpret.[247,312,314b]

Bouheys et al.[168] used the NHLI questionnaire to obtain information on the prevalence of respiratory symptoms in study subjects 7 years old or more in an industrial urban and a rural community in Connecticut in 1973. Annual mean TSP concentrations had been 88 to 152 $\mu g/m^3$ in the urban area during the

previous 7 years, but similar data were not available for the rural area. In 1973, the year of the study, SO_2 annual concentration was 13.5 ± 1.7 and 10.9 ± 1.6 $\mu g/m^3$, respectively, for the urban and the rural area, both low. Annual mean TSP concentrations were 63.1 ± 3.7 and 39.5 ± 4.2 for the urban and rural areas, also relatively low. Means were based on approximately 1 measurement per week. Results, adjusted for sex, race, age, smoking, occupation, and previous residence of the bronchitic symptom of "usual cough and phlegm" showed significant decreasing gradient from lifetime urban to lifetime rural among non-smokers but not among smokers. Shortness of breath also showed an association with residence that was most pronounced among non-smoking women (12.8 percent lifetime rural and 19.2 percent lifetime urban). However, asthma occurred more frequently among the rural residents. Inconsistencies with indoor exposures were present in the data as well.

Irwig et al.[98] studied relationships between air pollution and respiratory disease in British schoolchildren. Information on 1816 children was collected by self-administered questionnaires. Positive responses to questions concerning the occurrence and frequency of respiratory symptoms were associated with results of pulmonary function testing (PEFR) and the data analyzed by a regression method specially designed to handle quantal data. The air pollution levels used were the mean smoke and SO_2 for November, 1973. Both pollutants were found to be significantly associated with a history of colds going to chest ($p < 0.05$). Over the range of smoke levels in the analysis (10 to 130 $\mu g/m^3$), it was predicted by the equation that for each increment of 10 $\mu g/m^3$ of smoke (ignoring SO_2) 0.77 percent more of the population would have colds to the chest. The authors report that similar results were obtained with SO_2, ignoring smoke, but the measured concentrations of SO_2 (H_2O_2 method) were not reported.

They did conclude that the analysis suggests that dimunition of smoke or SO_2 from 130 to 10 $\mu g/m^3$ would result in a decline in prevalence of colds going to chest of as much as 49 percent in the highest risk group, and at least 12 percent in the lowest risk group.

Kerrebijn et al.[99] collected data from fourth and fifth grade students on the relationships between respiratory symptoms or pulmonary function tests and the concentrations of pollution in areas in which they lived. Data on respiratory illness and social and domestic circumstances of the family were obtained by means of a self-administered questionnaire. Pulmonary function measurements for the approximate 2400 children were made over the period of April 2 to June 8, 1973 to correspond with the period of low viral infections and few high air pollution peak concentrations. At the time of examination, height and weight were recorded; peak expiratory flow rate was measured in standing position with a Wright Peak flow Meter (highest of five readings recorded), forced vital capacity and forced expiratory volume in 0.75 second were measured in the sitting position with Lode D-53 watersealed spirometers (the highest of three values recorded) and the maximum expiratory flow at 50 percent vital capacity and at 25 percent vital capacity were measured in the standing position with a Monaghan M402 pulmonary analyzer connected to a rapid recorder. The Peak Flow Meters were calibrated once a day over their full range with a Godart calibration set and with standard flows. All measurements were corrected to standard flows. The Monaghan instruments also were calibrated at their peak flow reading with the Godart set.

Children living in the high pollution area showed a higher prevalence of cough during the day or at night. Ventilatory function tests showed no differences between the high and low pollution areas. Depending on the

criteria used to define chronic respiratory disease, prevalence in the high
pollution area was 1.3 to 1.6 times that in the low pollution area. Annual
mean concentration of SO_2 in the low pollution area was 50 $\mu g/m^3$ as a result
of a change in fuel from oil to gas that began only 3 years earlier. Prior to
the change the annual mean SO_2 concentration had been equal to that in the
high pollution area or 150 $\mu g/m^3$ or higher. Particulate measured as standard
smoke (BS) was low in all areas, usually below 30 $\mu g/m^3$ for annual means.

Biersteker and van Leeuwen[104,105] reported on pulmonary function measure-
ments and bronchitis histories in 935 elementary schoolchildren living in two
areas of Rotterdam with differing air pollution levels. In a new suburb, the
winter median for smoke (BS) was 40 $\mu g/m^3$; that for SO_2 was 120 $\mu g/m^3$ (0.04
ppm). Concentrations of smoke and SO_2 in older downtown districts were about
50 percent higher. After adjustments for height, no differences in peak
expiratory flow rates were found for boys or girls. A history of bronchitis
was more common in the more polluted area; however, the differences in socio-
economic levels were not controlled and may have been be a factor in the
difference seen.

The results of the studies discussed above are summarized in Table 14-40a.
It can be seen there that various studies have demonstrated pulmonary function
deficits (as assessed by lung function tests) or chronic respiratory disease
rates to be associated with TSP and SO_2 air levels of approximately 100-200
$\mu g/m^3$. Still others (mainly EPA CHESS studies) have been reported as indicating
that such effects may occur at somewhat lower levels; however, questions have
been raised regarding the interpretation of these study results as discussed
in the 1976 Investigative Report (see also Appendix A). These include concerns
regarding some of the air quality measurements reported for TSP, SO_2, and
suspended sulfate (SS) levels, the specific nature of which may lead to

TABLE 14-40a. SUMMARY OF LONG-TERM EXPOSURE STUDIES OF PULMONARY FUNCTION
DEFICITS AND CHRONIC RESPIRATORY DISEASE

Type of Study	Reference	Effects observed	Annual average pollutant levels at which effect occurred	
			TSP ($\mu g/m^3$)	SO_2 ($\mu g/m^3$)
Cross-sectional and long (2 areas)	van der Lende[74][77]	Improvement in lung function accompanying an improvement in air quality	100 BS (24-hr avg.) (200 TSP)	300 (24-hr avg.)
Cross-sectional (3 areas)	Goldberg et al.[109]	Increased chronic respiratory disease	78-82	69-160
Cross-sectional (4 areas)	House et al.[108]	Increased chronic respiratory disease	70 (15 SS)	107
Cross-sectional (2 areas) (children)	Kerrebijn et al.[99]	Increased cough, no decreased pulmonary function*	low (<30 BS) (<80 TSP)	150 *(low area > 3 years ago same, now lower)
Cross-sectional (2 areas) (children)	Yoshida et al.[176]	Increased asthma	?	110-120
Cross-sectional and long (2 areas)	Sawicki and Lawrence (1977)[181]	Increased previous CB and asthma. Increased persistence, males 31-50. Increased incidence, females, some ages.	169	114
Cross-sectional (3 areas) children	Rudnick[182]	Increased respiratory symptoms in boys. Increased Rh. in girls	150-227 BS (240-340 TSP)	180-148
Cross-sectional and retro-long (4 areas) (children)	Nelson et al.[114]	Increased LRD (α residence)	70	107
Cross-sectional (2 areas) (children)	Hammer[113,257]	Increased LRD	133 (SS=14)	<25
Cross-sectional (3 areas) (children)	Shy et al.[215]	Decreased adjusted $FEV_{0.75}$ in children > 8 years	72-82	69-160

TABLE 14-40a (continued).

Type of Study	Reference	Effects observed	Annual average pollutant levels at which effect occurred	
			TSP ($\mu g/m^3$)	SO_2 ($\mu g/m^3$)
Cross-sectional (2 areas) (children)	Shy et al.[215]	Decreased adjusted $FEV_{0.75}$	96-114	(= and low)
Cross-sectional (2 areas) (children)	Chapman et al.[213]	Decreased adjusted $FEV_{0.75}$	45 RSP	(= SO_2 & low)
Cross-sectional and	Neri et al.[34][35]	Decreased FEV_1/FVC and increased CB	93 with peaks	with higher average in lower AP areas

reinterpretation of those findings suggesting that reported health effects may be associated with somewhat higher TSP or SO_2 levels (i.e., >100 to 150 $\mu g/m^3$).

14.6 CHAPTER SUMMARY AND CONCLUSIONS

14.6.1 Overview Summary of Chapter Contents .

In the preceding sections of this chapter, an extensive array of information was discussed concerning: (1) methodological considerations that must be taken into account in evaluating community health epidemiology studies (Section 14.1); (2) critical assessment of practical applications of air quality measurement techniques employed in the collection of sulfur oxides and particulate matter data utilized in related community health studies (Section 14.2); (3) critical review of such studies on mortality effects associated with acute and chronic exposures to sulfur oxides and particulates (Section 14.3); (4) critical review of studies of morbidity associated with acute exposures to the same pollutants (Section 14.4); and (5) critical assessment of morbidity effects associated with chronic exposures to sulfur oxides and particulate matter.

Through the discussion in Section 4.1, it was seen that numerous methodo- logical factors, including covarying or confounding variables, can potentially affect the results and interpretation of community health studies. It was also seen, through material summarized in Section 14.2, that a number of sources of errors have been identified as having affected sulfur oxides and particulate matter air quality measurements obtained in both the United Kingdom and the United States and used in British and American epidemiology studies which provide the bulk of the information reviewed in this chapter. It was further noted that while such errors in air measurements can at times be fairly large, they also often act to introduce both positive and negative biases into air quality data sets that tend to cancel each other out, especially when considering data grouped or averaged over long time periods (monthly;

annually) from the same sites or across several geographic areas classed as "low" or "high" pollution areas. At other times, however, it also became clear that certain measurement errors were such as to introduce either consistently negative or positive bias into particular British or American sulfur oxides or particulate matter data sets used in various community epidemiology studies providing information on quantitative air pollution/health effects relationships. It was further noted that such biases due to air quality measurement errors must be taken into account in evaluating such epidemiology studies -- not for the purpose of discrediting such studies but rather to understand better the error limits likely associated with the reported quantitative findings derived from them and to thereby allow for more accurate interpretation of overall patterns of pertinent results.

Turning to the critical assessments of pertinent community health mortality and morbidity studies contained in Sections 4.3, 4.4 and 4.5, results of many of the better known and often cited quantitative studies discussed in this chapter are summarized in Tables 14-41 and 14-42. More specifically, Table 14-42 summarized chronic exposure study results. If the results of all the various studies summarized were accepted as being valid, then certain conclusions might be drawn regarding air levels of sulfur oxides and particulate levels associated with mortality or morbidity effects, as discussed in the next several chapter overview subsections.

TABLE 14-41   SUMMARY TABLE - ACUTE EXPOSURE EFFECTS

Type of Study	Reference	Effects observed	24-hour average pollutant levels at which effects appear	
			TSP ($\mu g/m^3$)	SO$_2$ ($\mu g/m^3$)
Mortality (episodic)				
British	Table 14-1	Excess deaths	546*	994
Dutch	Table 14-2	Excess deaths	300-500	500
Japanese	Table 14-2	Excess deaths	285	1800
USA	Table 14-2	Excess deaths	570 (5 CoH)	400-532 (1 hr max: 2288)
(Non-episodic)	Martin and Bradley[11]	Increases in daily mortality	500*	300
	Martin[6]	Increases in daily mortality above the 15 moving average	500*	400
	Glasser and Greenburg[222]	Increases in daily mortality	350-450**	524
Morbidity	Martin[16]	Increases in hospital admissions for cardiac or respiratory illness	500*	400
	Lawther et al.[53]	Worsening of health status among 195 bronchitics	344* (250 BS)	300-500
	Greenberg et al.[196]	Increased cardio-respiratory ER visits	357** (260 BS)	715
	Lawther et al.[52]	Increased clinical condition in CB patients	529* (400 BS) 344* (250-350 BS)	450 300
	Stebbings and Hayes[190]	Increased symptoms in chronic bronchitis (CB) patients	200 (60 RSP) (12SS) 8 SN)	100

TABLE 14-41 (continued).

Type of Study	Reference	Effects observed	24-hour average pollutant levels at which effects appear	
			TSP ($\mu g/m^3$)	SO_2 ($\mu g/m^3$)
	Cohen et al.[55]	Increased AS attacks	150 (20SS)	200
	McCarroll et al.[163]	Increased ARI daily inc/prev	160* (1.2 COH)	372
	Cassell et al.[208][209]	Increased ARI average daily inc/prev	205* (2 COH)	452
	Stebbings and Fogleman et al.[216]	Decreased $FEV_{0.75}$ (children)	700	300

*Converted from BS (British Smoke).

TABLE 14-42   SUMMARY TABLE - CHRONIC EXPOSURE EFFECTS

Type of Study	Reference	Effects observed	Annual average pollutant levels at which effect occurred	
			TSP ($\mu g/m^3$)	SO_2 ($\mu g/m^3$)
Mortality (geog.)	Winkelstein[188]	Increased mortality	125-140	not significant
	Zeidberg and colleagues[16-18]	Increased mortality	55-60	30
Morbidity				
Longitudinal and cross-sectional	Ferris et al.[41 42 46 47]	Higher rate of respiratory symptoms; and decreased lung function	180	55
Cross-sectional (2 areas)	Sawicki (1972)[31]	More chronic bronchitis, asthmatic disease in smokers; reduced FEV%	250*	125
Cross-sectional study of school-children in 4 areas	Lunn et al.[96 97]	Increased frequency of respiratory symptoms; decreased lung function in 5-year olds	260*	190
Follow-up of school-children in 4 areas	Douglas and Waller[90]	Increased lower respiratory tract infection	197* (130 BS)	130
Cross-sectional study of children in 4 areas	Hammer et al.[214]	Increased incidence of lower respiratory diseases	85-110	175-250
Cross-sectional study of high school children in 2 areas	Mostardi and colleagues[177 258]	Lower FVC, $FEV_{0.75}$ and maximal oxygen consumption	77-109	96-100
Cross-sectional (multiple areas)	Lambert and Reid[28]	Increased respiratory symptoms	160* (100 BS)	100-150
Cross-sectional (3 areas)	Goldberg et al.[109]	Increased CRD	78-82	69-160

TABLE 14-42 (continued)

Type of Study	Reference	Effects observed	Annual average pollutant levels at which effect occurred	
			TSP (µg/m³)	SO$_2$ (µg/m³)
Cross-sectional (4 areas)	House et al.[108]	Increased CRD	70 (15SS)	100-150
Cross-sectional and Long (2 areas)	Sawicki and Lawrence (1977)[181]	Increased Prev CB and AS Increased persistance, Males 31-50; Increased incidence, Females, some ages	169+	114-130
Cross-sectional (3 areas)	Rudnick[182]	Increased respiratory symptoms in boys. Increased Rh in girls	221-316* (150-227 BS)	108-148
Cross-sectional and retro-long in 4 areas (children)	Nelson et al.[114]	Increased LRD	70	107
Cross-sectional 2 areas	Hammer[113 257]	Increased LRD	133 (SS=14)	<25
Cross-sectional 3 areas (children)	Shy et al.[215]	Decreased adjusted FEV.$_{75}$ in children > 8 years	78-82	69-160
Cross-sectional 2 areas (children)	Shy et al.[215] Chapman et al.[213]	Decreased adjusted FEV.$_{75}$	96-114 (45 RSP)	(= and low)

*Converted from BS (British Smoke).
**Converted from CoH.

14.6.1.1 Health Effects of Acute Exposure to SO_2 and Particulate Matter

Studies providing evidence of acute health effects of sulfur oxide and particulate matter are summarized in Table 14-41. Overall, various British, Dutch, Japanese and American episodic mortality studies appear to suggest that mortality effects can occur at or above 300-500 $\mu g/m^3$ SO_2. The three non-episodic mortality studies listed in the table suggest that mortality effects can be seen when TSP levels reach 500 to 600 $\mu g/m^3$ and SO_2 concentrations reach 300 to 500 $\mu g/m^3$. These three studies summarize a relatively small body of data from two winters in London and five winters in New York City. The stated effect levels may be conservative, however, since examination of the detailed evidence from these studies presented in Section 14.3 suggests the possibility of an exposure-response relationship at lower levels of these pollutants. More complex time series studies of daily mortality have also found associations between mortality and these pollutants at lower levels. The size of the estimated effects has proved to be sensitive to model specification and choice of other adjustment variables. Although the possibility of mortality effects of TSP and SO_2 levels below those cited in Table 14-41 cannot be excluded, it is unlikely that this question can be resolved in the near future by observational studies. Thus, the minimum air levels at which acute mortality increases might be projected to be seen would be 300-500 $\mu g/m^3$ for both TSP and SO_2, based on the studies summarized in Table 14-41.

Numerous studies reporting morbidity effects associated with acute exposures are also listed in Table 14-41. Worsening of symptoms in bronchitis patients and increased hospital admissions in Britain were reported to occur at TSP and SO_2 levels of 300 or 350 to 500 $\mu g/m^3$ or more. A United States study, however, found exacerbation of symptoms among bronchitics at 200 $\mu g/m^3$ TSP and 100 $\mu g/m^3$ SO_2 and asthmatics were reported to show increased attacks at 150 $\mu g/m^3$

TSP and 200 $\mu g/m^3$ SO_2. Also, spirometry tests were reported to show decreases in lung function at 700 $\mu g/m^3$ TSP and 300 $\mu g/m^3$ SO_2. However, van der Lende saw improvement in lung function among adults when pollution levels were reduced from 245 $\mu g/m^3$ (TSP) and 300 $\mu g/m^3$ (SO_2). Acute upper and/or lower respiratory illness also has been reported to occur at levels as low as at 160 $\mu g/m^3$ TSP (24-hour averages). Overall, then, the summarized studies suggest that (1) very severe morbidity effects, e.g., worsening of symptoms in bronchitic patients, clearly occur at TSP and SO_2 levels of approximately 300 or 350 to 500 $\mu g/m^3$, and (2) less severe but significant morbidity effects may occur with acute exposure at levels of approximately 150-300 $\mu g/m^3$. These studies do not, however, provide a basis for separately estimating the health effects of SO_2 and particulates. Since these two forms of pollution have important common sources, their levels tend to usually vary together over time.

14.6.1.2 Health Effects of Chronic Exposure to SO_2 and Particulate Matter

Mortality and morbidity studies that have been reported as demonstrating associations between mortality, illnesses, or decrements in pulmonary function with annual average levels of particulate matter of SO_2 are summarized in Table 14-42. As seen in that table, the two mortality studies suggest that mortality effects can occur at annual levels of 125 to 140 $\mu g/m^3$ or less of TSP and SO_2. In the morbidity studies, lower respiratory disease, chronic bronchitis, and reduced pulmonary function results were reported that are indicative of morbidity effects likely clearly occurring at annual average TSP or SO_2 levels of 150 to 250 $\mu g/m^3$ or more. Other study results summarized in the table suggest an association of various morbidity effects with concentrations in excess of about 70 to 80 $\mu g/m^3$ TSP and SO_2 concentration in excess of 96 to 107 $\mu g/m^3$. As with studies of acute effects, many of these studies could be

further interpreted not only as demonstrating that health effects are exposure-related but also that they increase as these pollutants increase over the entire range of exposures studied and no clear "no effect" level can be determined on the basis of presently available information. Also, in general, these studies cannot be used to distinguish between the effects of sulfur oxides and particulates. In several studies, however, TSP effects were reported to occur in the presence of low or non-significant levels of SO_2.[188,212,213,215,257]

14.6.1.3 Health Effects of Atmospheric Sulfates

Conversion to sulfate compounds, including sulfuric acid, has been proposed as a major pathway by which sulfur dioxide and possible other sulfur compounds may exert toxic effects. However, only a few community health studies have attempted to measure and assess health effects associated with suspended sulfates (SS). Stebbings and Hays,[190] for example, reported increased symptoms in patients with 24-hour averages of 12 μg/m^3 SS (200 TSP, 60 RSP, 8 SN, 100 SO_2). Also, Chapman et al.[212] reported increased chronic respiratory disease prevalence rates in a high pollution community with an annual average of 15 μg/m^3 SS (70 TSP and 107 SO_2). Hammer[257] further reported increased lower respiratory disease prevalence rates in a high pollution community with an annual average of 14 μg/m^3 SS (133 TSP and SO_2 >17). Thus, suspended sulfate levels of 12 μg/m^3 (daily) or more and 15 μg/m^3 (annually) might be interpreted as being important based on those results.

14.6.1.4 Respirable Particulates Effects

As discussed in Chapter 11, particles below 15 μg/m^3 MMAD are important. Respirable suspended particulates (RSP) ≤3μm, have been measured in only a few American epidemiology studies, e.g., those by Hammer,[113,257] Stebbings and Hays,[190] and Shy and Chapman et al.[213,215] The latter study was reported as

demonstrating decreased adjusted $FEV_{.75}$ in children in an area with higher pollution with RSP of 45 $\mu g/m^3$ (96 to 114 $\mu g/m^3$ TSP and SO_2 very low). Thus RSP of 45+ $\mu g/m^3$ may be important.

14.6.2 METHODOLOGICAL FACTORS IMPACTING INTERPRETATION OF RESULTS

If it were assumed that all of the results summarized in Tables 14-41 and 14-42 were derived from methodologically sound studies and were universally accepted as valid, then the above summary of their results could be accepted as a reasonable representation of the likely atmospheric particulate and sulfur oxides levels found to be associated with mortality and morbidity effects. However, the matter of the methodological soundness and validity of various studies has been a matter of considerable controversy and discussion during the past decade. Such controversy has derived, in large part, from the fact that certain additional risk factors can often be as important as the air pollution variables studied in affecting human health. For example, in earlier discussions (Sections 14.1, 14.3, 14.4), it has been strongly emphasized that smoking is one such factor, as are occupational exposures. Furthermore, age and sex co-variables can also be critical in the evaluation of health effects. Race or ethnic group characteristics likely fall into this catagory as well. In addition, numerous social variables may be highly critical in terms of their existing direct effects on human health, as well as how they may modify the health effects of environmental pollutants. Such social factors include social economic status (income, education, and occupational levels and associated social class status), migration, and household characteristics. Finally, meterological variables such as sudden temperature changes or shifts in humidity levels may also be critical co-variables which, along with air pollutants, might affect health in a deleterious manner. Parental smoking and other

sources of indoor pollutants may also be critical. Other less-well defined
social/ environmental variables, such as a greater degree of crowding
in housing conditions, too, may represent a set of "urban factors" differen-
tially acting to affect health in comparison to "rural" conditions.

Studies of the episodic effect of pollutants reviewed above usually
considered meterological variables and age as important possible co-variables;
but many essentially ignored other variables as being relatively unimportant.
Studies of urban vs. rural differences in health effects, similarly, have
often not attempted to assess the nature of possible contributing factors
other than the relative differences in concentrations of air pollutants; and
some have demonstrated urban-rural differences in health measurements that are
independent of or unrelated to air pollutant concentrations. Only relatively
few have been successful in providing reasonably good analyses of results that
take such possible confounding urban-rural differences into account.

For studies of geographical comparison, investigators generally have
attempted to achieve as much homogeneity among populations in different study
areas as possible. In situations where this is difficult, many have tried to
record measurements of the confounding and co-variables such that they can be
adjusted for in statistical analyses. In these studies, for instance, it is
usually considered satisfactory to either have equal sex ratios and 10-15 year
age groupings, or otherwise, to analyze results by sex and age. Essentially
no one would claim that it is necessary to examine age groups defined by one
or two year age intervals.

In studies of adults, results have either been analyzed by taking
smoking and pollutant levels into account separately, so that one can determine
any additive effects of smoking and air pollution; or study groups that have

very similar smoking habits but different pollutant exposures have been compared. On the other hand, in longitudinal studies, it has been necessary to also measure changes in smoking habits in regard to number of cigarettes, and whether they are low in tar/nicotine. Many longitudinal changes may be associated with changes in smoking habits (Ferris et al.; Fletcher et al.).

Social class, as mentioned before, may affect reports of health outcomes or the actual health outcomes themselves, and this has often been controlled for in one form or another, e.g., either through selection of similar social groups or via statistical analyses techniques. Some geographical studies have ignored social class as well as other factors (e.g., Burn and Pemberton), which makes them difficult to evaluate. Controlling for social class in British terms, however, may in effect also adequately control for occupational differences, although not occupational exposures. Studies elsewhere more often used education or income to control for socioeconomic factors, because such variables are highly correlated with overall socioeconomic status and related factors. For example, smoking and migration are highly correlated with social class in many countries. Social class is also correlated with household characteristics, such as the number in a family, the number of rooms per house, and crowding (number of people per room). Exposure to parental smoking and/or sources of indoor pollution may or may not be critical, as the relevance of those exposures remain to be more clearly established. Ethnic group differences, in some ways similar to social class differences, may also be related to physiologic differences, as in regard to pulmonary functions. It has usually been easier either to exclude all but one ethnic group/race from a given study or to analyze results for them separately (Mostardi et al.; Chapman et al.; Hammer et al.; French et al.; Bouhuys et al.). Failure to do so may have confounded and confused the results derived from certain other studies.

Also, some investigations studied only one sex within a specific occupation group in order to minimize occupational and social class differences (for example, British Ministry of Pensions, Burn and Pemberton, Gervois, Ipsén, Bouhuys et al., Lambert and Reid, Holland et al., Deane et al., Fletcher et al.). This may not always have been sufficient, however, in that urban/rural differences, economic differences, or activity differences may have still existed and affected health. Even so, this approach is generally considered to be an acceptable way to control for occupational and social class differences. Differential specific occupational exposure conditions, however, are almost never considered in such epidemiological studies.

Some studies have focussed on children only, generally including children too young to have started smoking as a means of eliminating this as a possible important confounding factor. Many such pediatric studies also consider parental factors (including social class), as well as race, age, sex, and urban/rural differences. Occasionally, past history of illness was also considered. Studies of children also gain the advantage of being able to better quantitate life-time air pollution exposure histories.

In addition to the above considerations, many studies have recognized that certain factors, such as education (or social class), may affect health endpoint reporting levels, and therefore attempted to control for them. Generally, controlling for or adjusting for any similar (highly correlated) factor across study groups has been considered sufficient to help alleviate or minimize possible differences attributable to reporting artifacts.

Different migration (self-selective residence) patterns, also, may have been important in some studies, especially those of geographical comparisons or of a longitudinal nature (e.g., the Winklestein, Ferris, Petrilli, Hammer et al., French et al., and Neri studies). Migration patterns and self-selection

In regard to evaluating other (less well-designed) studies, it should be noted that some studies exist which indicate that possible confounding variables are not always as important as they were originally thought to be. For example, follow-up studies on an adult cohort previously studied as children by Douglas and Waller did not confirm original social class differences between the groups to be of much significance in accounting for health findings for the groups later in life. Also, Manfreda did not find "urban" characteristics to be relevant in explaining his study results, and other studies have shown that household/familial factors are not necessarily important in all cases in accounting for observed results. Therefore, care must also be taken not to over-emphasize the relative importance of potential confounding or covarying factors not ruled out as possible alternative explanations for the results of a given study. In other words, being overly critical where information is lacking to support the likelihood of a specific confounding factor or co-variable affecting the pattern of results obtained in a study at a particular time represents as much of a disservice in trying to achieve an objective, balanced appraisal of study results under discussion as would any countervailing lack of reasonable regard for the potential importance of such factors.

It must also be recognized that no single study alone, no matter how well-designed or conducted in and of itself completely establishes what comes to be accepted as a "scientific fact" defining either a relationship between two or more variables studied or a lack thereof. Rather, excellence in the design and conduct of a given study, internal consistency and biological plausibility of its results, and their consistency with other known results or information all help to heighten confidence in the likely existence of relationships indicated by that study's results. Even greater certainty is attributed

to the probable existence of such relationships if further independent studies, regardless of particular individual flaws, yield results consistent with such relationships. Thus, consistency in the overall pattern of results indicative of particular relationships or the overall "weight of the evidence" from more than one study are crucial in establishing given relationships as "scientific facts" or in determining the degree of certainty ascribed to them.

14.6.3 Quantitative Dose-Response Relationships Defined by Community Health Studies

In order to elucidate dose-response relationships established by community health epidemiology studies of the type reviewed above, numerous attempts besides the present one have been made to examine both negative and positive information concerning such studies. This has usually been done to determine which are sufficiently sound methodologically to allow for reasonable conclusions to be drawn from them in evaluating the overall meaning of their results individually and collectively. Such attempts include critical reviews and commentaries written by Rall (1974),[245] Higgins et al. (1974),[248] Goldsmith and Friberg (1977),[247] Ferris (1978),[314a] and Waller (1978).[314b] They also include the following evaluative documents appearing in 1978: an American Thoracic Society (ATS) review of Health Effects of Air Pollution (Shy et al., 1978);[251] a National Research Council/National Academy of Science (NRC/NAS) document on Airborne Particles by Higgins and Ferris (1978)[307] and an NRC/NAS document on Sulfur Oxides by Speizer and Ferris (1978)[308] More recent such reviews and commentary appearing in 1979 include: the 1979 World Health Organization (WHO) document, Environmental Health (8): Sulfur Oxides and Suspended Particulate Matter;[312] a report by Holland et al. (1979)[301] written for the American Iron and Steel Institute and appearing in the

American Journal of Epidemiology; and a reply to that report in the same journal by Shy (1979).[313] Some of the more salient points of these reviews and commentaries are concisely highlighted below.

As will quickly become apparent through the course of the discussion below, there are certain studies that many reviews consistently rate as being methodologically sound and their results valid. Also, when those study results are viewed together, collectively, fairly consistent patterns of quantitative relationships emerge regarding exposures to sulfur oxides and particulate matter associated with the occurence of various types of health effects, including (1) mortality and-morbidity effects associated with acute exposures to fairly high ranges of air concentrations of those substances and (2) mor- bidity effects associated with chronic exposures to lower atmospheric levels of the same agents. Given the general concensus that appears to exist regarding the validity of these studies, then, there seems to exist very good support for placing considerable confidence in the overall patterns of quantitative relationships defined by their findings.

In regard to other reasonably well-designed studies, but for which less of a concensus exists regarding their likely validity, several interesting points emerge from the subsequent discussion. First, it becomes apparent that, beyond some small modicum of agreement among the reviews concerning problems associated with certain studies, the various reviews often differ considerably in regard to their assessments of the methodological soundness or validity of any given individual study. This derives mainly from different reviewers emphasizing or citing different possible confounding or covarying factors as potentially being important in affecting the results of a given study -- at least in their respective subjective opinions. Secondly, it is

also notable that very rarely, if ever, have any of the reviewers presented actual data or other information, e.g., new or additional statistical analyses of study results, to support their speculations as to what factors might represent reasonable alternative explanations, besides the air pollution variables studied, for the observed study results. Lastly, despite whatever real or imagined flaws might be associated with the particular individual studies, a surprisingly great degree of consistency exists both between most of their results and, also, in comparison with the findings of the other studies alluded to above as being widely recognized as being valid. In some cases, however, the results of some of the supposedly "flawed" studies point toward still lower levels of sulfur oxides and particulate matter being associated with significant mortality or morbidity effects. Thus, whereas not as much confidence can yet be placed in such findings as those from the more universally accepted studies, it is still not appropriate scientifically to completely disregard or ignore them. This is especially true in view of the fact that, all too often, relationships indicated to exist by "suggestive" evidence derived from numerous "flawed" studies are later confirmed by more carefully designed and conducted "definitive" studies.

14.6.3.1 <u>Review Articles and Commentary (1974-1978)</u>--Turning to discussion of the different reviews and commentaries listed above, Rall published a review in 1974 on the health effects of sulfur oxides and particulate matter that examined the then existing scientific information. Rall's 1974 summary of studies showing pertinent dose-effects relationships is presented in Table 14-43. In addition, Rall drew attention to the then current WHO evaluation shown in Table 14-44. In summarizing his evaluation, Rall[245] stated that

TABLE 14-43. SUMMARY OF DOSE-RESPONSE RELATIONSHIPS FOR EFFECTS OF PARTICLES AND SO_2 AND HEALTH*

Averaging time for pollution measurements	Place	Particles, $\mu g/m^3$	SO_2 $\mu g/m^3$	Effect
24 hr	London	2000	1144	Mortality
24 hr	London	750	700	Mortality
24 hr	London	300	600	Deterioration of patients
Weekly mean	London	200	400	Prevalence or incidence of respiratory illnesses
24 hr	New York	6[b]	1500	Mortality
Winter mean	Britain	100-200	100-200	Incapacity for work from bronchitis
Annual	Britain	70	90	Lower respiratory infections in children
	Britain	100	100	Upper and lower respiratory infections in children
	Britain	100	100	Bronchities prevalence
	Britain	100[a]	100	Prevalence of symptoms
	Buffalo	100[a]	300[c]	Respiratory mortality
	Berlin, N.H.	180	731[c]	Increased respiratory symptoms Decreased pulmonary function

[a]"Old" results, leading to original standards.

[b]In coefficient of haze units (COHS).

[c]As μg $SO_2/100$ cm^2/day.

*From Rall (1974)[245]

TABLE 14-44. EXPECTED HEALTH EFFECTS OF AIR POLLUTION
ON SELECTED POPULATION*

Effect	Pollutant	
Excess mortality and hospital admissions (24 hr mean)	500	500
Worsening of patients with pulmonary disease (24 hr mean)	250	500-250
Respiratory symptoms (annual arithmetic mean)	100	100
Visibility and/or annoyance (annual geometric mean)	80	80
World Health Organization (WHO) data		

*From Rall (1974)[245]

Disease and death seldom, if ever, result from pollution alone. They are the outcome of many factors, both individual and environmental, acting together. Acute episodes of high air pollution have clearly resulted in mortality and morbidity. In addition to these acute episodes, pollutants can attain daily levels which have been shown to have serious consequences to city dwellers. There is a large and increasing body of evidence that significant health effects are produced by long-term exposures to air pollutants. It is not possible to state a concentration below which such health effects will not occur.

Rall (1974)[245] elaborated further on the above points in his review, as follows:

Health effects may range from discomfort through physiological deviations from the norm, prevalence of symptoms, appearance of illness, lost working time, and premature retirement to complete incapacity and death. In practice, it is better to consider these indices in the reverse order, starting with death, serious illness, and significant disability, about which there can be little argument, and to proceed thence to physiological deviations and minor disorders, the significance of which may be open to question. Disease and death seldom, if ever, result from pollution alone. They are the outcome of many factors, both individual and environmental, acting together. Any epidemiological study of the effects of air pollution must allow adequately for these other factors. Indeed, the quality of such studies often depends on the success with which such allowance has been achieved. At the other end of the range of health effects, the implication of minor symptoms and small deviations from some physiological or biochemical norm between persons living in polluted and nonpolluted neighborhoods may be imperfectly known. Until it can be shown that such effects predispose to disease, disability, or reduced expectation of life, the weight that should be given to them in setting standards will remain a matter for personal judgment.

Acute episodes of high pollution have clearly resulted in mortality and morbidity. Often the effects of high pollutant concentrations in these episodes have been combined with other environmental features such as low temperatures or epidemic diseases (influenza) which many in themselves have serious or fatal consequences. This has sometimes made it difficult to determine to what extent pollution and temperature extremes are responsible for the effects. Nevertheless, there is now no longer any doubt that high levels of pollution sustained for periods of days can kill. Those aged 45 and over with chronic diseases, particularly of the lungs or heart, seem to be predominantly affected.

In addition to these acute episodes, pollutants can attain daily levels which have been shown to have serious consequences to city dwellers. For many years in London, daily deaths and illnesses were clearly related to daily levels of smoke and SO_2. Comparable observations have been made in New York City, Philadelphia, and Chicago. In the New York - New Jersey Metropolitan area, an analysis of daily mortality for the years 1962-66 showed that deaths were 1.5% below expectation at the lowest SO_2 concentrations and 2% above expectation at concentrations of 500 μg/m^3 and above. A similar though weaker relationship was found in Philadelphia but not in Chicago.

The implication of daily levels of SO_2 and particulates has been studied in particularly vulnerable groups, such as patients with chronic bronchitis and emphysema. Deterioration in their respiratory well being has resulted from a daily concentration of SO_2 of about 500 μg/m^3 which is not much above the 24-hr primary standard. A few studies have even suggested that deterioration in particularly vulnerable groups may occur with daily concentrations which are below this standard. Confirmation of this is urgently needed."

In reference to chronic exposure effects Rall (1974)[245] concluded:

There is a large and increasing body of evidence that significant health effects are produced by long-term exposures to air pollutants. Acute respiratory infections in children, chronic respiratory diseases in adults, and decreased levels of ventilatory lung function in both children and adults have been found to be related to concentrations of SO_2 and particulates, after apparently sufficient allowance has been made for such confounding variable as smoking and socioeconomic circumstances.

It is not possible to state a concentration below which such health effects will not occur. In many studies the proportion of persons affected increases from the lowest to highest categories of pollution. Had even lower categories of pollution been used in the analyses, even lower critical levels might have been suggested.

Thus, as in the case of daily mortality, the concept of no-effect level may be a chimera. A reasonable conclusion from these studies would however be that health effects have been found when annual levels of particulates or SO_2 exceed 100 μg/m^3.

The essential points of these conclusions stated by Rall in 1974 have been consistently echoed in virtually all of the other major reviews appearing throughout the remainder of the decade, with few notable exceptions (e.g., the "Holland Report"[301]) discussed later. Also, a fairly high degree of consistency

or consensus among the reviewers can be seen as to what their published opinions indicate to be reasonable quantitative estimates of sulfur oxides and particulate matter air concentrations associated with the occurrence of human mortality or morbidity effects, this overall consistency emerging despite differences in opinion regarding the strengths or weaknesses of any given individual studies.

For example, in another 1974 review, by Higgins,[248] there was provided a dose response table as presented below (Table 14-45). In the conclusion of that report, Higgins states, "Although these are rather inadequate data, it would perhaps be reasonable to conclude that average annual levels of particulates and SO_2 should both be under 100 $\mu g/m^3$. It should further be noted that, although not necessarily crucially used in arriving at that conclusion or listed in Table 14-45, several additional studies were considered by Higgins to be positive as well: that is, the McCarroll et al., Cassell et al., and Lebowitz et al. studies; several of Lawther's studies; the Speicer studies, the Shephard studies, and the Becker study. Higgins also pointed out the relevance of the Ciocco and Thompson follow-up study, which indicated the major influence of episodic conditions on the elderly and infirmed. Higgins (1974)[248] went on in his review, however, to speculate that the Fletcher et al. and Angel et al. studies, showing decreases in signs and symptoms potentially associated with decreases in air pollution, might be more related to decreases in tar in British cigarettes (if so, this would presumably also affect many later studies in Great Britain, including the Waller et al. and Lawther et al. studies, the Emerson study, etc.). The influence of ethnic differences, he suggested, might have affected results from certain other studies such as those by Ferris and Anderson; and usual inter-city differences were suggested

TABLE 14-45.   PARTICULATE AND SULFUR DIOXIDE LEVELS AND EFFECTS ON HEALTH*

Averaging time for pollution measurements	Place	Particulates		SO$_2$ levels		Effect	Reference
		µg/m^3	cohs	µg/m^3	mg/100 cm^2-30 days		
24 hours	London	2000		1000		Mortality	Scott, (1959)[332] Gore and Shaddick (1958)[8] Burgress and Shaddick (1959)[9]
		1000		500		Mortality	Martin (1964)[6]
		250		500		Exacerbations of bronchitis	Waller et al. (1969)[7]
		200		250		Increased absence from work	Angel et al. (1965)[69]
	New York		6	1500		Mortality	McCarrol and Bradley (1966)[331]
	Chicago	Not specified		700		Exacerbations of bronchitis	Carnow et al. (1968)[174]
Winter	Britain	200		200		Correlation of pollutants with bronchitis incidence	Ministry of Pensions and National Insurance (1965)[62]
Annual	Britain	70		90		Lower respiratory infections in children	Douglas and Waller (1966)[90]
	Britain	100		100		Bronchitis prevalence	Lambert and Reid (1970)[28]
	Buffalo	100		--	0.30	Respiratory mortality	Winkelstein et al. (1967 and 1968)[333,188]

*Adapted from Higgins (1974)[248] review.

as perhaps influencing certain studies such as those by Prindle. The lack of both smoking and social status analyses were also noted as potentially affecting interpretation of still other studies, such as the one by Burn and Pemberton.

Higgins[248] also cited the Winklestein and Kantor results on smoking for White females in areas of Buffalo previously studied by Winkelstein in collecting data for evaluating air pollution - mortality relationships; the later smoking data appeared to ameliorate criticism regarding the lack of smoking information in the earlier Winklestein studies. Higgins went on to discuss studies showing positive associations with air pollution after occupation was controlled for; such as: Fairbairn and Reid, Cornwall and Raffle, Holland et al., Deane et al., Holland and Reid. Other studies, Holland et al., Colley and Holland, Colley and Reid, in which smoking, residence, family size, past history of illness, and occupation were controlled, were also discussed in terms of the relevance of these factors in producing chronic lung diseases and SO_x/TSP health effects. Certain other studies by Toyama, Watanabe, and Lunn were noted as showing that declines in disease symptoms or improvements in lung function might be related to declines in air pollution. Some difficulties were noted, however, as complicating the determination of precise levels of SO_x or particulate matter assoicated with the various changes observed.

The Goldsmith and Friberg (1977) review,[247] although not summarizing specific estimates of dose-response relationships, did emphasize the positive findings of certain critical studies deemed to be adequate scientifically, as part of an overall review of health effects of air pollution in a book chapter. Where appropriate, pollutant levels were indicated. For example, in evaluating Lawther's[53] studies, Goldsmith and Friberg (1977) stated:

When two winters (1959-60 and 1964-65) were compared in terms of the association of exacerbations with SO_2, the general impression was of slightly reduced and less consistent effect during the latter period. The mean BS concentrations had then decreased from a mean of 342 $\mu g/m^3$...to 129... while SO_2 had decreased only from 296 to 264 $\mu g/m^3$.

They also further stated in their 1977 review that:

> ... even during the winter period of 1967-68, when the daily data were treated statistically, a significant correlation (5% level) was found with both smoke and SO_2, with mean BS concentrations of only 68 $\mu g/m^3$ (sd=48) and 204 $\mu g/m^3$ (sd=100) of SO_2." (Note that the BS level of 68 $\mu g/m^3$ would be approximately equivalent of 130-140 $\mu g/m^3$ TSP.)

Certain studies were also considered by Goldsmith and Friberg (1977) to be "representative" of the effects of the SO_x/TPS pollutant complexes on emplysema, chronic bronchitis, and asthma, including the following: the studies of the Royal College of General Practitioners, Buck and Brown, Toyama; Nose; Takahashi; Yoshida; Comstock; Deane: Holland; Deane; Carnow; Spizer; McCarroll et al.; Cassell et al.; Lebowitz et al.; Winklestein; and Ishikawa. Representative studies of the effects of SO_x/TSP on asthma were: the studies of Tokyo, Yokohama asthma, Zeidberg et al., Sim and Pattle, Peranio, and several EPA studies. Additional studies thought to be worthwhile and pertinent were those of Martin, Schimmel, Buechley, Lawther et al., Goldsmith, Fletcher, Holland, Douglas and Waller, Lunn, Holland et al., Colley and Reid, Zaplatel.

A more recent (1978) review by Ferris[314a] provides both a dose-response table (14-46) and summary statements about his evaluation of the health effects of exposure to levels of sulfur oxides and particulate matter. He states:

TABLE 14-46. SUMMARY OF EFFECTS OF SULFUR DIOXIDE AND PARTICULATES
ON HUMAN HEALTH - LONG TERM EFFECTS*

SO_2 $\mu g/m^3$	(ppm)	Suspended particulates $\mu g/m^3$	Effects	Reference
250	(0.095)	250[a]	Increased phlegm production	274
130	(0.05)	240[a]	Increased respiratory disease	181
120	(0.046)	180[a]	Increased respiratory illness and decreased pulmonary function	96,97
120	(0.046)	230[a]	Increased lower respiratory illness	90
98	(0.037)[b]	93	Decreased FVC, $FEV_{0.75}$[c]	177,258
23	(0.009)	110	Decreased $FEV_{0.75}$[c]	212
425-50	(0.162.-0.019)	195-85	Increased lower respiratory disease morbidity[c]	214
55	(0.021)[b]	180	Increased respiratory symptoms, decreased pulmonary function	43
37	(0.014)[b]	131	No effect	43
66	(0.025)[b]	80	No effect	46

[a]Corrected from original data to TSP equivalents.[89]

[b]SO_2 equivalent calculated from lead peroxide data.

[c]See text for discussion of results.

*Adapted from Ferris (1978)[314a]

There is not much information with respect to the short term effects. A study by Cohen et al. on asthmatics indicates an effect at a level below present 24 hour standards for SO_2 and particulates; van der Lende noted small reversible changes in pulmonary function. The other study where effects have been noted is either above or close to the present standard, one showed no effect at levels considerably above the standards. More information is available on the long term effects, and it appears that the present annual averages for SO_2 and particulates are reasonable. More information is still needed with respect to an effect, if any, of higher SO_2 levels associated with low levels of particulates. Information should also be obtained to develop the standard for fine particles, and in due course to try to make a better chemical characterization of the fine and coarse particles. The health effects of a considerable fluctuation above a mean also need a evaluation.

For the sake of clarity, it should be noted that the 24-hr standards referred to by Ferris[314a] for SO_2 and particulates are 365 and 260 μg/m^3, repectively; the present annual average standards for SO_2 and particulates referred to, respectively are: 80 μg/m^3 and 75 μg/m^3 (annual geometric mean).

Ferris [314a] also opined that his studies[43] may demonstrate certain levels at which no effects appear to occur. In addition, the Emerson[46] study was noted as possibly yielding information on "no effects" levels. Despite minor criticisms, the Chapman et al. study and the Mostardi et al. studies were also considered sufficiently satisfactory to include in the dose-response summary of the review.[314a] However, the van der Lende et al. studies, the Cohen et al. study and the Lawther study were apparently not considered sufficiently adequate to include in the table, whereas the studies of Goldstein and Block, Dohan et al. (Ipsen et al.) were considered to be inadequate.

In the same 1978 issue of JAPCA containing the above Ferris review[314a] Waller[314b] discussed the Ferris review. There, Waller commented on the Lawther 1970 report, and also stated that British smoke is not more important than total suspended particulates. He, too, felt that the Cohen study was weak in some respects and that the Emerson study was weak, but not a study demonstrating

"negative" findings or a "no-effect" level. He pointed out other results published by van der Lende in 1975, which confirmed a later decline in function with age. In regard to the Ferris et al. 1973 follow-up study, Waller opined that the air pollution measurements were often sporadic and inappropriate and that there may have been a change in smoking habits vis-a-vis filters and/or low tar/nicotine cigarettes. In addition, Waller apparently generally felt that many of the other studies that Ferris utilized in arriving at his dose-response estimates were not necessarily appropriate or adequate.

14.6.3.2 <u>Major Evaluative Documents (1978)</u>--In regard to the series of major evaluative documents appearing in 1978, the ATS document by Shy et al.[251] pointed out several studies considered to be critical in establishing associations between air pollution and health effects. Besides many of the above-mentioned studies alluded to by Rall[295], Higgins[248] and Ferris,[314a] the Toyama and Watanabe studies, which showed an increase in peak expoloratory flow rate with declining air pollution, were noted in the ATS report as being pertinent and important. The relevance of the WHO conclusions regarding SO_2 any particulate health effects (see below) was also noted and endorsed in the ATS document.

In another 1978 document, the NRC/NAS review on <u>Airborne Particles</u>[307] prepared by a study group chaired by Ian Higgins, Higgins and Ferris formulated a dose-response table (14-47), utilizing those studies they felt to be adequate and critical. Studies by Schimmel and by Emerson were considered indicative of negative levels. Also, changes in funciton from an early study of Lunn's to a later one were used by Higgins and Ferris to estimate SO_2 and particulate levels below which they thought health effects were not occurring. Certain positive studies, such as those of Shephard's, although not discounted, were not utilized in the Higgins and Ferris[307] dose-response table.

TABLE 14-47. NRC/NATIONAL ACADEMY OF SCIENCES*
HEALTH EFFECTS AND DOSE/RESPONSE RELATIONSHIPS FOR PARTICULATES AND SULFUR DIOXIDE

Averaging time for pollution measurements	Place	Particles, mg/m^3	SO$_2$ mg/m^3	Effect	References
24 hour	London	2.00	1.04	Mortality	(Gore et al.[8])[9]
		0.75	0.71	Mortality	Burgess et al.[9]
		0.50	0.50(4)d	Exacerbation of bronchitis	Lawther[13] Lawther et al.[53]
	New York City	6 COHS[a] (5)[d]	0.50	Mortality	Greenberg et al.[151]
		3 COHS	0.70	Morbidity	Greenberg et al.[196]
	Chicago	Not Stated	0.70	Exacerbations of bronchitis	Carnow et al.[174]
	New York City	0.145 (+?)	0.286	Increased prevalence of respiratory symptoms	Chapman et al.[212] (Hammer et al.[214])
	Birmingham	0.18-0.22	0.026	Increase prevalence of respiratory symptoms	Hammer et al.[257]
	New York City	2.5 COHS	0.52	Mortality	Glasser[222]
Weekly Mean	London	0.20	0.40	Increased prevalence or incidence of respiratory illnesses	Angel et al.[69] (Fletcher et al.[274])
6 Winter Months	Britain	0.20 (>.1)[d]	0.20 (>.1)[d]	Bronchitis sickness absence from work	Min. Pensions[62]
Annual	Britain	0.07	0.09	Lower respiratory infection in children	Douglas and Waller[90]
		0.10	0.10	Bronchitis prevalence	Lambert and Reid[28]
		0.10	0.12	Respiratory symptoms and lung function in children	Lunn et al.[96,97]
	Buffalo	0.08	0.45[b]	Mortality	Winklestein et al.[21,188]
	Berlin	0.18	0.73[c]	Decreased lung function	Ferris et al.[43]

* Adapted from NRC/NAS Airborne Particles Report.[307]
a Coefficient of Haze Units.
b mg SO$_3$/cm^2/30 days.
c mg SO$_3$/100 cm^2/day.
d as stated in text

In summarizing the dose-responses relationships defined by the findings included in their dose-response table (14-47), Higgins and Ferris stated that the table:

> provides estimated concentrations of particulates and sulfur dioxide that may affect health. To reiterate, these two pollutants may not be the most important. They serve only as indices of other, perhaps more important, pollutants. In London, mortality has clearly resulted when 24-hr smoke concentrations have exceeded 1.0 mg/m^3 and sulfur dioxide concentrations have reached 0.750 mg/m^3 (0.288 ppm). These peaks used to occur in London during average annual background concentrations of 0.3 to 0.4 mg/m^3 of smoke and 0.25 to 0.30 mg/m^3 (0.1-0.12 ppm) sulfur dioxide. Such concentrations are now fortunately only of historical interest. They should certainly not be tolerated.
> In London, 24-hr concentrations of ~0.5 mg/m^3 of smoke and 0.4 mg/m^3 (0.15 ppm) of sulfur dioxide exacerbated bronchitis. With the present lower concentrations, such exacerbations are infrequent. Some correlation still existed when the average annual concentration of smoke was 0.06 mg/m^3 and of sulfur dioxide was 1.70 mg/m^3 (0.654 ppm). Since then, pollution has declined further in London but it is not clear if exacerbations still occur with increases in pollution.
> In Britain, sick leave attributed to bronchitis appeared to correlate linearly with winter smoke and sulfur dioxide concentrations over 0.1 mg/m^3 (0.038 ppm). It would be very interesting to know if similar correlations can still be demonstrated at the present lower pollutant concentrations.

It should be clarified that the above noted levels of 0.06 mg/m^3 and 0.1 mg/m^3 for smoke concentrations would be approximately equivalent to 120 and 200 $\mu g/m^3$ TSP.

Turning to findings for American cities, Higgins and Ferris noted that:

> In New York City, 24-hr coefficient of haze units (CoHs) of 5 or more and sulfur dioxide of 2.0 mg/m^3 (0.769 ppm) have resulted in deaths; 3 CoHs and 0.7 mg/m^3 (0.269 ppm) sulfur dioxide have caused illness. Studies of daily mortality in relation to pollution suggest that excess deaths may occur when sulfur dioxide is as low as 0.35 mg/m^3 (0.013 ppm). In Chicago, exacerbations of bronchitis were associated with daily sulfur dioxide concentrations of 0.75 mg/m^3 (0.288 ppm), probably in the presence of high concentrations of particulates.*
> In Buffalo, mortality from respiratory illness appeared to increase progressively from the lowest to the highest pollutant concentrations. The lowest level of smoke was <0.08 mg/m^3 and of sulfation, 0.045 $mg/cm^2/day$. A number of other British studies suggest that average annual concentrations of particulates and sulfur dioxide should both be held to under 0.100 mg/m^3.

In final summary, Higgins and Ferris[307] stated:

>   There is good evidence that exceptional episodes of pollution
> (>1.0 mg/m^3 [0.385 ppm] sulfur dioxide and particulates) caused
> illness and death. There is also a good deal of evidence that
> sustained lower levels of pollution >0.1 mg/m^3 (0.039 ppm) of sulfur   **
> dioxide and particulates for a number of years affect health adversely.
> Pollution predominantly affects those who are already suffering from
> disease, particularly of the heart or lungs; however, evidence,
> especially from studies of children, suggests that pollution can
> initiate disease as well as exacerbate it. Particulate pollution,
> especially from sulfur compounds, probably plays a considerable role
> in the development and progression of bronchitis and emphysema.
> There have also been suggestions that it plays a role in lung cancer;
> however, this is much more debatable.

In another 1978 NRC/NAS report, on Sulfur Oxides,[308] Speizer and Ferris

(308) developed graphs (figures 14-5 A and B) to depict estimates of dose

reponse relationships. In the process, they had to accept certain studies,

despite their minor limitations. On the other hand, certain studies were

excluded in the judgment of the authors because of questions raised about the

adequacy of those studies. Thus, the studies by Greenburg et al., Goldstein

and Block, and Chiaromonte on acute effects in asthmatics have been deemed

unacceptable. The works of Buechley and of Schimmel were utilized to demonstrate

negative short-term effects below 300 μg/m^3. Martin's study of short term

mortality, showing mortality effects at 277 μg/m^3 SO$_2$ and 417 μg/m^3 BS and

morbidity effects at 340 and 515 μg/m^3, respectively, of SO$_2$ and British

smoke, although discussed as valid, were not included in the plotting of acute

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*Particulate levels expressed as 3 or 5 CoHs units are approximately equivalent
to 350 or 550 µg/m^3 TSP, respectively.
**TSP and SO$_2$ levels of 0.100 mg/m^3 = 100 µg/m^3
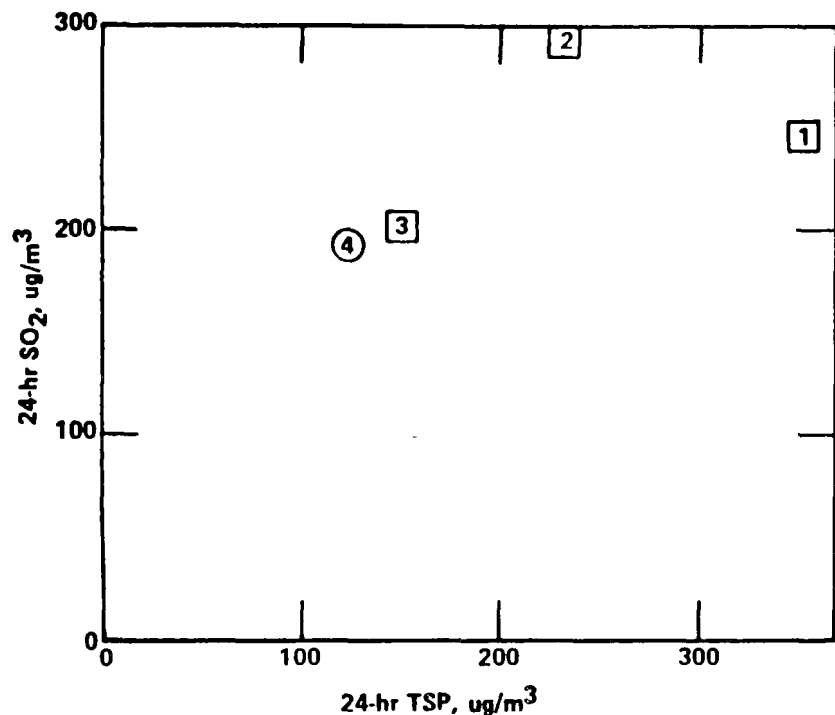
FIGURE 14-5 A. Acute dose-response relationships from selected studies.*

1. Lawther et al.[53]
2. van de Lende et al.[74]
3. Cohen et al.[36]
4. Emerson[37]

*Speizer, Ferris, et al.; NRC/NAS[308]
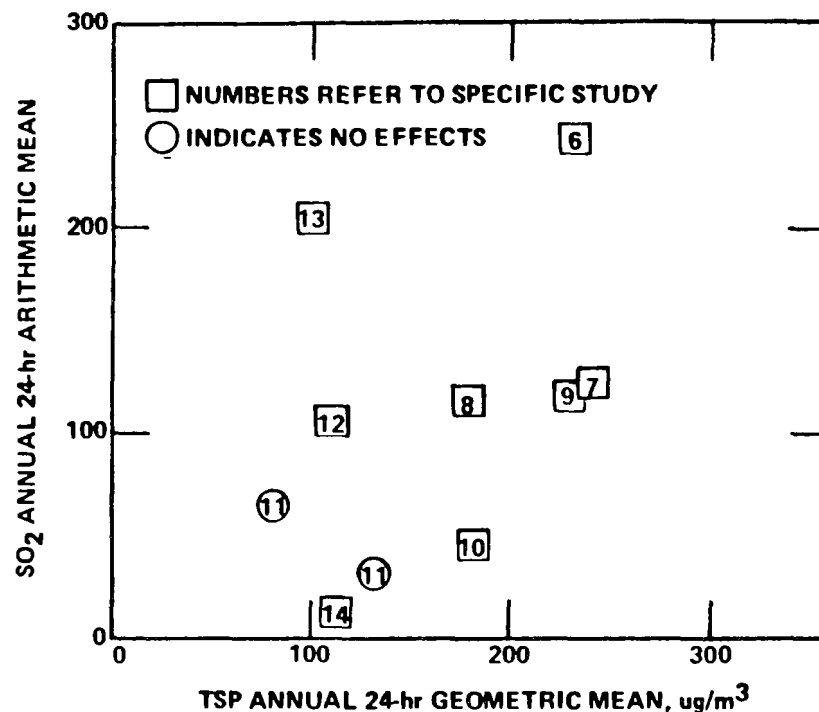
FIGURE 14-5 B. Chronic dose-response relationships from selected studies.*

6. Fletcher et al.[274]
7. Sawicki and Lawrence[181]
8. Lunn et al.[96,97]
9. Douglas and Waller[90]
10. Ferris et al.[43]
11. Ferris et al.[46]
12. Mostardi and Martell[258]
13. Hammer et al.[214]
14. Chapman et al.[212]

dose-response estimates shown in Figure 14-5A. The work of Stebbings et al. in the Pittsburgh episode was excluded because of a lack of prior baseline information. Overall, Speizer and Ferris[308] concluded that short term exposure effects occur above 300 micrograms/cubic meter of both SO_2 and TSP, although the data used by them to plot dose-response relationships likely demonstrate some effects at 200 - 230 $\mu g/m^3$.

In terms of chronic effects, Speizer and Ferris[308] excluded the work of Mostardi and Leonard because of small sample size and lack of sufficient smoking information, even though a later study of a similar group showed that smoking was not a significant factor. (Mostardi's study showed effects at levels of SO_2 96-100 $\mu g/m^3$ and levels of TSP of 77-109 $\mu g/m^3$). Overall, it was concluded,[308] for chronic exposures, that annual mean 24-hour exposures somewhat above the current SO_2 primary standard (75 $\mu g/m^3$) are associated with increased morbidity.

In regard to possible effects of suspended sulfates, results of studies by Winklestein did not appear to be sufficiently clearly presented to allow conclusions to be drawn. Also, other studies from the EPA CHESS Program were not considered, e.g. Chapman et al., and Hammer et al.. Thus, Speizer and Ferris[308] did not feel that they could draw meaningful conclusions about the effects of suspended sulfates.

The World Health Organization in 1979 published a report on Environmental Health Criteria for Sulfur Dioxides and Suspended Particulate Matter. They formulated dose response relations for short term exposures (Table 14-48), for long term exposures (Table 14-49), and have published tables on the expected effects of air pollutants on health in selected segments of the population in terms of both short term exposures and long term exposures (Tables 14-50 and 14-51). The tables themselves provide indication of the studies that the

TABLE 14-48.   EXPOSURE-EFFECT RELATIONSHIPS OF SULFUR DIOXIDE, SMOKE; AND TOTAL
SUSPENDED PARTICULATES: EFFECTS OF SHORT-TERM EXPOSURES*

Concentration 24-h mean values ($\mu g/m^3$)			
Sulfur dioxide	Smoke	Total suspended particulates	Effects
>1000	>1000	-	London, 1952. Very large increase in mortality to about 3 times normal, during 5-day fog. Pollution figures represent means for whole area: maximum (central site) sulfur dioxide 3700 $\mu g/m^3$, smoke 4500 $\mu g/m^3$ (Ministry of Health, UK, 1954)
710	750	-	London, 1958-59. Increases in daily mortality up to about 1.25 times expected value (Lawther, 1963; Martin & Bradley, 1960).
500	500	-	London, 1958-60. Increases in daily mortality (as above) and increases in hospital admissions, becoming evident when pollution levels shown were exceeded (magnitude increasing steadily with pollution) (Martin, 1964).
500	-	-	New York 1962-66. Mortality correlated with pollution: 2% excess at level shown (Buechley, 1973).
500	250	-	London, 1954-68. Increases in illness score by diary technique among bronchitic patients seen above pollution levels shown (means for whole area) (Lawther et al., 1970).
300	140	-	Vlaardingen, Netherlands, 1969-72. Temporary decrease in ventilatory function (Van der Lende et al., 1975).
200[a]	-	150[b]	Cumberland, WV, USA. Increased asthma attack rate among small group of patients, when pollution levels shown were exceeded (Cohen et al., 1972).

*From WHO 1979 Criteria Document for Sulfur Oxides and Particulate Matter.[312]

[a]West-Gaeke method.

[b]High volume sampling method.

Other measurements by Organization for Economic Cooperation and Development or British daily smoke/sulfur dioxide methods (Ministry of Technology, UK, 1966)

Organization for Economic Cooperation and Development, 1965).

TABLE 14-49. EXPOSURE-EFFECT RELATIONSHIPS OF SULFUR DIOXIDE, SMOKE, AND TOTAL SUSPENDED PARTICULATES: EFFECTS OF LONG-TERM EXPOSURES*

Concentration 24-h mean values ($\mu g/m^3$)		Total suspended particulates	Effects
Sulfur dioxide	Smoke		
200	200	-	Sheffield, England. Increased respiratory illnesses in children (Lunn et al., 1967, 1970)
-	-	180[b]	Berlin, NH, USA. Increased respiratory symptoms, decreased respiratory function in adults (Ferris et al., 1973)
150	-	-	England & Wales. Increased respiratory symptoms in children (Colley & Reid, 1970).
125	170	-	Cracow, Poland. Increased respiratory symptoms in adults (Sawicki, 1972).
140[d]	140[d]	-	Great Britain. Increased lower respiratory tract illnesses in children (Douglas & Waller, 1966).
60-140[a]	-	100-200[c]	Tokyo. Increased respiratory symptoms in adults (Suzuki & Hitosugi, unpublished data, 1970).

*From WHO 1979 Criteria Document for Sulfur Oxides and Particulate Matter.[312]

[a]Automatic conductimetric method.

[b]High volume sampler (2-month mean, possible underestimation of annual mean).

[c]Light-scattering method, results not directly comparable with others.

[d]Estimates based on observations after end of study; probable underestimation of exposures in early years of study.

Other measurements by Organization for Economic Cooperation and Development or British daily smoke/sulfur dioxide methods (Ministry of Technology, UK, 1966; Organization for Economic Cooperation and Development, 1965).

TABLE 14-50. EXPECTED EFFECTS OF AIR POLLUTANTS ON HEALTH IN SELECTED
SEGMENTS OF THE POPULATION: EFFECTS OF SHORT-TERM EXPOSURES[a]*

Expected effects	24-h mean concentration ($\mu g/m^3$)	
	Sulfur dioxide	Smoke
Excess mortality among the elderly or the chronically sick	500	500
Worsening of the condition of patients with existing respiratory disease	250	250

[a]Concentrations of sulfur dioxide and smoke as measured by OECD or British
daily smoke/sulfur dioxide method (Ministry of Technology, UK, 1966;
Organization for Economic Cooperation and Development, 1965). These
values may have to be adjusted in terms of measurements made by other
procedures.
*From WHO 1979 Criteria Document for Sulfur Oxides and Particulate Matter.[312]

TABLE 14-51. EXPECTED EFFECTS OF AIR POLLUTANTS ON HEALTH IN SELECTED
SEGMENTS OF THE POPULATION: EFFECTS OF LONG-TERM EXPOSURES[a]*

Expected effects	Annual mean concentration ($\mu g/m^3$)	
	Sulfur dioxide	Smoke
Increased respiratory symptoms among samples of the general population (adults and children) and increased frequencies of respiratory illnesses among children	100	100

[a]Concentrations of sulfur dioxide and smoke as measured by OECD or British daily smoke/sulfur dioxide method (Ministry of Technology, UK, 1966; Organization for Economic Cooperation and Development, 1965). These values may have to be adjusted in terms of measurements made by other procedures.
*From WHO 1979 Criteria Document for Sulfur Oxides and Particulate Matter.[312]

TABLE 14-52. GUIDELINES FOR EXPOSURE LIMITS CONSISTENT
WITH THE PROTECTION OF PUBLIC HEALTH[a],*

Expected effects	Concentration ($\mu g/m^3$)	
	Sulfur dioxide	Smoke
24-h mean	100-150	100-150
Annual arithmetic mean	40-60	40-60

[a]Values for sulfur dioxide and smoke as measured by OECD or British daily
smoke/sulfur dioxide method (Ministry of Technology, UK, 1966; Organization
for Economic Cooperation and Development, 1965). Adjustments may be necessary
where measurements are made by other methods. For example, smoke concentrations
of 100-150 $\mu g/m^3$ convert to approximately 200-300 $\mu g/m^3$ TSP and smoke levels
of 40-60 $\mu g/m^3$ convert to approximately 80-120 $\mu g/m^3$ TSP.
*From WHO[312]

the WHO felt were relevant in these dose response determinations. In addition, the guidelines arrived at by the WHO[312] for protection of public health are shown in Figure 14-52.

The WHO[312] report also comments on several additional studies which they felt were positive; the study published by Watanabe in 1966, show that 20% increase in mortality at 200 $\mu g/m^3$ SO_2 and 1000 $\mu g/m^3$ of TSP (24 hours). The Yoshida study showed effects with weekly SO_2 above 140 $\mu g/m^3$ (no TSP or BS). A study by Toyama et al. published in 1966 shows prevalence of respiratory symptoms in males (ages 40 to 59) adjusted for age and smoking in areas with SO_2 concentrations of less than 30 $\mu g/m^3$ and TSP less than 106-341 $\mu g/m^3$. Tani (1975) reported a study around a pulp mill (compared to a controlled area) which showed a consistent increase with prevalence of bronchitis with sulfation rates of 1.2gm/100cm^2 per day (approximately 48-96 $\mu g/m^3$ SO_2). In their report, WHO points out that they think that the Cohen et al. study of asthma was positive. They also commented that the Lambert and Reid study did control for social status as well as smoking, such that one can assume that there were not likely to be further confounding factors in that study. In regard to the Ferris study in 1962, the report questions the air pollution measures and indicates they were also limited to SO_2 reading in the 1973 survey. The WHO report also questions the health index used by Lawther et al. in their series of studies extending from 1954 to 1968. In regard to the Waller report of 1971, they felt that discrimination between effects of pollution and those of adverse weather was poor. The WHO report[312] presented further information on sensory and reflex function resulting from short-term exposures to H_2SO_4, and SO_2 and exposures of H_2SO_4 and SO_2 combined. The review indicates that a physiological response occurs at short-term H_2SO_4 concentrations of

from 400 to 730 $\mu g/m^3$ and short-term SO_2 concentration of from 600 to 2800 $\mu g/m^3$. When concentrations of H_2SO_4 and SO_2 are combined, however, the same effects occur for H_2SO_4 at concentrations ranging from 150 to 600 $\mu g/m^3$ and SO_2 at concentrations ranging from 250 to 1200 $\mu g/m^3$.

Other recent evaluations of dose-response relationships in a review by Ware et al.[304] are summarized in Tables 14-53 and 14-54. Many of the same studies accepted by WHO and others in earlier reviews are taken by Ware et al. (1980) to be valid and to demonstrate health effects of the levels listed in the two tables. Certain other findings were also thought to indicate a possible lack of effect at the levels studies, including specifically Emerson's, possibly Ipsen's, and possibly Schimmel's results. Ware et al.[304] also discussed Bennett's interpretation of the Waller and the Lawther data concerning the decline of symptoms in bronchitis with declining air pollution, without however clarifying the bases of that interpretation. They / also considered certain studies of acute asthma (Derrick, Goldstein et al., Glasser et al.) as being essentially negative. They did not think that the initial Stebbings studies of the 1975 Pittsburgh episode could be utilized, since pre-episodic lung function data were not obtained as a comparison baseline. However, a later Stebbings article in which post-episodic function was examined and "sensitive" individuals were examined did not seem to be considered. They also did not Sawicki appear to consider the later study of / , although earlier studies were included in their dose response table, and the study by Hammer in the Southeastern United States was not mentioned. The Cohen et al. study of asthma was considered weak, for unclearly specified reasons. Morbidity during episodes was examined, but not included in the table (Shrenk, Ministry of Pensions and Health, Fry) and a few other studies were examined. Overall, though, despite some of the

TABLE 14-53. SUMMARY OF EVIDENCE FOR HEALTH EFFECTS OF ACUTE EXPOSURE TO SO_2 AND PARTICULATES

Type of study	Reference	Effects observed	24-hour average pollutant levels at which effects appear
Mortality	Martin and Bradley[11]		500 $\mu g/m^3$ (TSP) 300 $\mu g/m^3$ (SO_2)
	Martin[16]	Increases in daily total mortality above the 15 moving average	500 $\mu g/m^3$ (TSP) 400 $\mu g/m^3$ (SO_2)
	Glasser and Greenburg[222]		580 $\mu g/m^3$ (TSP) 780 $\mu g/m^3$ (SO_2)
Morbidity	Martin[16]	Increases in hospital admissions for cardiac or respiratory illness	500 $\mu g/m^3$ (TSP) 400 $\mu g/m^3$ (SO_2)
	Lawther et al.[53]	Worsening of health status among 195 bronchitics	312 $\mu g/m^3$ (TSP) 500 $\mu g/m^3$ (SO_2)
	Van der Lende[74]	Improvement in lung function accompanying an improvement in air quality	245 $\mu g/m^3$ (TSP) 300 $\mu g/m^3$ (SO_2)

TABLE 14-52. GUIDELINES FOR EXPOSURE LIMITS CONSISTENT
WITH THE PROTECTION OF PUBLIC HEALTH[a],*

Expected effects	Concentration ($\mu g/m^3$)	
	Sulfur dioxide	Smoke
24-h mean	100-150	100-150
Annual arithmetic mean	40-60	40-60

[a]Values for sulfur dioxide and smoke as measured by OECD or British daily
smoke/sulfur dioxide method (Ministry of Technology, UK, 1966; Organization
for Economic Cooperation and Development, 1965). Adjustments may be necessary
where measurements are made by other methods. ~~For example, smoke concentrations
of 100-150 $\mu g/m^3$ convert to approximately 200-300 $\mu g/m^3$ TSP and smoke levels
of 40-60 $\mu g/m^3$ convert to approximately 80-120 $\mu g/m^3$ TSP.~~
*From WHO[312]

the WHO felt were relevant in these dose response determinations. In addition, the guidelines arrived at by the WHO[312] for protection of public health are shown in Figure 14-52.

The WHO[312] report also comments on several additional studies which they felt were positive; the study published by Watanabe in 1966, show that 20% increase in mortality at 200 $\mu g/m^3$ SO_2 and 1000 $\mu g/m^3$ of TSP (24 hours). The Yoshida study showed effects with weekly SO_2 above 140 $\mu g/m^3$ (no TSP or BS). A study by Toyama et al. published in 1966 shows prevalence of respiratory symptoms in males (ages 40 to 59) adjusted for age and smoking in areas with SO_2 concentrations of less than 30 $\mu g/m^3$ and TSP less than 106-341 $\mu g/m^3$. Tani (1975) reported a study around a pulp mill (compared to a controlled area) which showed a consistent increase with prevalence of bronchitis with sulfation rates of 1.2gm/100cm^2 per day (approximately 48-96 $\mu g/m^3$ SO_2). In their report, WHO points out that they think that the Cohen et al. study of asthma was positive. They also commented that the Lambert and Reid study did control for social status as well as smoking, such that one can assume that there were not likely to be further confounding factors in that study. In regard to the Ferris study in 1962, the report questions the air pollution measures and indicates they were also limited to SO_2 reading in the 1973 survey. The WHO report also questions the health index used by Lawther et al. in their series of studies extending from 1954 to 1968. In regard to the Waller report of 1971, they felt that discrimination between effects of pollution and those of adverse weather was poor. The WHO report[312] presented further information on sensory and reflex function resulting from short-term exposures to H_2SO_4, and SO_2 and exposures of H_2SO_4 and SO_2 combined. The review indicates that a physiological response occurs at short-term H_2SO_4 concentrations of

from 400 to 730 $\mu g/m^3$ and short-term SO_2 concentration of from 600 to 2800 $\mu g/m^3$. When concentrations of H_2SO_4 and SO_2 are combined, however, the same effects occur for H_2SO_4 at concentrations ranging from 150 to 600 $\mu g/m^3$ and SO_2 at concentrations ranging from 250 to 1200 $\mu g/m^3$.

Other recent evaluations of dose-response relationships in a review by Ware et al.[304] are summarized in Tables 14-53 and 14-54. Many of the same studies accepted by WHO and others in earlier reviews are taken by Ware et al. (1980) to be valid and to demonstrate health effects of the levels listed in the two tables. Certain other findings were also thought to indicate a possible lack of effect at the levels studies, including specifically Emerson's, possibly Ipsen's, and possibly Schimmel's results. Ware et al.[304] also discussed Bennett's interpretation of the Waller and the Lawther data concerning the decline of symptoms in bronchitis with declining air pollution, without however clarifying the bases of that interpretation. They / also considered certain studies of acute asthma (Derrick, Goldstein et al., Glasser et al.) as being essentially negative. They did not think that the initial Stebbings studies of the 1975 Pittsburgh episode could be utilized, since pre-episodic lung function data were not obtained as a comparison baseline. However, a later Stebbings article in which post-episodic function was examined and "sensitive" individuals were examined did not seem to be considered. They also did not appear to consider the later study of / Sawicki , although earlier studies were included in their dose response table, and the study by Hammer in the Southeastern United States was not mentioned. The Cohen et al. study of asthma was considered weak, for unclearly specified reasons. Morbidity during episodes was examined, but not included in the table (Shrenk, Ministry of Pensions and Health, Fry) and a few other studies were examined. Overall, though, despite some of the

TABLE 14-53. SUMMARY OF EVIDENCE FOR HEALTH EFFECTS OF ACUTE EXPOSURE TO SO_2 AND PARTICULATES

Type of study	Reference	Effects observed	24-hour average pollutant levels at which effects appear
Mortality	Martin and Bradley[11]		500 $\mu g/m^3$ (TSP) 300 $\mu g/m^3$ (SO_2)
	Martin[16]	Increases in daily total mortality above the 15 moving average	500 $\mu g/m^3$ (TSP) 400 $\mu g/m^3$ (SO_2)
	Glasser and Greenburg[222]		580 $\mu g/m^3$ (TSP) 780 $\mu g/m^3$ (SO_2)
Morbidity	Martin[16]	Increases in hospital admissions for cardiac or respiratory illness	500 $\mu g/m^3$ (TSP) 400 $\mu g/m^3$ (SO_2)
	Lawther et al.[53]	Worsening of health status among 195 bronchitics	312 $\mu g/m^3$ (TSP) 500 $\mu g/m^3$ (SO_2)
	Van der Lende[74]	Improvement in lung function accompanying an improvement in air quality	245 $\mu g/m^3$ (TSP) 300 $\mu g/m^3$ (SO_2)

TABLE 14-54. SUMMARY OF EVIDENCE FOR HEALTH EFFECTS OF CHRONIC EXPOSURE TO SO_2 AND PARTICULATE MATTER

Type of study	Reference	Effects observed	Annual average pollutant levels at which effects occurred
Longitudinal and Cross-Sectional	Ferris et al.[4,42,46,47]	Higher rate of respiratory symptoms; and decreased lung function	180 $\mu g/m^3$ (TSP) 55 $\mu g/m^3$ (SO_2)
Cross-Sectional (2 areas)	Sawicki[31]	More chronic bronchitis, asthmatic disease in smokers; reduced FEV%	250 $\mu g/m^3$ (TSP) 125 $\mu g/m^3$ (SO_2)
Cross-Sectional study of school children in 4 areas	Lunn et al.[96,97]	Increased frequency of respiratory symptoms; decreased lung function in five-year-olds	260 $\mu g/m^3$ (TSP) 190 $\mu g/m^3$ (SO_2)
Follow-Up of school children in 4 areas	Douglas and Waller[90]	Increased lower respiratory tract infection	230 $\mu g/m^3$ (TSP) 130 $\mu g/m^3$ (SO_2)
Cross-Sectional study of children in 4 areas	Hammer et al.[214]	Increased incidence of lower respiratory diseases	85-110 $\mu g/m^3$ (TSP) 175-250 $\mu g/m^3$ (SO_2)
Cross-Sectional study of high school children in 2 areas	Mostardi and colleagues[66,67]	Lower FVC, Fev_{075} and maximal oxygen consumption	77-109 $\mu g/m^3$ (TSP) 96-100 $\mu g/m^3$ (SO_2)

above nuances of their evaluation that might differ from some of the evaluations contained in earlier reviews, their assessment appeared to agree fairly well with those of others regarding studies accepted as being valid and their interpretation.

One additional recently appearing review remains to be discussed, the report by Holland et al.[301] published in November, 1979. That published review was based on a more extensive report commissioned by certain American industrial interest groups (the American Iron and Steel Institute and member steel companies) to be written for the purpose of reappraising epidemiologic and other scientific evidence bearing on criteria underlying United States National Ambient Air Quality Standards (NAAQS) for particulate matter.

More specifically, the following was stated at the outset of the 1979 publication[301] by Holland and colleagues:

> The aim of this review is to consider available epidemiologic evidence on the health effects of particulate pollution, and to examine, in the light of this evidence, criteria for setting standards for levels of suspended particulate matter in the atmosphere.

Elaborating further on their intent, Holland et al.[301] opened the final discussion of their "Conclusions" with the following statements:

> Our purpose in this report, in which for ease of comparison we have followed the format of the Criteria Document, has been to assess the epidemiologic evidence for the effects of suspended particulates in the presence of other air pollutants on various aspects of health, and to critically analyze the basis for setting standards for levels of suspended particulate.

Close examination and critical assessment of the Holland et al. (1979)[301] published review reveals that one of its most outstanding features is notable divergence of certain of their evaluations and conclusions from scientific appraisals of the same subject matter by other equally prominent and knowledgeable international experts. This not only includes divergence from

evaluations and conclusions contained in reviews by Rall, Higgins, Goldsmith and Friberg, and Ferris published in the 1974 to 1978 period, but also marked divergence on certain key points from the more recent appraisals contained in the ATS, NRC/NAS, and WHO documents published within the past two years (1978-79)

One point of partial agreement between Holland et al.[301] and the published views of other experts concerns levels of sulfur oxides and particulate matter capable of inducing mortality. Holland and colleagues concluded that

> increases in deaths were discernable when smoke exceeded something in the range of 500-800 $\mu g/m^3$ (as 24-hour averages by smoke (BS) or equivalent method) together with sulfur dioxide of more than 700-1000 $\mu g/m^3$ (24-hour average).

This can be compared with roughly comparable conclusions by some other evaluators and the levels of 500 $\mu g/m^3$ for both BS and SO_2 concluded by WHO[312] to be associated with acute mortality effects. However, the studies of McCarroll and of Greenberg et al. in New York were the only ones outside of Britain considered by Holland et al.,[301] Dutch, Japanese, and other U.S. studies suggesting possible mortality effects at particulate levels below 500 $\mu g/m^3$ were largely ignored by Holland et al.[301].

Similarly, in their summary table for studies of acute morbidity related to short term pollution exposure Holland et al.[301] ignore all but British studies and accept only a few of those as being valid. Holland et al.,[301] further did not mention acute or chronic pulmonary function changes in discussing the basis for their conclusions to the effect that the evidence reviewed by them "does not substantiate any level of air pollution below 250 $\mu g/m^3$, smoke (BS) as a 24-hour average, as having a harmful effect on health." Holland et al.[301] also stated: "There is no scientifically acceptable evidence... which can implicate a level at which mortality is associated with long term

exposure to SO_x/TSP." This is in contrast to several other reviews citing certain studies as showing such effects. In addition, it is asserted by Holland et al. (1979)[301] that no scientifically valid epidemiology studies exist by which to establish associations between health effects and long-term (annual average) exposures to sulfur oxides or particulate matter. This is, of course, at variance with all of the published expert views summarized above. Importantly, it should be noted that Holland et al.[301] did not exclude all studies on the basis of scientific merit, but excluded many as somehow simply being irrelevant (e.g., Neri et al.) or completely ignored others yielding results not supporting their conclusions. Furthermore, they failed to discuss or note many countervailing opinions existing in the literature, eg., those expressed in the reviews by Rall, Goldsmith and Friberg, Shy et al., Higgins, Ferris, NAS, and WHO discussed above. Figure 14-8 illustrates some of the striking differences between evaluations of various key studies by Holland et al.[301] in comparison to those by WHO (1979)[312] or other reviews such as the present EPA (1980) assessment.

In view of the divergence of various Holland Report[301] evaluations and conclusions from those of other published expert reviews, it is not surprising that the Report[301] has not been universally well received or accepted as a scientifically objective or accurate reappraisal of the evidence regarding the health effects of particulate pollution. Thus, for example, commentary critical of the appraisal by Holland et al.[301] appeared in the next issue of the publishing journal. In that commentary on the Holland et al. review, Shy[313] states that Holland Report[301] comments fall into three categories:
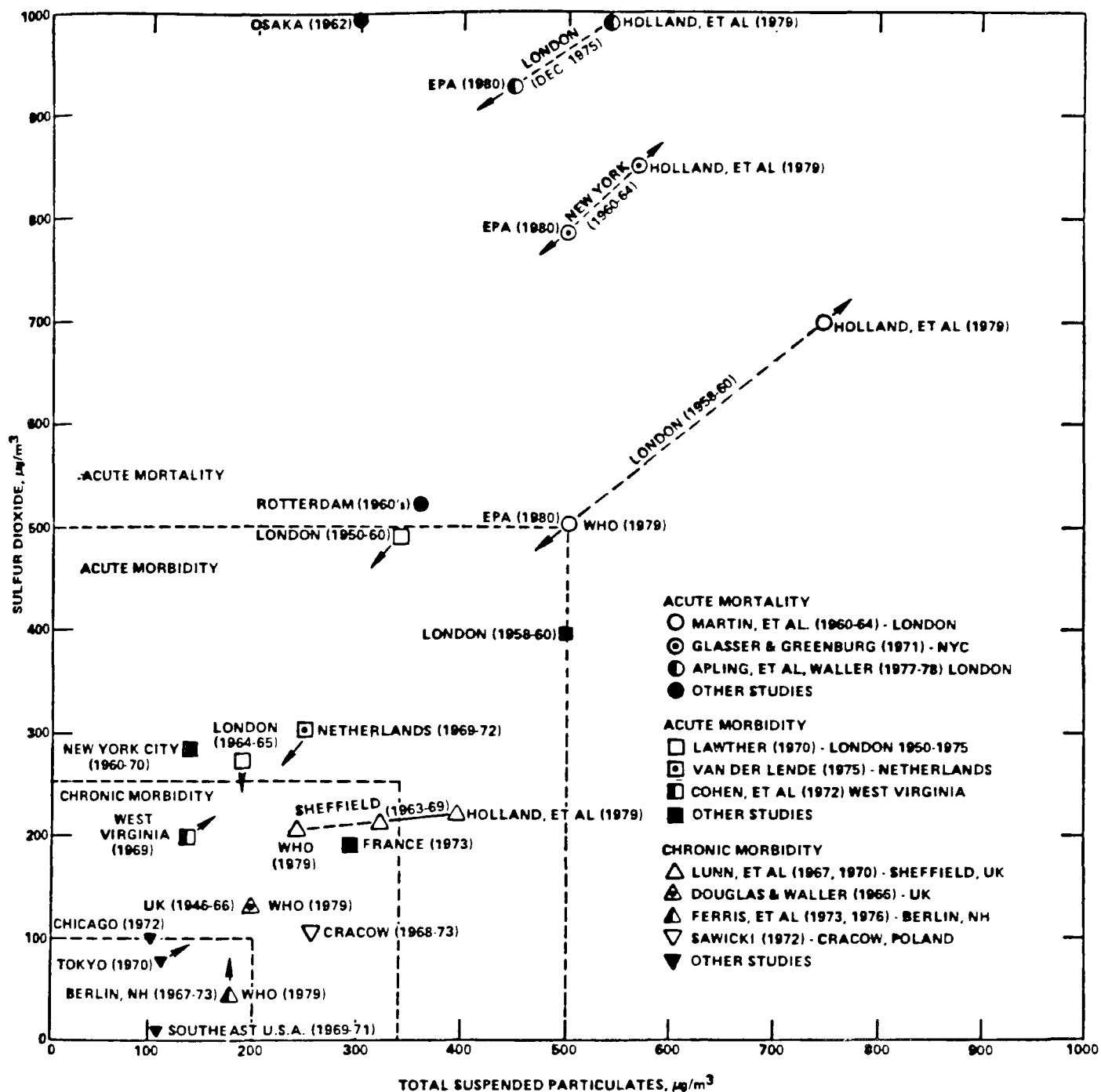
Figure 14-8. Comparison of interpretations of studies evaluated by Holland et al. (1979),[301] WHO (1979),[312] or other reviews such as those in the NRC/NAS documents[307,308] and the present chapter. Aside from the British studies noted for London and Sheffield and the 1960-64 New Youk City mortality study, Holland et al.[301] either ignored the other studies shown or evaluated them as being in-valid based on methodological flaws or reinterpretation of their findings. "OTHER STUDIES" not specifically identified in the above key include those reported by: Gervois et al.[61] □ France (1973); Martin[16] □ London (1958-60); Mostardi et al.[117,258] ▽ Chicago (1972); Hammer[113,257] ▽ Southeast USA (1969-71); Suzuki and Hitosugi ▽ Tokyo (1970). The dashed lines depict HO (1979)[312] conclusions regarding SO$_2$ and particulate levels associated with acute (24-hr) mortality, acute morbidity, and chronic (annual) morbidity.

1) a low level of criticism of negative studies; 2) a high level of criticism of most positive studies; 3) a polemical, often broad-brushed criticism of EPA Studies.

In regard to the negative studies, Shy[313] further notes: "the possibility of systematic measurement errors or of confounding, that may have biased the results toward the null hypothesis of no effect, is not addressed..." Shy[313] also states that it appears that Holland et al.[301] rejected positive studies if there were any possible confounder, even if they lacked evidence that the potential confounder was indeed differentially distributed between exposed and referent populations. Shy[313] provides a table (Table 14-55) listing comments by Holland et al. regarding certain studies, as well as his own rebuttal remarks, and questions whether the Holland et al. group adequately addressed the concepts of sensitive populations groups, appropriate margins of safety, or other considerations relevant to a determination of health effects criteria in their discussion of dose-response relationships.

It should also be noted that the Holland Report,[301] while in press, was submitted for consideration by international experts of the WHO Task Group on Environmental Health Criteria for Sulfur Oxides and Particulate Matter as they neared finalization of the WHO (1979) document "Environmental Health Criteria (and) Sulfur Oxides and Suspended Particulate Matter."[312] That group of international experts individually reviewed the Holland Report and provided comments on it to the WHO. Those comments, together with others received from international organizations such as the International Iron and Steel Institute, were then considered by the Chairman of the Task Group

TABLE 14-55. EPIDEMIOLOGIC STUDIES SUGGESTING AN EFFECT OF PARTICULATE AIR POLLUTION AT CONCENTRATIONS AT OR NEAR THE U.S. AMBIENT AIR QUALITY STANDARD AND COMMENTS BY SHY[313] ON THE REVIEWS OF THEM BY HOLLAND ET AL.[301]

Author and location of study	Findings	Comments
Lindeberg[321] Oslo, Norway	Average deaths per week during 1958 - 1965 winters were significantly correlated with levels of SO_2 but not smoke	Holland et al. state that there may be confounding with long-term trends in air pollution levels and with influenza epidemics. However, no evidence is presented showing a correlation of influenza epidemics with air pollution levels, nor are data presented on the long term air pollution trends.
Winkelstein et al.[188] Buffalo, New York	Geographic association between mortality from chronic respiratory disease among 50 - 69-year-old men and particulate levels over the range of 80 to more than 135 $\mu g/m^3$ annual average (HV).	Holland et al. state that these results were not adequately standardized for age, social class, ethnicity, occupation, mobility or smoking habits. These limitations are inherent in mortality-based geographic studies. However, the authors did stratify on age and social class, and there is no positive evidence that other risk factors were correlated with the distribution of particulate levels.
Van der Lende et al.[74] Netherlands	Comparison of lung function between 1969 and 1972 revealed improved function in the residents of a polluted area that experienced improved air quality over the 4-year interval. No similar functional change occurred in residents of a cleaner rural area.	Air quality changed from 160 $\mu g/m^3$ (smoke, BS) to 40 $\mu g/m^3$ during the 1969 - 72 interval. Holland et al. state that firm conclusions cannot be drawn "in the absence of direct evidence on changes in lung function in random samples of urban populations." This scientific purism would tend to cause rejection of the results of most air pollution epidemiologic data.

TABLE 14-55. EPIDEMIOLOGIC STUDIES SUGGESTING AN EFFECT OF PARTICULATE AIR
POLLUTION AT CONCENTRATIONS AT OR NEAR THE U.S. AMBIENT AIR QUALITY STANDARD
AND COMMENTS BY SHY[313] ON THE REVIEWS OF THEM BY HOLLAND ET AL.[301]

Author and location of study	Findings	Comments
Gervois et al.[61] Two towns in France	An association was reported between employee sickness absence records, adjusted for temperature, and day-to-day variations in smoke and SO_2. Highest daily values for each were 200 µg/m³, with 3-month means of 53 µg/m³ (smoke, BS) and 37 µg/m³ SO_2.	Holland et al. claim that "the seasonal distribution of respiratory infections could have had some confounding effect." Adjustment for temperature would remove some of the seasonal effect, but no evidence was provided that season was correlated with air pollution levels.
Levy et al.[70] Hamilton, Ohio	A significant correlation was found for weekly hospital admission for respiratory infections and an index of air quality over a 12-month period. Effect was adjusted for temperature.	Holland et al. feel that there may be confounding of seasonal respiratory disease frequency and air pollution. Again, no evidence for actual confounding is presented, and temperature adjustment provides at least a partial control for seasonal effects.
Ferris et al.[46] Berlin, N.H.	An improvement in respiratory symptoms and pulmonary function was noted in the same persons examined in 1961 and 1967, and these changes were accompanied by a decline in particulates from 180 µg/m³ (HV) in 1961 to 131 µg/m³ (HV) in 1967. A later follow-up study in 1973 showed a further decline in particulates by 1973 to 80 µm/m³ (HV), even while SO_2 levels increased. The latter decline was not accompanied by a change in pulmonary function or respiratory symptoms.	The orginal investigators interpret these results to indicate that all the benefit occurred from the reduction in particulates, and that the gaseous sulfur compounds did not have an effect at these levels. Holland et al. state that data from different years are not comparable. However, the original investigators specifically addressed this issue and failed to find evidence for lack of comparability.

TABLE 14-55. EPIDEMIOLOGIC STUDIES SUGGESTING AN EFFECT OF PARTICULATE AIR POLLUTION AT CONCENTRATIONS AT OR NEAR THE U.S. AMBIENT AIR QUALITY STANDARD AND COMMENTS BY SHY[313] ON THE REVIEWS OF THEM BY HOLLAND ET AL.[301]

Author and location of study	Findings	Comments
Lambert and Reid[28] England	A gradient of respiratory symptom prevalence corresponded with the pollution gradient. Data were derived from a self-administered questionnaire sent to a national probability sample. Prevalence ratios are adjusted for smoking and age.	Holland et al. for unexplained reasons discount the correspondence of the symptom and air pollution gradients. Particulate levels range from less than 100 $\mu g/m^3$ to 200+ $\mu g/m^3$ (smoke, BS).
Sawicki[181] Cracow, Poland	Prevalence of chronic respiratory disease was significantly greater in residents of a high air pollution area (annual average particulates, 170 $\mu g/m^3$ (smoke, BS) vs. those in a low pollution area (annual avg.: 90 μ/m^3). Data were stratified for smoking and age.	Holland et al. state that differences are not adjusted for occupational and social class, but they fail to provide evidence that these factors are confounding variables in this study. The reviewers admit that the strong differences are unlikely to be explained away by one confounding factor, but the use of these data is discounted in their final assessment.
Holland et al.[101,102] and Bennett et al.[103] Kent, England	Within urban areas, air pollution levels were associated with lung function of children ages 5-14 years. Effects were adjusted for social class, family size and previous history of bronchitis. Smoke levels (BS) were less than 100 $\mu g/m^3$ in both urban areas.	Holland et al. (1) reject the association with air pollution because the lung function effect was "inconsistent" across the mix of urban and rural study areas. However, urban-rural differences are to be expected, and, within the urban stratum, the air pollution effect could not be accounted for by other risk factors.

TABLE 14-55. EPIDEMIOLOGIC STUDIES SUGGESTING AN EFFECT OF PARTICULATE AIR POLLUTION AT CONCENTRATIONS AT OR NEAR THE U.S. AMBIENT AIR QUALIXX,STANDARD AND COMMENTS BY SHY[313] ON THE REVIEWS OF THEM BY HOLLAND ET AL.[301]

Author and location of study	Findings	Comments
Tessier et al.[322] Bordeaux, France	An association was found between absenteeism due to respiratory disease among schoolchildren ages 6-11 years and short-term levels in air pollution less than 100 $\mu g/m^3$ (smoke level by method similar to BS).	Socioeconomic and other factors were not included in the analysis. However, these risk factors are unlikely to be determinants of temporal variations in disease frequency among the same group of children. Likewise, there is no evidence for an effect of meteorologic factors and temporal variations in absenteeism, as Holland et al. allege.
Irwig et al.[98] 10 areas of England	Investigators reported a statistically significant relationship between the frequency of chest colds during 1972-1973 and air pollution measurements taken in November, 1973, after allowing for differences in the distribution of age, sex and social class.	Holland et al. state that the effect of smoking in the home was not considered but offer no evidence that this factor was a confounder. Reviewers state that a second report from this study indicated no relationship with air pollution but they fail to provide details on this study.

Meeting, the Rapporteur, and members of the WHO Secretariat; and, it was determined that the Task Group experts' opinions of the Holland Report contents were such that the Task Group's views, as expressed in the now published 1979 WHO document,[312] remained unaltered. See Appendix 3C for further information regarding this matter.

One other important consideration should be noted in regard to the recently published Holland Report.[301] That concerns the fact that Holland and colleagues apparently failed to apply the same standards of review to the British air quality measurement data (critically appraised in Chapter 3 of this document and summarized earlier in this chapter) and study designs employed by British epidemiologists in evaluating quantitative air pollution/health effects relationships of the type assessed in their report.[301] This possible flaw in their appraisal, especially in view of their dismissal of results of various American or other studies on the basis of criticisms of errors in their pertinent methodologies and aerometry data need to be further evaluated (together with other points noted above) since it may raise questions regarding their review and its conclusions. Full judgement by the scientific community regarding such questions remains to be more completely formulated and voiced; pertinent comments on views expressed in the Holland Report[301] are, therefore, invited as input in order to assist in the evaluation of its potential usefulness as it might bear on the present review of health criteria for sulfur oxides and particulate matter.

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Changes to References for Chapter 14 - PM/SO$_x$

Certain Chapter 14 reference numbers represent studies deleted from earlier drafts of Chapter 14 or designate studies now to be deleted in keeping with changes in text noted earlier in Chapter 14 corrigenda comments. Thus, the following Chapter 14 reference numbers should be disregarded: 98; 108-111; 113-117; 120-124; 190; 212-214; 314; 342.

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APPENDIX 14-A

CONGRESSIONAL INVESTIGATIVE REPORT (1976)
COMMENTARY ON U.S. EPA CHESS PROGRAM

APPENDIX A

Congressional Investigative Report (1976) Commentary
on U.S. EPA CHESS Program

As first discussed on p. 14-93 of this chapter, the various epidemiologic
studies carried out under the EPA CHESS Program (Community Health and Environ-
mental Surveillance System) have engendered a great deal of controversy. Most
controversial was a 1974 Monograph reporting on certain of these studies and
entitled: "Health Consequences of Sulfur Oxides: A Report from CHESS, 1970-1971".
Subcommittees of the House Committee on Science and Technology later produced
a report on the Monograph, the CHESS Program, and EPA's air pollution programs
in general--a report entitled: "The Environmental Protection Agency's Research
Program with Primary Emphasis on the Community Health and Environmental Surveillance
System (CHESS): An Investigative Report." This report, referenced throughout
this document as the Investigative Report or "IR (1976)," is a comprehensive
reference for qualifying the use of the CHESS Monograph, and the CHESS studies
generally. The full text of the IR (1976) is contained in an Addendum to the
CHESS Monograph, EPA-600/1-80-021, which is available from EPA as noticed in
the Federal Register of April 2, 1980, 45 FR 21702.

Because of the controversy surrounding CHESS, all references in this
document to CHESS have been very carefully considered. An effort was made to
discuss only those studies which have undergone scientific peer review and
have been published in the open literature apart from, or in addition to,
official EPA publications. Further, in this chapter (14), each study has been
assessed on its own merits, considering pertinent published criticisms and
qualifications. Many such qualifications concern errors in aerometric measure-
ments, and these have been discussed at length in Chapter 3. Other qualifications

concern the analysis of CHESS data and the conduct of epidemiology generally; these are

discussed as appropriate throughout this chapter and further below.

A proper evaluation of any CHESS study cited in this document should include careful reference to the entire IR (1976). To put the evaluation of epidemiologic studies in context, however, the following passage from Section VI A of the IR (1976) is presented. Following that passage, critiques from the IR (1976) which specifically address studies cited in this chapter are reproduced. Finally, a review of CHESS air quality analysis procedures and results is presented, based on Sections V and VI of the IR (1976). Section VI A of the IR (1976) opens with the following passage:

A. GENERAL PROBLEMS OF EPIDEMIOLOGIC INVESTIGATIONS OF POLLUTION EFFECTS

Before discussing health effects problems specific to CHESS, some discussion of general difficulties inherent to pollution epidemiology may be helpful.

Exposure to suspect pollutants is not controlled in population studies. Indeed with current technologies, it is not possible to be sure that the correct pollutant is even being measured. Combinations of pollutants may be more harmful than any single pollutant, and the number ot studies needed to investigate such synergisms (interactions) increases rapidly with the number of pollutants under consideration. The analysis of synergisms is often impractical since sites with the needed configurations of pollutants are seldom at hand.

Not only is exposure uncontrolled, it is often difficult to measure. Even when aerometric measurements are valid, special meteorologic conditions or personal habits may cause a given subject to experience pollution levels very different from those measured at a nearby fixed monitoring station. These problems are exacerbated in long term studies during which the quality of aerometric data has been variable and individuals have changed jobs and residences. Aerometric methods for measuring hourly or daily pollution levels are often less reliable than required for studies associating pollution levels with short-term health effects.

The health measurements are often subjective responses to a questionnaire or interview. An individual may give one answer on a self-administered questionnaire and another to a friendly interviewer. Other factors, such as the public announcement of a pollution alert, can also influence subjective health measurements. Some health measurements, such as pulmonary function tests or blood analyses, are less influenced by poorly defined conditions surrounding the measurements and are said to be objective. However, even objective endpoints respond to uncontrolled events like an undetected influenza epidemic or high pollen count.

Whether the health measurement is subjective or objective, the response is often affected by factors (covariates) associated with the subject studied and unrelated to pollutant exposure. Whether the individual smokes or is subjected to cigarette smoke at home or work is a covariate of dominant importance in pollution studies. Educational attainment may affect responses to questions about phlegm or pneumonia. Occupation, age, sex, race, immunity to influenza, allergy, access to air-conditioning and countless other covariates complicate the interpretation of epidemiologic data. Epidemiologists treat covariates in two ways. They try to choose study populations which have similar covariate characteristics so that health differences between such populations can be ascribed to pollution effects. Alternatively, they make mathematical adjustments to nullify the effects of covariate imbalances. Both strategies have weaknesses, and neither works if the investigator is unaware of an important covariate or has failed to measure it.

The epidemiologist has little control over the subjects studied. He cannot assign them at random to reside in polluted communities of interest. Thus, a clean town may contain many asthmatics because asthmatics have wisely chosen to live there rather than in a more polluted community. This fundamental problem of self-selection must qualify any conclusions obtained from non-randomized population studies: it may be possible to demonstrate temporal or spatial associations between health and pollution measurements, but a causal relationship cannot be inferred on the basis of a single epidemiologic study.

Students of pollution counter these weaknesses in several ways. One strategy is to replicate an epidemiologic study in a variety of circumstances and serially in time. If a consistent association between pollution and health measurement is observed, it is held to be reliable since covariate imbalances and problems of self-selection are unlikely to affect all sites and to persist over time. Clinical studies, in which healthy volunteers are subjected to controlled pollution exposures, and toxicological studies, in which animals are subjected to various combinations and doses of pollutants, complement information obtained from epidemiologic studies. This body of information from clinical and toxicological studies and from several epidemiolgic studies may substantiate an interesting association suggested by the health and pollution measurements of a single epidemiologic study.

In addition to these general issues, several questions directly pertinent to the CHESS health measurements were examined, namely:

(1) Was the health measurement a reliable and meaningful indicator of public health?

(2) Was the statistical analysis sound and impartial?

(3) Were the methods used to ascribe specific health effects to specific pollutants and to establish dose-response relationships logically compelling?

The following critiques from Appendix A, Part B, of the IR (1976) may be helpful in assessing studies cited in this chapter.

No.1, "Prevalence of chronic respiratory disease symptoms in adults:

1970 survey of Salt Lake Basin Communities." Reported by Chapman et al.[212]

APPENDIX A

A RECAPITULATION OF THE AEROMETRIC AND METEOROLOGICAL FINDINGS OF THE INVESTIGATION AS THEY RELATE TO SPECIFIC SECTIONS OF THE CHESS MONOGRAPH AND THE HEALTH FINDINGS

A. INTRODUCTION

This section contains citations of errors and omissions found in a careful review of the CHESS Monograph which show that the use of aerometric and meteorological data in correlation with health effects end point measurements can easily mislead the reader of the CHESS document into inferences which are not wholly or even partially supported by the data in the report. Page, paragraph, and figure references are to the 1974 CHESS Monograph.

Since an important application of the aerometric data is to determine correlations with health effects, any errors or overusage of aerometric data based upon estimates or improper measurements will obviously reduce or negate the value of any health effects correlations which are attempted. This misusage or overusage of aerometric data will be particularly damaging as the extension of the conclusions is made in an attempt to discover possible threshold effects.

B. CRITIQUE

1. Prevalence of Chronic Respiratory Disease Symptoms in Adults: 1970 Survey of Salt Lake Basin Communities

Observed concentrations for only one year have been used to crudely estimate concentrations of sulfur dioxide and suspended sulfates relating to a 4-7 year exposure. The 1971 observed annual average concentration of sulfur dioxide was used with the 1971 emission rate from the smelter to obtain a ratio that was then multiplied by emission rates for other years to estimate concentrations for the other years. The estimated sulfur dioxide concentrations were then used in a regression equation based on a 1971 relationship to estimate suspended sulfate concentrations. Possible changes in meteorological conditions and mode of smelter operations were neglected. Acknowledgment is not given in the discussion and summary that the critical concentrations relating to health effects are nothing more than estimated concentrations.

It is questionable whether or not long-term exposures should have been attempted for Magna, based on only one year's record of observations that are abnormal because of the smelter strike. It would certainly have been appropriate to have mentioned that only estimated long-term data were available and indicated their degree of uncertainty in the discussion and summary.

Further, we find many errors on Page 2-37, Table 2.1.A.14. It seems that this table should have never been included in the report. Aside from the misuse of the diffusion model (discussed in Chapter IV) this table lists suspended sulfate values for Magna for the years 1940–1970, that are not the same as listed in Table 2.1.A.16, on page 2-39. The values are estimated by a simple ratio from the smelter emission rates, but this is not explained. On page 2-39 a regression equation is used for the same purpose. All of the sulfate concentrations under the heading CHESS are estimated observations except those for the year 1971. This has not been properly indicated, e.g. by the use of parentheses.

On pages 2-37 emission rates are not sulfur dioxide rates as indicated but emission rates in tons of sulfur per day. This means that the sulfur dioxide emissions were twice the values listed. It also means that the dispersion model estimates are incorrect. However, the listed estimated concentrations in Magna and Kearns, which are based on a simple ratio between observed concentrations in 1971 and some emission rate for 1971, whatever it might be, are not changed.

Note that the regression equation for suspended sulfates, Salt Lake City, (pages 2-39) which is:

$$SS = 0.101(TSP) - 3.65$$

is quite different than that which can be obtained from Table 2.1.4, i.e.:

$$SS = 0.065(TSP) + 1.93$$

SO_2 exposures were derived by multiplying the yearly smelter emission of SO_2 by the ratio of the 1971 measured annual average SO_2 concentration to the 1971 SO_2 emission rate (193 tons/day).

Estimates of suspended sulfates were derived from the estimates of SO_2, using the following regression equation for 1971:

$$SS = 0.09(SO_2) + 6.66$$

The annual TSP exposures were derived by multiplying the yearly smelter production of copper by the ratio of the 1971 measured annual arithmetic mean TSP concentration to the 1971 copper production rate (260,000 tons/year).

Smelter emissions of sulfur dioxide in the early 1940's were roughly three times greater than they were after 1956 although copper production has remained more or less constant. The method for estimating suspended sulfate, which is based on sulfur dioxide estimates leads to very high values in the 1940's whereas the total suspended particulate are estimated lower in 1940 than in 1971. The procedure used produced very high ratios between SS and TSP for the earlier years. For example, the 1940 ratio (34.6/63) is 0.55. This ratio is so large that it is obviously questionable.

The audacity of the estimates can be seen in Figure 2.1.17. The lowest value, which occured in 1971, is extrapolated all the way back to 1940, reaching unusually high annual average concentrations of more than one part per million. Considering the effects of wind direction, which would result in low concentrations much of the time because the smelter stack plume would not be blowing toward the town, such an annual average would result in short-period concentrations many times

the annual average. It is questionable that such high concentrations ever occurred. If they did, they would be well-remembered, and living conditions in Magna would be different than in 1971. Such unreasonably high estimates should have been further investigated before being presented.

The grossness of the estimates made overrides other shortcomings in this study pertaining to exposure that might be mentioned. However, more carefully made estimates would have required considerably more work, including obtaining meteorological records and details of smelter operations affecting plume behavior over the period of years studied. Such a large effort may not have been worthwhile considering the inexactness of some of the other aspects of the study. Nevertheless, a study of this nature seems to call for actual observations, more accurate estimates, or considerably less exactitude in its conclusions.

2. Frequency of Acute Lower Respiratory Disease in Children: Retrospective Survey of Salt Lake Basin Communities, 1967–1970

The same comments apply to this study as for the preceding study on the prevalence of disease symptoms in adults. Inadequate recognition is given to the fact that only estimated concentration data are being used in the discussion and summary.

3. Aggravation of Asthma by Air Pollutants: 1971 Salt Lake Basin Studies

In this study, daily entries in a dairy were used to determine weekly asthma attack rates. A statistical relationship was then determined between the attack rates (weekly) and observed air pollution concentrations (averaged weekly). Participants lived within a 2-mile radius of air monitoring stations.

Daily exposure of asthmatics in a community such as Magna, which is close to the smelter, are poorly characterized by a single monitoring station. On a given day, one side of the community could be much more affected by the smelter stack plume than the other, and high concentrations from looping or fumigation might affect one neighborhood but not others. The study inadequately assesses the effects of peak exposures and episodes.

This report does not make clear that the minimum temperatures used were from the Salt Lake City airport. The assumption seems to have been made that temperature was uniform over the entire study area. This is not true because of the differences in elevation and the effects of the mountains, and the lake. Perhaps the differences were not important, but they should have been considered. It is not clear why days were stratified by minimum rather than mean temperature.

Minimum temperatures occur during the early morning when people are generally indoors and perhaps in bed. When temperatures are low, windows are generally closed. Also, lower minimum temperatures are correlated with other meteorological phenomena that could also affect asthma attack rates, e.g., lower humidity and lower wind speed. Further there may be a correlation with wind direction. A lower than average minimum temperature probably is also associated with a strong temperature inversion which would be conducive to lofting the smelter stack plume. Because of the many questions raised, the findings pertaining to temperature merely suggest further study and have no general application.

Near the middle of the left hand column, page 2–89, the following sentence appears. "The shut-down of operations by the strike was accompanied by a pronounced improvement in air quality and a reduction in asthma attack rates that occurred sooner and were larger than seasonal reductions observed in the more distant study communities some 2 weeks later." Here there is a lack of appreciation of the natural climatic differences that exit in the Salt Lake Basin. Some effects of summer weather could easily be delayed two weeks before reaching Ogden. The average date for the last killing frost in Ogden is about May 6, whereas the average date of the last killing frost at Saltair (the climatic station nearest to Magna with a long record) is about April 12.

On Page 2–76 (near middle of page, right hand column) the smelter is not "5 miles north of Magna."

On page 2–81 the first graph in Figure 2.4.1 is incorrectly drafted. After the 17th week the broken line should be solid and the solid line broken. The temperature curve should appear as in the graph for the high exposure community.

Figure 2.4.2, page 2–81, shows a weakness in the argument that the sulfur dioxide concentrations are responsible for the asthma attack rate. In the High Exposure Community the attack rate starts up at the 18th week as the sulfur dioxide concentrations approach zero, or near zero, and remain very low for about six weeks. It is noted that this same graph shows the highest SO_2 peak occurring at the 9th week, which seems to begin about May 9. The graph on page 2–16 seems to show the peak in April.

In Figure 2.4.4, page 2–82, with respect to the High Exposure Community, it may be noted that the sulfate concentrations are not particularly well-correlated with the sulfur dioxide concentrations plotted in Figure 2.4.2, on the preceding page. The highest sulfate reading occurs in the 3rd week, whereas the sulfur dioxide levels build up to a peak in the 9th week.

On page 2–87, left hand column, it is stated that a threshold concentration of 1.4 $\mu g/m^3$ was calculated for suspended sulfates for the higher temperature range. In Figure 2.4.4 all of the plotted concentrations are greater than this value. Considering the background of suspended sulfates generally observed, this low threshold value seems to have no practical significance.

The third paragraph that appears in the right hand column, page 2–89, probably applies to Magna, however, this is not made clear. There is a possibility that the paragraph could be given broader interpretation than actually intended since the last three sentences seem to refer to conditions in urban areas generally. The paragraph probably should have been divided into two separate paragraphs. However, the main fault with the paragraph is that important conclusions are drawn that are not supported by information presented elsewhere in the report. It says "excess asthma attributable to sulfur dioxide might be expected 5 to 10 percent of summer days", "total suspended particulates could occur on up to 5 percent of summer days and 30 percent of fall and winter days", and "excesses due to suspended sulfates are likely to occur on 10 percent of fall and winter days and 90 percent of summer days." Assuming that the stated relationships

between concentrations and temperature are true, the report does not explain how the percentages of days were obtained. The study covered only 26 weeks, but these conclusions apply to an entire year. The percentages given seem to be rough estimates since they appear to be given only to the nearest 5 or 10 percent. The percentages might have been obtained from daily values for the minimum temperature, pollutant concentrations and asthma attack rate; but it is not clear how they were obtained.

Presumably daily average concentration levels of specific pollutants were used in the construction of the "hockey stick" curves shown on pages 2–86 and 2–88. The discussion implies that "24-hour levels" were used, but the precise nature of the air quality data used in the threshold analyses is not made clear.

There could be various reasons not explored by the study why the thresholds for asthma attacks were lower on warmer days. One of these is that there may be more plume looping on warmer days. This might result in localized, short-period, high concentrations, but relatively low average concentrations.

The validity of scientific work can be tested by the repeatability of results. In this and the other CHESS studies there were factors affecting asthma attack rates that were not considered and whose effects are unknown. Such factors are: time spent outdoors, percentage of time windows are open, temperature change, relative humidity, etc. The incompleteness of the study and the lack of understanding of the causes of the asthma attacks suggest that it might be repeated with significantly different results.

Short-term exposures to concentrations much higher than average annual or weekly concentrations could have occurred in the communities studied that were near large sources of air pollution such as smelters. There exists the possibility that asthma attacks could be triggered by brief-duration high concentrations. Such exposures could have been determined only inadequately by the procedures used in the study. The report does not make clear why more attention was not devoted to peak concentrations.

4. Human Exposure to Air Pollutants in Five Rocky Mountain Communities, 1940–1970

On pages 3–7 through 3–12 beginning with the second column, paragraph near middle of page, which begins "By comparing . . .". There is not a simple relationship between average daily pollutant emissions and average annual pollutant concentrations because the receptor area is often now downwind. Also, some consideration should have been given to determining if the years for which data are available were representative meteorologically.

(Page 3–11) Second paragraph, left hand side of page. Information obtained during this investigation indicates that the ratio 1.63 ± 0.21 should be 1.42 ± 0.21. (The value 1.63 is the upper limit of this ratio.)

(Page 3–12) Emission ratios of particulate and sulfur dioxide for 1971 are omitted from this report. Therefore, it is not possible to verify the ratios given here.

(Page 3–12) According to information obtained during this investigation, the two values for TSP listed as 99.5 for the years 1971–70, should be 98.1 for both years.

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ties where certain health effects were observed, the source of the suspended sulfate is inadequately determined. The study findings are much too incomplete to call for the stringent control of suspended sulfates as has been done on page 3-51.

7. Prevalence of Chronic Respiratory Disease Symptoms in Military Recruits: Chicago Induction Center (Paragraph 4.2)

Exposure estimates in this study are extremely crude. In the summary the following statement is made, "Available evidence indicates that exposures lasting 12 years or more to ambient air pollution characterized by elevated annual average levels of sulfur dioxide (96 to 217 $\mu g/m^3$), suspended particulates (103 to 155 $\mu g/m^3$) and suspended sulfates (14 $\mu g/m^3$) were accompanied by significant increases in the frequency of chronic respiratory disease symptoms."

The 96 $\mu g/m^3$ value is the average urban core value for 1969–70, which ranges from 54 to 138 $\mu g/m^3$, whereas the 217 $\mu g/m^3$ is an average value for five suburban communities for the year 1969. Going back 12 years concentrations were much higher. During the period 1960 through 1965, the lowest value was 222, and there was a high of 344 in 1964. For the five suburban communities there was data only for one other year. It averaged 183 $\mu g/m^3$. The 14 $\mu g/m^3$ concentration for sulfates is for a period of 7 years, not 12 as stated. It basically represents data for the Chicago core area, with some scattered observations from East Chicago and Hammond, Ind. The average concentrations for the city should be somewhat less than in the core area. Use of the core area value would generally result in an overestimate.

It is difficult to characterize exposures lasting 12 years for the entire Chicago area. Either this should have been done in very general terms, nonquantitatively, or a greater effort should have been made to present more representative estimates.

The assumption is being made that sulfate observations made at a central urban location in Chicago, averaged with a few observations from East Chicago and Hammond, Ind. are generally representative of the entire Chicago area.

(Page 4-8) Referring to the Chicago area the following statement is made: "Each sampler location, identified by a station name in Figure 4.1.2, represents the central business-commercial district of that particular area." This statement is not true. Practically all, if not all the samplers are located on the roofs of school buildings in an effort to obtain representative community values: They were not located deliberately in business commercial districts and do not slightly overestimate area-wide concentrations as suggested.

(Page 4-23) In reading this paper about the prevalence of chronic respiratory disease symptoms in military recruits, questions arise about the actual locations from which the men came and the local pollution levels to which they might have been exposed. Some rural occupations result in high exposures to dusts, plant allergens, etc.

(Page 4-35) (Summary) The 12-year value for suspended sulfates should be 16 micrograms per cubic meter, not 14, as stated. Also, it appears that the concentrations of sulfur dioxide and suspended particulate are for only the period 1969-1970 and not for 12 years as is stated. (See Table 4.1.A.6)

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8. Prospective Surveys of Acute Respiratory Disease in Volunteer Families: Chicago Nursery School Study, 1969-1970

On page 4-41, in Table 4.3.1, it is not clear where the sulfur dioxide data for the years 1959-63 come from. The Chicago network, which would have provided community data, was not operating effectively until 1964.

On the same page the suspended sulfate data are probably representative for the core area but are high to be used as an average for the city as a whole.

A serious weakness in this study is that the communities are ranked Intermediate, High, and Highest according to a ranking that was determined by suspended particulate values, whereas the most important finding pertains to sulfur dioxide. Referring back to Table 4.1.A.1, it can be seen that a considerably different ranking would have resulted if the communities had been ranked according to sulfur dioxide concentrations. In Table 4.3.1, it may be noted that during the study that the "High" community had the lowest concentration of sulfur dioxide.

Also note in Table 4.1.A.1 that the Highest communities include GSA, which happens to be on the south edge of the Chicago Loop area. This station probably contributed considerably to the high concentration of sulfur dioxide attributed to the Highest community during 1969-1970, yet it is very nonrepresentative of a nursery school. Also, note that the Highest stations include Carver, which for some reason ranks highest because of suspended particulate concentrations whereas the sulfur dioxide concentrations are relatively low.

Sulfates are not considered in the summary of this study, which seems to focus on sulfur dioxide without quantitative considerations of suspended sulfate levels.

(Page 4-54) In the first paragraph of the Summary, the following statement appears: "It is also possible that more recent lower air pollution levels contributed to increased respiratory illness." On page 4-51 the following statement is found. "Acute respiratory morbidity was significantly lower among families living in neighborhoods where sulfur dioxide levels had been substantially decreased." These two statements are contradictory and require clarification. The first statement is remarkable. It can be interpreted to mean that some air pollution is good for you. Did the authors intend to say this? Such an important finding is inadequately supported by the contents of the report.

9. Human Exposure to Air Pollution in Selected New York Metropolitan Communities, 1944-1971

An overusage of estimated data can be found on page 5-19. The following two statements appear: (Left hand column, middle paragraph) "Measured values for suspended sulfates for 1956-1970 were available from the Manhattan 121st Street Station, and these values were used for citywide values." (Last paragraph on page) "The observed annual ratios of suspended sulfate to dustfall for New York City were used to estimate the suspended sulfate levels in Queens and Bronx."

No. 10, "Prevalence of Chronic Respiratory Disease Symptoms in Adults

1970 Survey of New York Communities." Report by Chapman et al.[212]

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10. Prevalence of Chronic Respiratory Disease Symptoms in Adults: 1970 Survey of New York Communities

Three communities were compared: Riverhead, Long Island, a low exposure community, Queens, an intermediate exposure community, and the Bronx, a high exposure community. Parents of all children attending certain elementary schools located within 1.5 miles of an air monitoring station in each community were asked to participate in the study. Each child was given a questionnaire to be filled out by his parents and returned.

Regarding exposure, were the concentrations measured at the monitoring stations generally representative? Assuming a person remains reasonably near the station, in this case within 1½ miles, and breathes the outside air, the station measurements would be generally representative for long-term average exposure. Maps of annual concentrations which are for sulfur dioxide and suspended particulate matter, show reasonably uniform concentrations across the study areas. However, as has been mentioned in the report (5.1) Human Exposure to Air Pollution Selected New York Metropolitan Communities, 1944–1971, by Thomas D. English, et al., the Queens Community lies about 1 mile west of the John F. Kennedy International Airport. The effect of this airport and the various other possible sources of air pollution that could have affected particular local areas were not determined.

The fact that the CHESS monitoring sites were the same as used in the city air pollution control programs suggests that the sites were picked and are being used because they seem to be generally representative.

More important than the representativeness of the monitoring site locations in this study is the proper interpretation of the effects of the greatly reduced pollution levels during the period 1969–1971. It is not meaningful to draw conclusions from sulfur dioxide exposures ranging from 144 to 404 $\mu g/m^3$ and sulfate exposures ranging from 9–24 $\mu g/m^3$, as was done in this study. The implication is that health effects can be caused by the lowest concentrations mentioned, and this is not shown in the study. Also, it is stated that annual sulfur dioxide levels of 50 to 60 $\mu g/m^3$ (accompanied by annual average suspended sulfate levels of about 14 $\mu g/m^3$ and annual arithmetic mean total suspended particulate levels of about 60 to 105 $\mu g/m^3$) could be associated with such effects. These are levels that were measured in 1971, whereas in the study there seems to have been no way to have differentiated between the effects of pollution in 1971, or that might have occurred during some earlier time. It is not reasonable to infer that lower pollution levels are responsible for the observed health effects.

11. Prospective Surveys of Acute Respiratory Disease in Volunteer Families: 1970-1971 New York Studies

In this study families were telephoned once every two weeks and questioned about possible health effects. The families resided within 1 to 1.5 miles of the air monitoring stations.

In the discussion it is stated that acute lower respiratory disease morbidity can be attributed to exposures to 2 to 3 years involving annual average sulfur dioxide levels of 256 to 321 $\mu g/m^3$ (accompanied by elevated annual average levels of total suspended particulate of

97 to 123 $\mu g/m^3$ and annual average suspended sulfate levels of 10 to 15 $\mu g/m^3$). These values are average values for the period 1966-1970, a five year period, and not period of 2 to 3 years as indicated. Also, they are the averages for the Bronx and Queens, respectively, and therefore do not represent a range of concentrations that would have occurred in any particular community, as implied. For example, the sulfur dioxide concentrations in the Bronx ranged from 184 to 472 $\mu g/m^3$ and in the Queens from 131 to 420 $\mu g/m^3$, during the five year period. Three year averages are 174 to 247 $\mu g/m^3$, and two year averages, lower still.

On page 5–16 the dustfall concentrations shown in Figure 5.1.21 seem to be greater than would be obtained from the data presented in Figure 5.1.16.

On page 5–36 (Table 5.2.1) the values in this table seem to come from Table 5.1.A.8. The values in the column headed 1949-58 are, except for dustfall, for shorter time periods. For example, the values for Queens come from data for the years 1956-58.

On page 5–45 (Summary) we find that since the concentration data base comes from Table 5.1.A.8, the long term exposure values represent a period of less than 20 years.

Further, it is stated that there is a distinct possibility that increased susceptibility to acute lower respiratory illness is maintained or induced by exposures involving annual average sulfur dioxide levels of 51 to 63 $\mu g/m^3$ (accompanied by annual average total suspended particulate levels of 63 to 104 $\mu g/m^3$ and annual average suspended sulfate levels of 13 to 14 $\mu g/m^3$). The 51 to 63 $\mu g/m^3$, is a range resulting from two different analyses of samples (see page 5–53). It represents uncertainty in measurement techniques rather than a range of exposure as would be interpreted. These concentrations and the suspended sulfate concentrations of 13 to 14 $\mu g/m^3$ happen to have occurred in the Intermediate I and the Intermediate II communities during 1971. This particular study as conducted could not have differentiated between the effects of these levels of pollution and the effects of higher levels that occurred earlier.

Only average annual concentrations were considered and not peak or episode concentrations.

12. Aggravation of Asthma by Air Pollutants: 1970-1971 New York Studies

Panelists who lived within a 1.5 mile radius of three monitoring stations in communities identified as Low, Intermediate I, and Intermediate II, because of their average air pollution concentrations, recorded asthma attacks each day in a diary for a period lasting 32 weeks, October 1970–May 1971. From a statistical association between asthma attack rates, 24-hour average concentrations from the monitoring stations, and daily minimum temperatures from airports near the study communities, it was concluded that 24-hour suspended sulfate levels of 12 $\mu g/m^3$ on cooler days (T_{min} equal to 30 to 50°) and 7.3 $\mu g/m^3$ on warmer days (T_{min} greater than 50°F) were thresholds for the induction of excessive asthma attacks. No firm evidence could be found to associate elevations in sulfur dioxide (100 to 180 $\mu g/m^3$ on 10 percent of days) with excessive asthma attack rates on either cold or warmer days.

Regarding exposure levels, there is much less assurance that daily average levels throughout a community would be more or less uniform than would be the case with annual average levels. More monitoring stations might have been operated, or mobile stations used, to determine how pollution exposure varied from location to location. The determination of such differences in air pollution concentrations might have been important, but probably more important is that the other factors (in addition to the observed air pollutants) that could have caused or contributed to the asthma attacks were not examined. It would not be worthwhile to refine the information on the distribution of the air pollutants studied, unless a greater effort were made to study all of the various possible causes of the asthma attacks more thoroughly.

The study focused on the effects of minimum temperature. The possible effects of other meteorological variables could also have been explored. Of particular interest would be the effects of sudden, large temperature changes.

It is not made clear why minimum instead of average, or even maximum, temperatures were picked for correlation. Generally there would be less actual exposure to minimum temperature, which usually occurs about sunrise, than to warmer temperatures. Asthmatics would generally be expected to protect themselves from colder temperatures, staying indoors and keeping windows closed, whereas on warmer days they might be more subject to exposure to outdoor air with its assortment of possible allergens. There are diverse reasons why temperature might be an important factor determining asthma attack rates. No attempt was made in the study to provide an explanation.

It is expected that there would be noticeable temperature differences between Riverhead (the Low community) and Queens (the Intermediate I, community). Although it is stated that the temperatures come from nearby airports, the temperature curves plotted in Figure 5.4.1 seem to be identical for both communities. It may be noted that a different curve is plotted for the low community Figure 5.5.2.

(Figure 5.4.4) Although at a glance it appears that for the Intermediate community that the "Attack Rate" and the "Suspended Sulfate" curves are similar, close inspection shows that more often than not, they are out of phase. Between the 2nd and 3rd week the attack rate (AR) curve continues down as the suspended sulfate (SS) curve starts up, between the 10th and 11th week the AR-curve continues down after the SS-curve starts up, between the 14th and 16th week the AR-curve goes up while the SS-curve continues down, between the 19th and 20th week the AR-curve starts up while the SS-curve continues down, and again on the 27th week the AR-curve rises a week before an increase in the suspended sulfate concentrations. In all, three of the five increases in attack rate precede, rather than follow, increases in suspended sulfate concentrations.

13. Frequency and Severity of Cardiopulmonary Symptoms in Adult Panels. 1970–1971 New York Studies (Paragraph 5.5).

Symptom diaries were maintained daily for the 32-week period October 8, 1970 through May 22, 1971, by four panels, depending on state of health. The panelists were distributed in three communities

and lived within 1.5 miles of air pollution monitoring stations. It was concluded that elderly panelists in the low exposure community reported higher symptom rates on days when sulfate levels exceeded 10 $\mu g/m^3$. There seemed to be good evidence of a threshold effect between 6 and 10 $\mu g/m^3$, with a greater morbidity excess on warmer days.

Since suspended sulfates seem to be more uniformly distributed than a pollutant such as sulfur dioxide, the concentrations determined by monitoring should be generally representative of outdoor exposure ar d in most cases indoor and outdoor average exposures would be expected to be similar. The question not answered by this study is whether or not the panelists are also being exposed to some other causative agent, or stress factor, that might happen to correlate with the sulfate concentrations. It, and not the suspended sulfate concentrations, might be the cause of the observed health effects.

(Page 5–91) (Figure 5.5.3) The low value of sulfur dioxide that began at the 19th week and continued until the 24th week are suspected of not being true values. Near the end of the last paragraph on the preceding page it is suggested that meteorological conditions may have been responsible. A careful study of the meteorological conditions and fuel usage would be necessary to determine if these might have caused the persistent low concentrations. However, a scanning of the daily local climatological data shows no obvious reason for the reported low values.

Furthermore, the minimum temperature curve for the Low community in Figure 5.5.2 is not the same as given in Figure 5.4.1.

The New York Department of Air Resources also reported a large drop in concentrations following the mid-winter peak}at the Queens (Intermediate I) monitoring station, but reported values were never as low, and a period of low values was not followed by a rise as shown in the Figure. Further, the low values shown, which are about 25 $\mu g/m^3$, or .01 ppm or less, are quite low for the New York metropolitan area. Average weekly low values two or three times this value would generally be expected for a comparable period.

*14. Ventilatory Function in School Children: 1970–1971 New York
Studies (Paragraph 5.6).*

Pulmonary tests were made in three elementary schools in communities with different air pollution levels, and there were four rounds of testing, November-December 1970, January 1971, February-March 1971, and April 1971. The children lived within 1.5 miles of a particular air monitoring station. The Queens monitoring station is on top of a school where the testing was done. However, the Bronx station is on top of a "court house in the center of a busy commercial area" (page 5–6) and may not be close to the school. For the Riverhead community it is not made clear whether or not the school and the monitoring station are at the same location or near each other. It is assumed that the schools in Riverhead and the Bronx were within 1½ miles of the monitoring stations, but this is not actually stated.

It was concluded that 9 or more years exposure to annual sulfur dioxide levels of an estimated concentration of 131 to 435 $\mu g/m^3$ (accompanied by suspended particulate levels of about 75 to 200 $\mu g/m^3$) and suspended sulfate levels of about 5 to 25 $\mu g/m^3$ can be

associated with a small but significant impairment in ventilatory function. These values are from Table 5.6.2, and are the extreme high and low values listed. There is an implication here that the low concentrations, 131 $\mu g/m^3$ for sulfur dioxide and 5 $\mu g/m^3$ for suspended sulfates represent threshold values. Actually they are only annual average concentrations for the years 1969 and 1970. The observed health effects may have been the result of exposure to much higher concentrations in other years, or to some other cause.

15. Ventilatory Function in School Children: 1967-68 Testing in Cincinnati Neighborhoods (Paragraph 6.1).

This study included a pair of public elementary schools in each of six neighborhoods differing in socioeconomic level, race, or pollution exposure. All children in one or two classrooms of the second grade of the elementary schools were asked to participate in the study to achieve sample sizes of 60 to 75 children in each·of the six study sectors. Ventilatory performance as measured by a spirometer was obtained 12 times from each child: once weekly in the months of November 1967 and February and May 1968. The tests were administered on Tuesday and Wednesday mornings.

Air monitoring stations were placed in locations within three blocks of each school to provide samples representative of the air quality in the neighborhood served by the school. No information is reported on the distances of the homes of the children from the school. Apparently it was assumed that the home environment and the school environment were the same. Indoor soiling index and sulfur dioxide observations were taken in the schools, but results are not reported. It is reported that it was determined that indoor and outdoor sulfur dioxide, soiling index, and suspended particulate levels measured over the 24-hour or 4-hour period directly preceding pulmonary function tests did not consistently correlate with the test values.

Details of this lack of correlation are not given, but it was concluded that "ventilatory performance of children thus did not appear to be acutely affected by variations in pollutant levels on the day of the test." Possible exposures over intermediate periods, say three days or one week, prior to testing were not considered. Conclusions seem to be based on possible long-period exposures, probably over a lifetime.

Concentrations of sulfur dioxide were low (less than 52 $\mu g/m^s$) in all areas, so health effects were attributed to particulate pollutants independent of atmospheric levels of gaseous sulfur dioxide.

Average sulfate levels during the period of the study were observed to be between 8.9 and 10.1 $\mu g/m^s$, in the polluted lower middle white community, but previous average exposure was estimated to be 10.7 to 12.1 $\mu g/m^s$, based on the National Air Surveillance Network station. The average suspended sulfate level in the clean white sectors was 8.3 $\mu g/m^s$, a relative difference of 13 percent. (The largest differences in area exposure were in the concentrations of suspended particulates. Levels of total suspended particulates were 131 $\mu g/m^s$ in polluted sectors and 61 to 92 $\mu g/m^s$ in clean sectors.

In reading this paper one wonders about the psychological interaction between the children and the team members administering the tests, who could anticipate the outcome of the experiment. The curves for the black children in Figure 6.1.3, are particularly interesting.

SUMMARY ASSESSMENT OF CHESS POPULATION STUDIES

The 1976 Investigative Report (IR) on page 76 states:

> No formal methods are used to link specific pollutants with specific health effects in the CRD, LRD, ventilation, and ARD studies. If a demonstrated health difference between communities cannot be explained in terms of imbalances in known covarieates, it is generally ascribed to pollution. It is not possible to know which specific pollutants, if any, or what concentrations of any suspect pollutants, were responsible for the health effects. The health effects data provide at most a rough guide for making general judgments about probable health effects in other communities with similar pollutant sources, meteorology and population composition.

> The methodology used in the panel studies (asthma and cardio-pulmonary) attempts to disentangle the effects of the several pollutants. The multiple regression and relative risk calculations are interpreted as implicating...

> ...these formal methods do not provide logically compelling evidence that SS, or indeed any of the measured pollutants is of dominant importance. The remarks are meant to aid in the assessment of the validity of the conclusions presented in the Monograph and to assist researchers performing similar studies and encountering similar difficulties. This endeavor was greatly assisted by hindsight.

Other specific criticism of the 1974 CHESS studies have been that:

1. Since ARD incidence has not been related to smoking habits consistently all of the results must be suspect. The results from studies of ARD have been inconsistent and the reason is not clear.

2. Since increases in some adverse effects, e.g., LRD have not always been consistent with the indicated pollution gradient shown by multiple study communities the data are not valid.

3. Because the arbitrary scores developed to indicate LRD severity or ARD severity seem sometimes not to represent a consistent gradient, the entire system is suspect. An accurate gradient may not be expressed by an increasing numerical score, though the lowest scores represent less severe illness than do the highest.

4. Because consideration was not always given to exogenous smoking and thus secondary exposure, or because ethnic or religious factors were not considered in the analyses, the results are suspect.

5. Panel study comments:

a. Many relevant factors, including medication (steroids), humidity, exercise, daily temperature changes, nitrogen dioxide levels, and exposure to smokers at home or work were not evaluated.

b. The overreporting of asthma attacks on weekends would tend to invalidate results. Higher reported rates of asthma attacks occur on weekends when pollution levels generally are somewhat lower.

c. The underreporting of attacks as the length of subject participation grew longer.

d. Reporting of attacks on heavy consecutive days suggests a lack of association with pollution. In many individuals the occurrence of an asthma attack can be triggered by many stimuli.

e. Daily measurements of air pollution are so poor that they cannot be correlated with daily changes in symptom aggravation.

f. Failure to consider such factors as pollen density, indoor pollutant concentrations, location where episodes began, and medication taken by study subjects, cases doubt on the validity of the data collected.

Comments for the future contained in the IR (1976) on page 16 included:

"The overall impression left with the review groups was a general awareness of many of the problems we found in the air quality health effects research area.

Specifically, questions such as the following must be resolved for future epidemiological studies:

(1) How do CRD questionnaire responses change on serial administration in an area with unchanging pollution patterns?

(2) What is the sensitivity of the self-administered CRD questionnaire compared with its use in an interview?

(3) What is the nature of the statistical dependence of-ARD * attack rates, and what formal statistical methods are appropriate to the analysis of relative attack rates?

(4) What can be done to tighten the eligibility requirements
for asthma and cardiopulmonary panels?

(5) How can the statistical analysis of asthma and cardiopulmonary
panels be improved?

(6) What combination of CHESS health measurements is most
appropriate to long-term serial surveillance?

(7) What combination of CHESS health measurements is appropriate
to intensive studies of specific pollution hazards?"

It is apparent from previous comments in this chapter and this section

that the Investigative Reports' comments (IR, 1976) apply to all past related

epidemiologic studies. Yet, even the Committee indicated that the health

effects were there. Some sense can be made from previous findings as well

as for planning future studies.

Section IV of the 1976 Congressional
Investigative Report (IR) concerning
CHESS air quality measurements is as
follows:

IV. CHESS AEROMETRIC MEASUREMENTS

A. INTRODUCTION

As pointed out in the introduction, the attainment of precise, reliable, reproducible, and real time air quality measurements in the field (e.g., SO_2 and particulates) was a critical element of the CHESS program. This chapter provides a critical review of the aerometric measurement aspects of CHESS.

However, before reporting on this review two facts about CHESS aerometry should be mentioned. First, the methods used in CHESS, especially in 1970–71, were probably as good as any available. Second, quality control procedures were slowly introduced into the CHESS program. EPA cannot be criticised, and is not criticised in this report, for using the best available methods. However, EPA can be criticized for not pursuing a vigorous program of quality control throughout CHESS. The review reported here showed that CHESS did not employ well-established quality control measures. The quality control program described in Appendix A of the Monograph was not carried out. A thorough quality control program would have discovered, for example, the temperature effects on the method used to measure SO_2 (described below). It would also have placed bounds on the validity of the data and precluded overinterpretations.

In the design and implementation of any measurement system, the single most important consideration is the end user of the data produced by that measurement system. In the simplest of all measurement processes, an individual scientist conducting his own research, both measures the parameters of interest and uses the resultant data to draw conclusions about his experiment. In such a process the individual involved has at his disposal all of the information contained in the data, especially that concerned with the limitations of the data and the constraints under which they should be used. In this type of situation, few formal qualifications of the recorded data are necessary since those qualifications are implicit in the mind of the scientist.

In larger programs however, the measurement process and the utilization process are quite often compartmentalized such that one group of scientists is responsible for the collection, quality assessment and storage of the measurement data, and a second, usually nonrelated, group of scientists is responsible for the synthesis of all pertinent information into a final set of conclusions. In this type of systems research, the determination of the fundamental quality of the measurement data and transmittance of that quality assessment are the single most important qualifier in the process of going from observation to understanding.

The CHESS program, as designed and implemented by the Environmental Protection Agency, is a classic example of the large systems approach to research. The epidemiological measurements were designed, conducted, and stored by one group of scientists; the

(25)

aerometric measurements were designed, conducted and stored by a second group of scientists. The desired end product, a correlation of health effects with atmospheric pollution was then derived from these two independent sets of data accumulated in a large data storage network. It is important to reemphasize here that in such a research program it is incumbent upon the measurement personnel to transmit to the data user all of the information contained in the resultant data, especially that relative to accuracy and precision. In order to understand the problems encountered in a large research program such as CHESS, it is necessary to understand the types of measurements that were made.

The assessment of atmospheric pollution exposure received by a defined population can be derived from one of two broad classes of measurement. The first is a measurement that yields an "index" of pollution. The second is a measurement that yields quantitative information about a specific pollutant as it is found in the atmosphere.

A pollution index is a measure of the relative level of pollution which contains little or no information as to the specific chemical or physical properties of that pollution.* These indices can be useful in assessing short-term trends of atmospheric quality in well-defined and limited geographic regions. They cannot be used to deduce information about the source or chemical nature of the material being measured. They also cannot be used to assess long-term trends of pollution burden since gradual changes in pollution sources will distort the quantitative aspect of the index. Most importantly, they cannot be used to correlate atmospheric pollutant levels among diverse geographic areas. Here again, the difference in chemical and physical makeup of the pollutants being measured distort the quantitative aspect of the index.

An example of a measurement that gives a pollution index is the dustfall observations as applied in CHESS. In this method, an open topped cylinder called a dustfall bucket is used to collect any particulate matter that falls out of the atmosphere. This collection is carried out over a long time period, usually one month; and the total dry weight of material collected is used to estimate particulate burden of the atmosphere during that time period. A detailed description of this process is given later in this Chapter. This measurement falls in the index class because all solid material, regardless of its derivation or chemical nature, is included in the final quantitative result.

The second class of pollution measurement is that which contains information both on the specific species of pollutants and on the atmospheric concentrations of those pollutants. In this type or measurement the signal that is measured is derived from a process or property which is specific to the pollutant of interest and which correlates directly with the concentration of that pollutant in the atmosphere. An example of this type of method is the West-Gaeke procedure for the measurement of atmospheric sulfur dioxide. In this procedure, air is bubbled through an absorbing solution at a known rate. The solution is specific for the absorption of SO_2 from the air. After a known duration of sampling, the quantity of SO_2 which was absorbed from the air is quantitatively determined by the formation of a

* N.B. This index is not the kind of "air quality index" often used popularly (in radio broadcasts, etc.) to advise citizens of the relative air quality of a city. Such popular air quality indices are usually arrived at by combining measurements of several pollutants.

colored chemical complex of SO_2. If carefully carried out, the procedure gives an accurate value for the SO_2 concentration. The procedure is described in detail later in this Chapter.

Measurements such as the West-Gaeke procedure, which are specific and quantitative, can be used to compare atmospheric pollutant burdens across diverse geographic areas and through long time periods. They can also be used to assess short-term variations in pollutant levels provided that sufficient sensitivity exists in the method to obtain a meaningful signal for the short time period used. In conducting a program such as CHESS, where an attempt is made to relate health effects to pollution burdens, only those measurements that fall in the second class, specific and quantitative, can properly be used to assess the relation between health effects and pollutant burden.

In this chapter, an attempt will be made to evaluate the methodology used to measure aerometric parameters and to assess the validity of the resultant data. The review will encompass procedures used in the field situation, the quality control exercised over the procedures, and the data storage and retrieval network. Conclusions will be drawn as to the adequacy of the measured pollution levels to assess exposures received by specific CHESS population groups.

B. Review of Chemical and Physical Methods

1. THE WEST-GAEKE METHOD FOR THE MEASUREMENT OF AMBIENT SO_2

a. Description of the Method

The West-Gaeke colorimetric procedure for SO_2 determination is the designated Reference Method (Federal Register, 36, No. 84, 6105, April 30, 1971).* Atmospheric SO_2 is collected by bubbling air through a solution of potassium tetrachloromercurate (TCM). The product of the reaction between SO_2 and TCM is the nonvolatile dichlorosulfitomercurate that is then determined quantitatively by reaction with formaldehyde and pararosaniline hydrochloride, followed by photometric measurement of the resulting intensely colored pararosaniline methyl sulfonic acid.

b. Description of the Field Apparatus and Sample Collection

Outside air is drawn through a sample line at the rate of 200 ml min⁻¹, then through a 6-inch long glass bubbler stem (tip diameter of 0.025 in.) immersed in 35 ml (50 ml after January, 1974) of 0.1 M TCM solution contained in a 32 mm diameter by 164 mm long polypropylene sample container. The exhaust air passed through a glass wool moisture trap, then through a hypodermic needle used as a critical orifice to control the flow, through another moisture trap, and finally through a vacuum pump. A sample consisted of a 24-hour collection. Collected samples were stoppered, and mailed to EPA/RTP for analysis.

c. Validity as a Laboratory Procedure

A collaborative study by McKee et al. (H. C. McKee, R. E. Childers, and O. Saenz, Southwest Research Institute, SWRI Project 21-2811, EPA contract CPA 70-40) indicates that "the method can-

*Alternately see CFR Title 40, Part 50, Appendix A.

not detect a difference smaller than 10 percent between two observations by the same analyst in the range of 0 to 1000 μg m^{-3}. A difference of 20 percent or less may be detected above 300μg m^{-3}, and a difference of less than 50 percent may be detected above 100μg m^{-3}." For analyses conducted by different laboratories on the same sample, "the method cannot detect a difference of less than 20 percent between single-replicate observations of two laboratories in the range of 0 to 1000 μg m^{-3}. At a level of 100 μg m^{-3}, a difference of less than 100 percent is not detectable." The National Primary Ambient Air Quality Standard for SO$_2$ is: For 24 hour average, 365 μg/m^3. For annual average, 80 μg/m^3. Thus if the standard is met, most values will be around or below 80 μg/m^3, no more than one will be above 365 μg/m^3.

Regarding the lower limit of detection, the authors cited above propose a value of 25 μg m^{-3} as a practical figure. "A single determination less than this value is not significantly different from zero" (Instrumentation for Environmental Monitoring, Air-SO$_2$, Instrumentation, Lawrence Berkeley Laboratories, March 1972).

It is therefore evident that a single analysis is of little use, considering that the expected concentrations of SO$_2$ will usually be less than the ambient air quality standard of 80 μg m^{-3}. Results should be regarded as valid only in terms of the mean of multiple determinations, and only when the analytical method has been followed rigorously by experienced analysts.

2. TOTAL SUSPENDED PARTICULATES

Total suspended particulates (TSP) were measured using the EPA Reference Method as specified in the Federal Register (*36* (84): 8191–8194, April 30, 1971‡).

Total suspended particulates (TSP) were measured by drawing air through a prewieghed 8 x 10 inch glass fiber filter for a period of 24 hours. The apparatus used for this procedure was the standard High Volume Sampler. At the end of the 24 hour time period, the filter was reweighed, and the TSP computed on the basis of total air flow. The air flow rate was approximately 60 ft^{3}min^{-1} at the start, and must be not less than 40 ft^{3}min^{-1} at the end for the measurement to be acceptable. The average air flow rate was computed on the basis of a straight-line interpolation between beginning and ending flow rates.

The National Primary Ambient Air Quality Standard for TSP is: For 24 hour average, 260 μg/m^3. For annual geometric mean, 75 μg/m^3.

3. SUSPENDED SULFATE

Suspended sulfate was analyzed, during the CHESS program, using portions of the TSP samples. From the beginning of CHESS to September 1971 the turbidimetric method of analysis was used; then the turbidimetric method was dropped in favor of the methylthymol blue method, which was used throughout the remainder of the CHESS program.

The turbidimetric method consists of the water extraction of soluble sulfates on the TSP filter, the addition of a barium chloride preparation to the extract, and measurement of the resultant turbidity (from

‡ Alternatively see CFR Title 40, Part 50, Appendix B.

the formation of insoluble barium sulfate) with a spectrophotometer or colorimeter. Accuracy of the method is affected by the kind and concentration of other ions present, as well as pH, conductance, temperature, and barium concentration in the test solution.

The methylthymol blue method also utilizes the water extraction of soluble sulfates from the TSP. The filter extract is then passed through an ion-exchange bed to remove interfering ions, and barium chloride is added under slightly acid conditions, forming barium sulfate. Then the test mixture is made alkaline and methylthymol blue is added, which forms a chelate with the excess barium. The uncomplexed methythymol blue is equivalent to the amount of sulfate present, and is measured spectrophotometrically. The methylthymol blue procedure is automated (Technicon Autoanalyzer) in all steps following water extraction of the TSP, and this part of the procedure is reproducible within a range of 2 percent. Error in the determination of sulfate occurs predominantly in the steps preceding the methylthymol blue method.

4. DUSTFALL BUCKET, TAPE SAMPLER, CASCADE IMPACTOR, AND CYCLONE SAMPLER

In addition to TSP measurements using the Hi-Vol sampler, four other means of estimating particulate concentrations were used at various times. They are the dustfall bucket, the tape sampler, the cascade impactor, and the cyclone sampler.

(a) The name "dustfall bucket" is adequately descriptive. It is basically an open-topped cylinder, with some protection against wind and rain loss, that is left out in the open, close to the ground or on a rooftop, for a month. At the end of that time the dry matter collected is weighed, and sometimes analyzed for trace metals. The dustfall bucket method is very crude and misses almost completely the very significant part of the aerosol, including the respirable aerosol, that does not settle rapidly. It must be considered here, however, because dustfall measurements were extrapolated to obtain estimates of suspended sulfates and sulfur dioxide in New York City during the period 1949-58 ((Table 5.2.1, CHESS Monograph), and intermittently in Chicago (Table 4.1.A.3), CHESS Monograph). Dustfall measurements were used as the basis for these extrapolations because there was no other basis for such estimates, but it must be remembered that the relationship between suspended sulfates and dustfall is unknown, and that between sulfur dioxide and dustfall is another step removed from reality.

(b) Coefficient of Haze (COH) is determined by the automatically operating tape sampler. It is determined by measuring the optical density of an aerosol deposited on a filter tape. The aerosol deposit is obtained by drawing air at a given flow rate through white filter paper tape for a known period of time. If one could assume that the composition and physical characteristics of the aerosol in a given location did not change with time—that only atmospheric loadings would change—then the COH would give a fairly good approximation of the variations of particulate loading and visibility.

However, this assumption is seldom justified, and even at a given location the COH only roughly approximates the true particulate loading. The COH method is worthless, or nearly so, for comparisons between areas with dissimilar aerosols. For example, the aerosols

collected at the Utah sites are primarily the light-colored alumino-silicate dust, whereas the aerosol collected within the inner core of large cities has a predominantly sooty character. For a given particulate loading the Utah aerosol will often have as little as one-tenth the optical density of the urban aerosol.

(c) The cascade impactor operates on the principle that particles in an air stream will tend to follow a straight line when the air stream is deflected, and thus can be impacted on a surface in their path. The cascade impactor consists of a series of parallel plates separated by precisely determined spaces. Alternate plates contain a certain number of holes of a size that is decreased as one goes through the series of plates from entrance to exit. Alternating with the plates containing the calibrated holes are plates without holes. These may be coated with a medium for the trapping of impinged particles. Air is drawn through the apparatus at a known rate, and the particles are collected in decreasing size fractions related to the decreasing size of the holes in the plates.

(d) The cyclone sampler is a device for the collection of the respirable size fraction of an atmospheric particulate loading. It operates on the principle that the inertia of individual particles will tend to keep the particles moving in a straight line when the air stream in which they are carried is deflected. By this means the larger size particles are removed by impaction and settling, while the respirable particles are carried along with the air stream and are subsequently collected on a filter.

C. FINDINGS AND EVALUATIONS OF MEASUREMENTS AND DATA REDUCTION

It is important to preface this evaluation of the CHESS air monitoring program with a statement of the following facts. The investigative team looked backward at the program through a window in time with all of the subsequent knowledge built up during that time. More than ten years have passed since the initial planning of the CHESS program and more than six years have passed since the first data were collected. During that time there has been a vast improvement in the understanding of the methods used for pollution monitoring. Many of the procedures used in CHESS have subsequently been found to contain serious errors. These problems were often uncovered as a direct result of research and quality control programs ongoing within EPA. It would thus be unjustified to lay criticism on the principals in the CHESS program for using state of the art measurement technology.

On the other hand, some serious oversights in scientific judgement did occur. In the area of pollutant monitoring, these oversights could have been completely avoided had proper attention been paid to even rudimentary quality control procedures. Throughout the program, much more emphasis was placed on the uninterrupted collection of data than was placed on the systematic evaluation of data quality. The field investigation stage of this review identified numerous problems that resulted in the propagation of unnecessarily large errors in the aerometric data. These unevaluated errors persist even today in the data as it is stored in the CHESS computer system. They could have been avoided or easily discovered and quantified had a well-

designed quality control procedure been applied to the CHESS aero-
metric monitoring program. This statement is contrary to the state-
ment of the quality control procedures in appendix A of the 1974
CHESS Monograph. Appendix A was not a manual provided to
CHESS data gatherers, but was written long after the data in the
1974 Monograph were collected. However, during the field investi-
gation of the CHESS monitoring contractors, it was found that the
quality control procedures as described in Appendix A of the CHESS
Monograph were routinely disregarded. In fact, for the first two years
of the program, virtually no EPA-directed quality control program
was implemented at any of the New York, Salt Lake City or Los
Angeles CHESS monitoring sites. Problems that were found in this
time period were observed and documented by contractor personnel
and it was mainly through their personal professional conduct that
any of the field problems were corrected. Reasons for this rather
gross oversight on proper data management can only be conjecture,
but it did appear that inadequate staffing of the monitoring group,
coupled with the intense pressure to get the monitoring stations on
line and producing data, led to the situation described.

In fairness (regarding the time perspective mentioned earlier) the
problem of inadequate quality control on many large EPA programs
eventually was recognized internally and in 1974 a Quality Control
Branch was established in the Quality Assurance and Environmental
Monitoring Laboratory. This branch was given the authority to im-
plement proper quality control procedures on all large atmospheric
monitoring programs. Since the formation of this group, there has
been a significant and steady improvement in quality assurance as
applied to air monitoring methods and data.

In this section, major emphasis will be placed on review and evalu-
ation of the analytical methodology used in the CHESS program to
assess population exposures to sulfur oxides and total suspended
particulates. Conclusions will be general to all data taken at "official"
CHESS monitoring sites, regardless of location. Where local differ-
ences in procedures or resultant data did occur, these will be described
separately. Health studies, as described in the 1974 CHESS Mono-
graph, that used aerometric data derived from non-CHESS monitor-
ing sites will be reviewed separately.

1. SULFUR DIOXIDE

Atmospheric levels of SO_2 were determined using the EPA Ref-
erence Method, better known as the West-Gaeke or Pararosanaline
method. The specific details of this method are described in the
procedures section of this chapter (Part B.1.). However, a few im-
portant aspects of this method will be reiterated. This reference
method is basically a laboratory method adapted for field use. It is
a "wet chemical" procedure relying on a gas-liquid phase chemical
reaction between SO_2 and sodium tetrachloromercurate (TCM). To
accomplish this reaction, the SO_2 as a gas phase pollutant, must be
quantitatively absorbed into the liquid reactant solution. This is
accomplished by bubbling ambient air through the solution at a
controlled flow rate, thus, its description as a "bubbler method."

In an attempt to standardize the methodology and to eliminate problems associated with interlaboratory errors, a CHESS policy was instituted whereby all air sampling equipment was assembled and tested at the central EPA research laboratory and then shipped to the contractors for field use. Also, bubbler tubes were prefilled with the appropriate absorber solution, shipped to the contractor for their daily monitoring use, and shipped back to the central laboratory for chemical analysis. It was this long distance shipment of the chemical solutions that led to the first of a series of field-use problems with the procedure. These problem areas will be summarized below with an attempt to evaluate their net effect on the resultant CHESS SO_2 data. Following this summary of individual problem areas, an assessment of the overall SO_2 data quality will be given.

a. *Spillage of Reagent During Shipment*

The first field data were obtained in New York City and the Salt Lake area (Utah) in November, 1970. By mid-1971, field personnel at the Utah site reported to their CHESS field engineers that severe spillage was occurring during shipment. Many bubbler tubes were arriving partially filled with reagent and some were completely empty. At the Salt Lake area an attempt was made to refill with solution from extra tubes those tubes that were low. However, due to insufficient reagent, this was only partially successful. This problem was not officially recognized until October, 1972, at which time an internal EPA/CHESS memo was written outlining the problem and suggesting corrective action. The magnitude of the problem can be best assessed by quoting from the memo. "The present reagent tubes for SO_2 and NO_2 leak during shipment. . . . The SO_2 leakage rate (was found to be) 18% of the total volume, 50% of the time. . . . It follows therefore, that the resultant pollution data *are unreliable.*" Recommendations were made in this memo as to possible corrective measures. These recommendations were not instituted until March, 1973.

During the subsequent years, many attempts were made to correct this leakage problem. However, none were wholly successful and as late as January 1975, another EPA memo described losses of solution in SO_2 bubblers during shipment and suggesting appropriate corrective action.

The effects of the reagent spillage problem on the SO_2 data can be only grossly estimated. Certainly, many samples were totally lost. These lost samples were not the major problem. Of more significance was the undetermined amount of daily SO_2 data that were in error due to the loss of sample by spillage and yet included in the network system.

If the reagent was partially lost during shipment to the sampling site and used as received, an increased concentration of TCM-SO_2 complex would occur relative to normal sampling. This potential positive bias would be corrected by for the analytical procedure used (Page A-6 CHESS monograph—Analysis Procedure). "At the laboratory, the sample is brought back to its original volume by the addition of distilled water to compensate for water loss during sampling." If however, the reagent spillage occurred after sampling, the required addition of water would result in data that were biased low in proportion to the amount spilled relative to the total volume of solution.

According to the EPA Memo of October, 1972, one half of all SO_2 data taken between November, 1970 and March, 1973 are likely to have been biased low by an average of 17%. This problem was corrected after April, 1973.

b. Time Delay of the Reagent—SO_2 Complex

The Reference Method as originally described in the Federal Register, was to be conducted at 20° C. There was a known error in the method associated with time delay between sampling and analysis which was dependent on temperatures. This error was derived from the spontaneous decomposition over time of the TCM-SO_2 complex as a function of temperature. The magnitude of the error and its exact dependence on temperature was not known but a brief study was conducted to determine its magnitude by scientists of the CHESS monitoring group in November, 1971. As a result of this study, a correction factor of +1.5% per day was arithmetically applied to all CHESS SO_2 data to compensate for the time delay between sampling and analysis.

A more recent and comprehensive study has been carried out within the Quality Control Branch, Environmental Monitoring Laboratory at EPA on the effect of temperature on "The Stability of SO_2 Samples Collected by the Federal Reference Method." This study indicated a much more severe problem than was estimated by the original CHESS study. The evaluation was carried out over the range of 35 to 278 $\mu g/m^3$ SO_2 concentration. The following findings were presented in the report:

Over a normal range of temperature, the rate of decay of the TMC-SO_2 complex increases five-fold for every 10°C increase in temperature, respectively.

The rate of decay is independent of SO_2 concentration.

At 20, 30, 40, and 50° C the following SO_2 losses were observed: 0.9, 5, 25, and 74% loss per day, respectively.

This study makes abundantly clear a second and even more severe error associated with the SO_2 measurements conducted by CHESS. During the summer months, when the SO_2 absorber solutions were subjected to high and unknown temperatures between field sampling and laboratory analysis, significant degradation of the samples did occur. Estimates of time delay between sampling and analysis range from 7 to 14 days. Estimates of summer temperature exposures range from 25 to 40° C being most severe for the Utah CHESS sites. Thus, CHESS SO_2 data can be estimated to be negatively biased, mainly during the summer months. It would normally be difficult or impossible to estimate the magnitude of the bias except to say that it is probably large. However, simultaneous SO_2 measurements were taken by the New York City Department of Air Resources and by the Utah State Division of Health. These results were obtained by an independent method not susceptable to the temperature related error. A consistent pattern emerged when side by side data are compared. From May to October, the CHESS SO_2 data were low with the largest error occurring in the middle three summer months. The magnitude of the error varied from month to month and year to year, but the CHESS data were consistently low and represented only a portion of the true ambient SO_2 concentration.

c. *Concentration Dependence of Sampling Method*

The SO_2 reference method was subjected to a collaborative study program in 1973. Four participating laboratories tested the 24-hour version of the Federal Reference Method. A previously unknown source of error was documented that applies to the CHESS SO_2 data. It was found that the 24-hour sampling method does have a concentration dependent bias which becomes significant at the high concentration levels ($200\mu g/m^3$). Observed values tend to be lower than the expected (known) SO_2 concentration levels. This error source will yield a negative bias on the daily CHESS SO_2 data when they exceed 200 $\mu g/m^3$ and on all monthly and yearly average data.

d. *Low flow correction*

The determination of atmospheric SO_2 concentration was dependent on, among other factors, the accurate measurement of air that passed through the TCM solution. This flow was controlled by a critical flow orifice in the form of a standard hypodermic needle. In practice, the air flow through the sampling system was measured at the start and end of each 24-hour sampling period. This was done to detect low flow due to needle blockage. The Federal Register Method (Reference Method) calls for an air flow of 200 ± 20 ml/min. In field operation, the CHESS procedure substantially broadened these tolerances. Replacement needles were installed if the initial air flow was greater than 220 ml/min which is consistent with the Reference Method; however, needles were not replaced nor were samples voided until the measured flow dropped below 100 ml/min. Integrated flows were calculated by assuming a linear decrease in flow between the start and end of the 24-hour sampling period. If, however, the needle was partially blocked near either the beginning or the end of the sampling period, the linear flow correction would be in error. Using the Reference Method flow tolerance, only small errors would be introduced by this correction (less than 10%). Using the CHESS procedure, however, errors as large as 50% could be introduced and not detected. These errors would be random (either positive or negative) depending on when during the sampling period the needle blockage occurred. Thus a large random error component was added to the SO_2 daily data but this component was somewhat damped statistically in the monthly or yearly averages.

The modification of flow tolerance by the CHESS aerometric group is a procedure that would not have withstood the critical review of a competent quality assurance program.

e. *Bubbler train leakage*

The West-Gaeke method, as described in the Federal Register, employs a vacuum bubbler train. That is, the sampled air is drawn through the bubbler train by a vacuum pump rather than being pushed through by a positive pressure pump. There are many advantages to the vacuum procedure, most important is that the air does not come in contact with any internal pump mechanism. However, there is a modest pressure differential between the atmosphere and the internal bubbler; thus all fittings and joints must be gas tight. The bubbler train used in the CHESS program had two points where frequent air leak problems were encountered. One was around the rubber stoppers for the bubbler tube and moisture trap and the other was the

rubber tubing used to hold the glass assembly pieces together. Field operators reported consistent problems with leakage in the routine field use of the bubbler train. In a severe leak situation, the samples were voided due to out of tolerance (Low) flow rates. There were many cases however, where small leaks occurred but the final flow was within specifications so the sample was included as valid. In cases where the leaks formed around the rubber stoppers, no significant error would be introduced except due to the linear flow correction as applied to instantaneously developing leaks. This error is similar in nature to that discussed in the flow section. In the case of leaks upstream of the bubbler train, room air instead of outside air is drawn through reagent. In normal situations, it has been observed that room air is significantly less polluted than outside air. (See page 6-6. CHESS Monograph—comparison of school air to outside air). This effect may not be as large for the small buildings used to house CHESS stations, but a somewhat decreased pollutant level would undoubtedly be sampled. The absolute magnitude of this error cannot be adequately assessed but it can be stated that the error would be in a negative direction, that is, again to underestimate SO_2 levels.

2. GENERAL ASSESSMENT OF CHESS SO_2 DATA

The SO_2 data, accumulated at "official" CHESS sites, followed a remarkably uniform trend as the program progressed. The method used was the EPA Reference Method which is specific for the chemical species, SO_2. Thus, regional changes in pollutant mix, i.e., the proportion of other pollutant species relative to SO_2, had minimal effect on the SO_2 data. However, the sum effect of the errors detailed in this section did have a profound effect on both the accuracy and the precision of the data.

Under normal circumstances, a retrospective evaluation of a monitoring effort that occurred a number of years in the past and which had been terminated, could yield only the broadest of estimates of data quality. Fortunately for this review, two geographically different locations with six different monitoring sites were involved in the collection of simultaneous SO_2 data. Further, the groups responsible for the two data sets were managed independently and the methodology used was also independent. This fortunate circumstance enabled the reviewers to acquire a quantitative understanding of absolute differences among data sets as well as correlations with respect to time.

The locations where side by side data existed were the New York City sites at Bronx and Queens and the Salt Lake Basin sites at Ogden, Salt Lake City, Kearns, and Magna. In these locations, the local environmental monitoring agencies had sites located within 50 meters of the CHESS sites and at similar elevations. At these sites, the local agencies collected daily SO_2 and TSP data for the entire life of the CHESS program. The SO_2 methodologies used by both State agencies were variations of the peroxide bubbler method in which twenty-four 1-hour samples were integrated to form a single 24-hour SO_2 measurement. In New York the samples were measured acidimetricly and in Salt Lake City they were quantified conductiometrically. Neither method is as specific for SO_2 as is the Reference Method, that is,

pollutants that are in a significant concentration, relative to SO_2 and that also oxidize to form an acidic compound will be interpreted as SO_2. For this reason, when the NYC Department of Air Resources initially brought to the attention of the CHESS Aerometric team the large discrepancy between their respective data, the discrepancy was dismissed as method bias on the part of the New York method. An EPA memo dated November 3, 1971 described a limited study into the Reference Method. The conclusion reached was "On the basis of (this study) . . . I feel there is no sound basis for discrediting the EES (Environmental Exposure System) methodology."

No further attempt was made to uncover the cause of the discrepancy in SO_2 data. Had the CHESS EES team obtained and compared the Salt Lake Basin data, especially that from Magna site, a disturbing similarity would have been immediately apparent. This data confirmed in detail the discrepancies observed in New York. It is important that the Magna site data were confirmatory since it was in a region of single source pollution, that from the nearby copper smelter. In this site very low levels of other pollutants existed relative to SO_2, thus the peroxide method was capable of giving reasonably reliable estimates of the SO_2 concentration. Of equal importance the general pollutant mix was very different between this rural smelter site and the urban area of New York City. Despite these differences the comparison of side by side Federal-State data indicate the same discrepancies in both trends and absolute concentrations. The following conclusions as to SO_2 data validity can thus be reasonably drawn from the review of methodological errors and the comparison of existing side by side data.

From November 1970 until December 1971 the SO_2 data generated from CHESS sites using the modified Reference method were biased low by 50 to 100 percent in the High Exposure sites when compared with existing State SO_2 data. Thus, the 1971 annual average SO_2 exposure estimates of $60 \mu g/m^3$ as reported for Magna in the CHESS monograph (page 2-24) are more likely in the vicinity of 100 $\mu g/m^3$. Also, the same phenomenon occurred in New York and the reported values are also in similar error.

A confirming fact is that during cool months *after* 1971 SO_2 data correlated well both in trends and absolute concentrations between State and Federal analyses. It thus seems likely that the State data were reasonably accurate throughout that time period. However, one consideration must be applied here: namely, *that due to the difference between the independent methods an error bar of at least one hundred percent must be applied to the data and explicitly correct data cannot be drawn from these observations.* In other words, where two or more independent observations are in disagreement by a significant amount it cannot be said by inference alone that one data set is more correct than the other. It is reasonable to assume, however, from our review of all State and Federal data in the time period of 1970 through 1971, that the Federal SO_2 data as collected in the CHESS program were substantially low and went through an abrupt upward transition in concentration in December 1971 at all CHESS sites and Federal data taken before that time may reasonably be expected to have a large, unknown negative bias.

In November 1971, the CHESS monthly mean SO_2 data underwent an abrupt change in the positive direction. The cause of this change is not apparent. However, the result was profound. From that time until the conclusion of the CHESS program in July of 1975, the fall-winter data were in very good agreement with other existing data and very likely gave reliable estimates of SO_2 exposures.

Throughout the entire program, the CHESS SO_2 data had an associated negative bias during the summer months, becoming most severe during the hottest periods of July and August. This error usually reached a maximum of 60 to 80 percent underestimation of exposures and was variable. As a result, even though wintertime monthly SO_2 averages appear valid from 1972-1975, annual averages of the same data are biased low due to the inclusion of the summer errors. The best estimate of error in the annual average data 1972-1975 is approximately minus 15-20 percent relative.

The individual daily SO_2 levels, when compared to city or State data or to replicate CHESS measurements taken after 1973 had so large a random error component that they are not useful to assess daily SO_2 exposure (as attempted in the asthma panels). The random errors associated with the daily values were much larger than the differences observed over time.

Due to inherent methodological errors, the following may be considered as minimum differences between High and Low SO_2 exposures which may be considered "real." These are based on EPA's collaborative study of the reference method and used a 95 percent confidence interval.

Below 100 $\mu g/m^3$ SO_2, a difference of at least 50 $\mu g/m^3$ is necessary to be statistically significant.

Between 100 and 300 $\mu g/m^3$ SO_2, a difference of at least 60 $\mu g/m^3$ is necessary to be significant.

Below 25 $\mu g/m^3$, a single determination is not significantly different from zero.

3. TOTAL SUSPENDED PARTICULATE

The Reference Method for the determination of total suspended particulate matter (TSP) is probably the simplest and most reliable method used by CHESS. It has been well studied and most error sources are known. However, it is a method that measures an arbitrary and poorly defined portion of the total atmospheric particulate burden and the portion measured has unknown relevance to the human respirable portion. The size fraction measured is somewhat dependent on the design of the shelter used for Hi-Volume sampler. The design and dimensions of the Reference Method shelter are specified in the Federal Register, thus the portion of TSP that is collected by the method is generally uniform. Best estimates of particle size range included in the Reference Method are from 0.05 to 60 μm diameter. Above 60 μm diameter, the particle fall velocity is too great to navigate the bend around the roof of the shelter. Below 0.05 μm the collection efficiency of the glass fiber filter used in the method diminishes.

A collaborative study was conducted on the Reference Method using 12 different groups sampling ambient air at a common location. The results of this study indicate the method is capable of reproducible

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measurements with less than 5 percent error at the 95 percent confidence level. Also, the minimum detectable amount of TSP is approximately 2 µg/m³ for a 24-hour sampling period. This sensitivity is more than sufficient for most 24-hour TSP measurements.

The TSP measurement method, as used in CHESS, had one notable difference from the laboratory procedure which was collaboratively studied. The weighing procedure to determine TSP was performed at EPA/RTP laboratory not by the CHESS contractors on site. This necessitated the shipment of individual filter samples through the mail and the subsequent storages of the samples at EPA. During laboratory reorganizations at RTP, periods as long as 6 months elapsed between actual field sampling and laboratory analysis.

The following is a summary of individual errors and an assessment of overall TSP data quality.

Loss of particulate matter before weighing

In the TSP methodology there were field-related procedures that resulted in partial loss of particulate matter from the Hi-Volume filter samples. Due to the exposed location of the Hi-Vol TSP samplers, wind and cold sometimes made it very difficult to remove the filter paper from the apparatus without losing part of the sample. No estimate has been made of loss due to this problem; it would, of course, bias the reported results only in the direction of lower-than-actual atmospheric loadings. This was not a constant problem among CHESS sites. It was noted by field operators as being a particularly severe problem in the Salt Lake City area during the winter months.

Two other error sources have been identified in the determination of TSP, both of which would also produce a low-side bias: (1) the shaking-off of particles from the filter during transit from the field site to EPA/RTP, and (2) the evaporation of organic substances. In an attempt to quantify the mass loss during transit, David Hinton, EPA/RTP, made a comparison of filters collected in Utah, before and after mailing from Salt Lake City to RTP (22). He found that there was a average 4 percent loss. Carl Broadhead, of the Utah Division of Health, conducted a similar comparison; however, he noted an apparent loss of approximately 25%. This difference may, in part, be due to the time of year the studies were conducted. During the dry summer months in the Salt Lake City area, much of the TSP loading is due to windborn crustal material (sand). This material is much more easily lost in sample handling that is the finer anthropogenic particulate material.

A final error source, one more difficult to assess, derives from wind velocity versus collection efficiency. On days with relatively high wind (>15 mph), the Hi-Vol sampler is more susceptible to the inclusion of large diameter particulate material. To compound this problem, the design of the shelter makes the magnitude of the error dependent on the wind direction relative to the orientation of the shelter. The main result of this problem is that two side by side Hi-Vol samplers, oriented 90 degrees relative to each other, will produce dissimilar measurements with the discrepancy increasing as the daily wind velocity increases.

The overall effect of the summed errors with the Hi-Vol TSP measurement is a slight negative bias. This bias may be as small as 10% or may be as large as 30%. Side by side data from New York

and Salt Lake indicate that this assessment is reasonable. These data also indicate that the TSP data were by far the best quality data taken in the CHESS monitoring program. Differences measured between High and Low sites are probably reasonable estimates of the differences of TSP exposures as received by populations within these areas. Some local source variations undoubtedly did occur, but average annual exposures were reasonable.

In any overall assessment of the CHESS TSP data it should be noted that all of the sources of errors mentioned previously related almost exclusively to the loss of large particulate matter and most likely that matter is associated with crustal weathering. This material is outside of the normal human respirable size fraction and by composition, it would be unlikely to be associated with aggravated health. Thus, loss of that portion of the total material may not have diminished the quality of data for health effects studies. It may in fact have rendered that data a closer estimate of the respirable TSP exposure to which the CHESS population groups were subjected.

It has been suggested by some environmental scientists that whenever Hi-Vol measurements are made for health related studies, the filter pads should be "shaken out" much like a housewife does when shaking crumbs from a used tablecloth. The resultant TSP exposure estimates derived from such a procedure would then more closely relate to the human respirable size fraction of the total atmospheric particulate burden. Although never actually implemented, this suggestion indicates the general level of dissatisfaction with the TSP Hi-Vol measurement method.

4. TOTAL SUSPENDED SULFATE

The determination of atmospheric sulfate concentrations, as carried out in the CHESS program, was a methodological extension of the Hi-Vol TSP method. Thus, all errors associated with the TSP method also affect the sulfate method. Subsamples were cut from the exposed Hi-Vol filters and were analyzed for total water soluble sulfate. Methods available for sulfate analysis at the time of CHESS determined all water-soluble sulfates as a class rather than distinguishing them by chemical species. Two different methods were available for total sulfate and both were used in CHESS. From November 1970 until September 1971, the manual turbidimetric method was employed. From September 1971 until July 1975, the methylthymol blue (MTB) method was used. The methods are somewhat similar and are described in detail above.

The turbidimetric method is subject to interferences, many of them being other common pollutants. In areas like the Salt Lake Basin where the pollutants are dominated by a single source, the procedure may be adequate. However, in urban areas like Cincinnati or New York City, where the pollutant mix is derived from many independent sources and is variable even within the city, the method is capable of only the crudest estimates of sulfate levels. It should not be thought of as an accurate measurement of atmospheric sulfate. Especially, small differences between High and Low exposure communities, such as were reported in the Cincinnati Study in the CHESS Monograph (page 6-5) cannot be identified as real differences. When a realistic error estimate is applied to the reported sulfate concentrations, the differ-

ence becomes statistically insignificant. Any correlation of CHESS health effects with sulfate levels where the sulfate data were obtained using the turbidimetric method must be carefully qualified.

The MTB method is basically a better measurement method because most of the aerometric interferences have been eliminated by its revised methodology. The two remaining interferents, phosphate and barium, are not normally found in atmospheric concentrations high enough to cause inordinate problems. However, problems associated with the sampling aspect of the method have been documented and do impact on the general CHESS sulfate data quality.

First, problems associated with sulfate blanks (the level of sulfate on the filter pad as manufactured) were reported to be high and variable. In the 1971–1973 time period, problems of variable blanks within the EPA NASN program were documented. The general blank level was equivalent to an atmospheric sulfate concentration of 1–2μg/m^3. However, the major problem was variability of the blank among manufactured lots of the filters. The blank level often varied by more than 100 percent among lots so that routine and continuous blank assessment should have been mandatory.

No evidence of routine sulfate blank determination was found in the CHESS monitoring program until 1974. From that time period on, adequate blank assessment and correction were applied to the data. From 1971 until 1974 however, the blank contribution to the CHESS sulfate data was not adequately assessed and consequently a positive and highly variable bias of unknown magnitude was included in the data.

Second, adsorption of atmospheric SO$_2$ onto the fiberglass filter material followed by spontaneous oxidation of the SO$_2$ to sulfate had been well documented. A 1966 publication by R. E. Lee and J. Wagman provided results of their investigation of the problem. The conversion was clearly documented with severe effects demonstrated on four-hour samples. The conversion did appear to be an active-site catalytic conversion that decreased in magnitude after an initial saturation of sites. Thus, 24-hour samples were much less affected by this problem than were those taken for shorter time intervals. Even so, the paper by Lee and Wagman, presented data in which routinely 0.5 to 1 μg/m^3 of the measured sulfate was derived from SO$_2$ conversion products. The maximum conversion presented was 2.1μg/m^3 derived from SO$_2$; this constituted a 10 percent positive bias of the sulfate data. A more realistic average bias is likely in the 5 percent range. However, there is clear evidence that in regions of high levels of SO$_2$, relative to sulfate, the positive measurement bias becomes much more severe. This is probably the case in the Salt Lake Basin area.

The third and most devastating problem associated with the CHESS sulfate data occurred when the laboratory analysis of sulfates was contracted to an outside firm. During this time period (October 1972–June 1974) the reported sulfate data underwent a sudden and sustained decrease in apparent atmospheric sulfate level. Upon investigation it was determined that the laboratory analysis of all sulfate data from all CHESS sites were biased low by approximately 50 percent. The reason for this negative bias was and still is not completely clear, but the continued dissemination of poor data was clearly due to inadequate quality controls. An interim EPA report

on a retrospective quality assurance evaluation of CHESS Sulfate Data states:

A quality control protocol was designed for CHESS chemical analysis but has not been implemented as per the contract . . .. The quality control protocol should be implemented immediately.

In a series of following studies the magnitude of the affected data and of the error were documented and an attempt was made to correct and therefore recover the data. This type of procedure is difficult at best and impossible in most cases. The validity of this data correction was again assessed by the EPA Quality Assurance Branch. Their finding was:

The basic question . . . is—How does one make bad data good? Whatever is tried will be attacked for a multitude of (justifiable) reasons. Using the existing data set for relative pollution level assessment will be acceptable, but statements concerning absolute levels will not be. It would not be wise to submit these data to the NADB,[1] but rather answer all requests for these data internally.

Their statement gives a reasonable assessment of the CHESS sulfate data between 1972 and 1974. The assessment of other year CHESS sulfate data is more difficult. No comparative sulfate data exists from the local agencies as it did for SO_2 and TSP. Based on the intrinsic capabilities of the methods, and the error assessment of the field use procedures, it can generally be stated that:

1. From 1970 to September 1971 the sulfate data were obtained using the turbidimetric method. It should be used only as a sulfate level indicator. Due to interferences, there will be severe problems if an attempt is made to correlate sulfate levels in one part of the country with sulfate levels in another.

2. From October 1971 until October 1972, the data are subject to the following considerations:

    a. The data are likely biased in the positive direction from 1–2 $\mu g/m^3$. This bias may be more severe in areas of high SO_2 concentration relative to sulfate.

    b. The random error component of the measurement is probably in the order of $\pm 25\%$ at an atmospheric concentration of 10 $\mu g/m^3$

3. From October 1972 until June 1974, all CHESS sulfate data were biased negatively by approximately 50% on an annual average basis due to improper laboratory analysis by the contractor. These data should be used only on an adjusted annual average basis to establish local trends within site locations. The unknown cause of the bias prohibits use of the data in shorter time structure (i.e., day, week, month) increments.

4. From July 1974 until July 1975, CHESS sulfate data underwent a marked improvement and was somewhat better than that collected in the 1971–1972 era. The positive bias of the data is probably similar to that of the earlier period but the random error component was improved due to improved sulfate blanks on the TSP filters.

D. The CHAMP Air Monitoring Program

1. INTRODUCTION

Early in the execution of the CHESS program in 1969, a number of staff members in the air quality measurements organization of EPA

decided it was desirable, indeed imperative, to improve the efficiency and accuracy of short-term air quality data monitoring coverage. EPA coined the term CHAMP (Community Health Air Monitoring Program) for this concept of a second generation automatic system of air monitoring stations. Seven prototype stations were operated in California from January, 1972 to February 1974. The manpower ceiling placed on EPA resulted in a decision to contract for the development, installation, and operation of the CHAMP system. A contract for the development of the CHAMP system was awarded in February, 1973. The developmental monitoring system was to contain the newest technology in monitoring instrumentation. Accurate measurement of all critical air and liquid flows in the system was incorporated to enhance the accuracy of the system. The development continued to mid 1974 when the first station systems were installed in the Los Angeles area for field evaluation.

2. SYSTEM DESCRIPTION

The CHAMP air quality measurement system assembles the available discrete pollutant measurement devices and associated meteorological instruments into a complete system in an air-conditioned portable building. EPA specified the pollutants to be measured and selected the instruments with the advice of the CHAMP contractor. All data are recorded digitally in a mini-computer integral to each system. The data are checked and stored on tape at each CHAMP site for transmittal to the EPA/RTP Laboratory at Durham, North Carolina. SO_2 and NO_2, and TSP measurements are also taken periodically using older CHESS-type bubblers and Hi-Vol sampler instruments described previously for backup and validation of the CHAMP instruments. These bubbler and filter samples are sent to the contractor's chemical laboratory in California for analysis.

All the CHAMP systems measure ozone, total gaseous sulphur NO/NO_2, TSP,/RSP combinations, temperature, wind direction and velocity, and humidity. Selected systems also incorporate CO and hydrocarbon sampling. The CHAMP system while automatic in principle, requires periodic calibration and servicing by an operator to maintain a high duty factor and an acceptable quality of data (less than 15% error band). The operator repairs and adjusts instruments as required, checks for failures, and does periodic calibrations and data verifications. A quality assurance specialist continually spot-monitors the CHAMP sites carrying-out calibration and quality checks.

It should be noted that the instrumentation of the CHAMP stations is not completely uniform. Some stations do not have wind and pressure instruments; not all have CO and hydrocarbon instruments.

The manner in which meteorological data from the CHAMP stations is being analyzed and used has not been investigated. This is a subject of interest depending on the future of the CHAMP program.

CHAMP stations were visited in Thousand Oaks, California, and Salt Lake City, Magna, and Kearns, Utah. The kind of meteorological instruments in use appeared to be appropriate and they appear to be well-located and properly maintained. Problems have occurred with new dew-point measuring equipment that is now being replaced (this has to do with humidity measurement. Except for occasional failures of the sensing element of the dew-point apparatus, collecting meteorological data from the CHAMP stations should be routine.

There are at present 18 CHAMP stations on line at locations selected by EPA; six in the Los Angeles Basin, three in Birmingham, Alabama, four in New York City, four in the Salt Lake Valley, and one at the EPA Health Effects Research Laboratory at Research Triangle Park, North Carolina.

3. FINDINGS REGARDING THE CHAMP PROGRAM

As in the CHESS program, all the instruments incorporated in the CHAMP station were developed by the manufacturer for laboratory use. In fact, some non-commercial instruments were selected by EPA to try to use the most advanced technology. The CHESS experience has demonstrated the need for validation in field use and the contractor appears to be attempting to do this.

There was apparently some attempt to standardize on one instrument manufacturer for ease of maintenance, etc. Bendix ozone and NO_x instruments were employed. Flame photometric measurement was selected for SO_2 EPA apparently was interested in a pulsed flourescence device but the equipment cost was too high for the budget. The present instrument actually measures total gaseous sulphur and it is assumed that this is SO_2. (The only other likely gaseous sulfur compound H_2S, does not seem to be widely present.) The rest of the measurements appear to be well-validated. The backup measurement with bubbler methods have validated NO_2, to the extent possible. The TSP/Hi-Vol measurements were apparently validated at the beginning of the CHAMP program. However, because of the non-linear calibration character of the flame photometric instrument in the low concentration ranges of interest from 0 to 50 $\mu g/M^3$, calibration and range setting by the operator still results in 5% to 15% range of uncertainty in the total sulphur readings. Further, while the West-Gaeke bubblers used to check CHAMP SO_2 are stored at 70° F at the sites, they are shipped to the contractor's facilities for analysis without temperature control and are subject to the unpredictable temperature dependent decay of solutions prior to analysis. Thus, the SO_2 validation in the CHAMP system may be in greater error than EPA expects.

The execution of the CHAMP program has yielded validation and quality control of field measurements better than CHESS. However, there are clearly numerous unresolved problems with the operation which have led to delays in validating the data bank and which require high level attention for resolution before reliable quantitative aerometric data can be obtained.

The data processing was 2,900 data-days behind at the time of this investigation and no date agreed on for total backlog elimination. Drift of zero setting and data span of instruments have invalidated part of the earlier analyses. The data are only about 60 percent machine validated. Field operator problems have arisen possibly due, in part, to a lack of standardized operating procedures. Successful operation of the CHAMP system requires well-trained instrument technicians, and people of this high level of skill have not been employed in the past. Because of such circumstances, the SO_2 data obtained through 1975 have been lost and apparently are not recoverable.

Some months ago EPA found that significant data were lost in transmitting over leased lines to the RTP laboratory. Thus, the primary data source is the data tapes from the CHAMP site computer which are mailed to RTP.

The CHAMP contract is up for renewal in November 1976 and the bids are being solicited competitively. It is believed that at this time competitive bidding could be a destabilizing step in this program and could delay the achievement of reliable routine data gathering another year. On the other hand there are obvious advantages to open competitive bidding. When system development is more nearly complete, it would certainly be appropriate for competitive bidding to be adopted. The competition should include quality control considerations. Unfortunately, the EPA quality assurance group was not consulted on the renewal request for proposal, although that group did participate in evaluating proposals received.

4. SUMMARY

CHAMP appears to be an improvement in real time field measurement of air pollutants in comparison with CHESS. However, the system is still not completely validated and may not be ready for routine use for 6 to 12 months. Data should not be stored in an accessible data bank until it is validated.

The present best estimate of expected accuracy is ± 15 to 20% on the CHAMP measurements. However, this will be a significant improvement over previous CHESS aerometric network mesurement systems when and if it is realized.

Section V of the 1976 Congressional
Investigative Report (IR) concerning
CHESS air quality analyses procedures
and results is as follows:

V. REVIEW OF CHESS AIR QUALITY ANALYSIS
PROCEDURES AND RESULTS

A. INTRODUCTION

This chapter presents the results of the investigative team's critical
review of the utilization of aerometric data in the analysis and data
modeling presented in the CHESS Monograph. The citations to
pages, figures and paragraph numbers are to the 1974 CHESS Mono-
graph. The findings are highlighted in terms of examples wherein
it appears that estimates have been extended beyond the range of
credibility, models have been misused, or miscellaneous errors of
various types have occurred which lead to misinterpretation or over-
interpretation of data or results of analyses.

B. USE OF ESTIMATED DATA

A serious weakness in the CHESS study was acknowledged in the
last paragraph on page 7-9, which refers to the Salt Lake Basin study
and the Rocky Mountain study. It is in part:

Several factors should be remembered when interpreting the results of the
lower respiratory disease studies . . . a majority of the pollution exposure
data in both studies were estimated from emissions data.

This statement applies to one of the most important and contro-
versial paragraphs in the CHESS report, also on page 7-9, which
follows:

It is interesting to note that larger increases in total lower respiratory disease
and two of its components were observed in the High pollution community of
the Salt Lake Basin study than in the corresponding communities in the Rocky
Mountain study. Also, the mean annual suspended sulfate concentration was
higher in the High pollution community in the Salt Lake Basin study than in
the Rocky Mountain study; the opposite was true for sulfur dioxide. This suggests
that increases in lower respiratory disease frequency are probably associated
with suspended sulfates rather than sulfur dioxide.

The paragraph summarizes the argument that exposure to sus-
pended sulfates over a period of years produces significant adverse
health effects.

Analysis of the background material leading to the conclusion
shows that it is derived from an interpretation of the relationship of
four numbers all of which are estimated values. The sulfur dioxide
values are estimated from smelter emissions and the sulfate values
are estimated from estimates of sulfur dioxide in one case and esti-
mates of suspended particulate based on smelter emissions in the
other, assuming no difference in the ratio of sulfate to suspended
particulate in the communities, Kellogg, Idaho; Helena-East Helena
and Anaconda, Montana; and Magna, Utah.

The "High pollution community of the Salt Lake Basin" is Magna,
Utah. It is less clear what is meant by the words "than in the Rocky

Mountain study". However, this paragraph refers to the preceding paragraph of the CHESS report, which speaks of concentrations, "as low as 7.2 µg/m³ in the Rocky Mountain Study".

From this it can be concluded that reference is being made to concentrations of sulfates in Anaconda, Montana.

A comparison is being made, therefore, between average sulfur dioxide concentrations and average sulfate concentrations in Magna and Anaconda. The period of the records being compared covers the years 1968–1970.

From the preceding paragraph the values being compared may be obtained. They are as follows:

[The concentration values are given in micrograms per cubic meter, written as µg/m³]

	Sulfur dioxide	Sulfates
Magna	92	15.0
Anaconda	177	7.2

Because of the methods used for making estimates, the absolute values of these concentrations are questionable. The next four sections discuss these estimates.

1. ESTIMATED SULFUR DIOXIDE CONCENTRATION, 92 µG/M³ (MAGNA)

The concentration value 92 µg/m³ for Magna can be obtained from Table 2.1.A.14 or Table 2.1.A.16. It is based on the following *estimated* values for three years:

Year:	µg/m³
1970	84
1969	103
1968	90
Average	92

These estimates of annual sulfur dioxide exposures were derived by multiplying the yearly smelter emission for sulfur dioxide by the ratio of the 1971 measured annual average sulfur dioxide concentration (61.8 µg/m³) to the same year's sulfur dioxide emission rate (193 tons/day). The last chapter established that these data could be off by 100 percent, probably on the low side.

$$61.8/193 = .320 \ (µg/m³)/(tons/day)$$

The emission rates used were as follows (page 2-37):[1]

Year:	Tons/day (SO₂)
1970	261
1969	222
1968	281

In order to obtain the estimated sulfur dioxide concentrations, it must be first assumed that the meteorological conditions for each of the years 1968, 1969 and 1970, were identical to those conditions in

[1] These rates of emission are off by a factor of two. Tons of sulfur, not tons of sulfur dioxide, are listed. These values corrected should be 522, 644 and 562 tons/day. However, this does not change the estimates of sulfur dioxide concentrations, which depend on a ratio between measured 1971 concentrations and 1971 emissions, whatever they might be. Doubling the emission rate also doubles concentrations estimated by the application of a mathematical diffusion model (Page 2-23).

1971. There was no presentation, in the Monograph of the use of climatological data to show that 1971 was similar to the other years, an average year, or a generally representative year. Even if the meteorological conditions for all four years had been identical, there is still a problem because the year 1971, on which the estimates are based is not a normal year for smelter operations. Emissions were zero, or practically zero for two weeks during July, and nearly zero for six weeks in July and August. Therefore, the emission/concentration ratio is deficient in showing the effects of the summer season, when wind direction frequencies from the smelter to Magna might have been less than during the remainder of the year. This suggests that the average concentration of sulfur dioxide in Magna is likely to have been slightly over-estimated, but it supports rather than changes the conclusion that average concentrations of sulfur dioxide are less in Magna than in Anaconda. Primarily this estimate is criticized because it is not supported by climatological information.

Also it should be realized that the method used for estimating the annual average concentration can result in an incorrect estimate if there is a significant background of sulfur dioxide from a source or sources other than the smelter. Multiplying the emission rate of the smelter by a factor assumes that all individual observational values that make up the annual average can be multiplied by this same factor, when actually only those values totally resulting from the smelter emissions would be effected. The Salt Lake City airport wind rose (Figure 2.1.2) is probably not representative for estimating the percentage of time that Magna is downwind from the smelter because the smelter stack is at the base of the Oquirrh mountain range. However, the frequency of west northwest and northwest winds at the airport suggest that Magna is only downwind about 5% of the time. Allowing for the effect of calm and variable winds, it seems unlikely that Magna would be under the influence of the smelter more than 10% of the time. It follows then, sulfur dioxide values for only these hours would be affected. On the other hand, if the smelter is the only significant source of sulfur dioxide, as may be the case, then multiplying individual observation values of zero concentration would yield only zero, and the procedure for estimating yields a true result, assuming no change in meteorological or emission conditions. Since the sulfur dioxide background in Magna is not known, the error that could be produced by background concentrations cannot be determined. Probably most of the sulfur dioxide does come from the smelter, so this source of error is not significant.

2. ESTIMATED SULFUR DIOXIDE CONCENTRATION, 177 $\mu g/m^3$ (ANACONDA)

A paragraph in the right hand column of page 3–12 explains how the average concentration of 177 $\mu g/m^3$ for sulfur dioxide was estimated for Anaconda for the period 1968–70 using sulfation plate data and emission rates. However, the explanation is incomplete, because it requires the 1971 emission rate of the smelter, which has been omitted from the Monograph. Thus, the validity of the entire procedure is impossible to verify. Table 3.1.2., which lists the emission rates by year begins with the year 1970. The ratio of $0.343 \pm .253$ $(\mu g.m^3)/(ton\ day)$ was obtained by a very dubious procedure. To begin with, sulfation plate data are of somewhat uncertain nature. The document "Air

Quality Criteria for Sulfur Oxides", U.S. Department of Health, Education and Welfare, Public Health Service, National Air Pollution Control Administration, Washington, D.C., January, 1969, pp 24-25 says that sulfation "candles" (and plates) give only "an empirical estimate of the average concentration". It also says "results are influenced by wind movement and humidity" and that "the lead peroxide candle provides intelligence on the oxidizable sulfur compounds in the atmosphere which seldom can be directly related to sulfur dioxide".

The CHESS Monograph paragraphs refer to sulfation plate data for 1965. The sulfation plate is a variation of the lead peroxide candle. Developmental work on the plate was reported in the following reference: Huey, N.A. "The Lead Peroxide Estimation of Sulfur Dioxide Pollution" J. Air Pollution Control Association, Vol. 18, pp 610-611, Sept. 1968. Consequently it is unlikely that sulfation plates were in use in Anaconda in 1965.*

In order to determine sulfur dioxide from a lead peroxide candle or plate an empirical relationship must be used. For example, in the Helena Valley, Montana, Area Environmental Study, (EPA, Office of Air Programs, Research Triangle Park, North Carolina, January 1972) the sulfation values were converted to sulfur dioxide values by means of the relationship: 1 mg SO₃ per 100 cm² per day is equivalent to 0.035 ppm SO₂. In the history of the use of lead peroxide devices, there has not been general agreement as to what ratio should be used, and a belief prevails that sulfation candle or plate data are conservative, i.e., that sulfur dioxide concentrations are sometimes higher than indicated. Further, more information is needed concerning the location of the station, or stations, in the Anaconda area, where the sulfation data were obtained. In order to validate the Anaconda sulfur dioxide data further work needs to be done.

In 1965 the annual average concentration of sulfur dioxide was reported to be 80 μg/m³ with an emission rate of 609 tons/day. Since the 1971 emission rate is omitted from the report it cannot be compared with the corresponding concentration of 286 μg/m³. Assuming that the 1971 emission rate is also on the order of 600-700 tons/day, then there seems to be too great a difference between the 80 μg/m³ concentration and the 286 μg/m³ concentration. (Center paragraph, right hand side, page 3-12.)‡

The ratio 0.343±.253 has a large error factor. The range is from .090 to .597. If the low value is multiplied by the emissions for the years 1968-1970, the following concentrations are obtained:

[Tons per day]

Year	Table 3 1.2 (SO₂)	New value Montana SDES
1971	Omitted	636
1970	635	556
1969	543	5.4
1968	367	603
1967	346	459

NOTE.—The omission of the 1971 emission rate makes it impossible to check the effect of using the new value for 1971 on the estimated emission rates.

*The chemical reaction for "candles" and "plates" is the same.
‡According to information recently received from the Montana State Department of Health and Environmental Sciences, the emission rates listed for the Anaconda smelter are low.

Year	SO_2 emissions (tons per day)	Estimated average concentrations ($\mu g/m^3$)
1970	635	57
1959	545	49
1968	367	33

The average of these values is 46 $\mu g/m^3$. This concentration is considerably less than the 92$\mu g/m^3$ value at Magna. However, information received from a representative of the Montana State Department of Health and Environmental Services, suggests that the 80 $\mu g/m^3$ value and the 286 $\mu g/m^3$ value were measured in two different locations in Anaconda, and that the 80 $\mu g/m^3$ value is too low. This indicates that the estimated values of sulfur dioxide in the table comparing Anaconda and Magna values are somewhat too low.

The estimates are further weakened by the fact that an assumption is made that meteorological conditions during all of the year is identical for all years. No supporting climatological information is presented.

Also, note that the Table 3.1.7 lists a sulfur dioxide concentration of 177 $\mu g/m^3$ for 1971 instead of the 286 $\mu g/m^3$ value obtained from the Montana State Department of Health.

The procedure for estimating sulfur dioxide concentrations in Anaconda seems unnecessarily crude, making the average concentration value for the years 1968-1970 uncertain. However, since the reported 1971 values for Anaconda and Magna are 286 $\mu g/m^3$ and 61.8 $\mu g/m^3$, and these values are the basis for estimates, it would appear that it was fairly certain that there was more sulfur dioxide present in Anaconda, than at Magna during the '68 to '70 period of the CHESS studies.

3. ESTIMATED SUSPENDED SULFATE CONCENTRATION, 15 $\mu g/m^3$ (MAGNA)

The 15 $\mu g/m^3$ estimate is a *double estimate* since the sulfur dioxide concentration data on which it is based is also *estimated*. The sulfate value seems to be an average for the years 1968-1970. It is obtained by using the following regression equation, which is found on page 2-39.

$$\text{Magna}-SS=0.09(SO_2)+6.66$$

This equation is based on 1971 conditions.

It is of interest to note that with a zero concentration of sulfur dioxide there would still be 6.66 $\mu g/m^3$ of sulfate, or approximately half the average annual value reported on 1971, which was 12.4 $\mu g \cdot m^3$. Further, 44% of the 15 $\mu g/m^3$ of interest for the years 1968-1970 is unrelated to sulfur dioxide concentrations. The Figures 2.4.2 and 2.4.4 suggest some lack of complete correlation between sulfur dioxide and sulfate concentrations.

During the strike with zero sulfur dioxide concentrations, there still is an appreciable amount of suspended sulfate. Also, a peak value of sulfate occurred during the third week that does not correspond with sulfur dioxide value behavior during the same period. Similarly, the very large rise in sulfur dioxide that peaked in the ninth week hardly shows in the sulfate values. Consequently, the regression equation can be questioned because the reason for the

sulfate values is not understood. What is the physical source of the sulfates?

Since the sulfur dioxide concentrations used in the regression equation are themselves estimated, uncertainties in the sulfur dioxide estimates are compounded in the sulfate estimates. Further, since the source of a considerable amount of the sulfate seems to be not associated with the sulfur dioxide, it is not clear what effect the strike period has on the estimates.

The CHESS report lists the suspended sulfate concentration as 12.4 $\mu g/m^3$ in 1971 and this is the basis for the estimate of 15 $\mu g/m^3$ for the 1968-1970 period. Observations of sulfate in Magna area subsequent to 1971 support the argument that average annual concentrations are in the neighborhood of 15 $\mu g/m^3$, or that they are significantly higher than reported for Anaconda.

On page 2-79, in Table 2.4.1, it may be noted that suspended sulfate values for the High community do not follow the sulfur dioxide concentrations, particularly for the Spring and Summer. This raises a question about using sulfur dioxide as an indicator of sulfate, as was done with the regression equation on page 2-39. (Median values for the High community are: Sulfur dioxide, Spring 64, Summer 9, whereas for suspended sulfate they are 8 and 7, respectively.)

Wind blowing from the smelter stack to Magna would generally cross a portion of the Great Salt Lake and, therefore, might carry more moisture, thereby facilitating the conversion of sulfur dioxide to sulfate. Perhaps this mechanism helps to account for the high sulfate concentrations observed in Magna.

4. ESTIMATED SUSPENDED SULFATE CONCENTRATION, 7.2 $\mu g/m^3$ (ANACONDA)

The 7.2 $\mu g/m^3$ suspended sulfate value can be obtained from Table 3.1.7, page 3-12, by taking an average of sulfate values for three years, as follows:

Year:	$\mu g/m^3$
1970	8.9
1969	7.6
1968	5.1
Average	7.2

These sulfate values are estimates, based on estimates of total suspended particulate and an estimate of the ratio of suspended sulfate concentration to total suspended particulate concentration, based on results from East Helena and Helena, Montana, and Magna, Utah. The same procedure was used for Kellogg, Idaho.

On page 3-11, in an attempt to explain how the suspended sulfate estimates were made for Kellogg, it is stated that "Data observed for Magna during the period January 1971–June 1972 indicated an average ratio of suspended sulfate concentration to total suspended particulate of 0.159." Following this is the reference number "22," referring to National Air Pollution Control Administration Publication No. AP-61, "Characteristics of Particulate Patterns 1957-1966." This publication presents graphs of suspended particulate concentrations for various cities over a ten year period. In it, suspended sulfates are not mentioned, the time period is wrong, and there are no data

for Magna; therefore, it must be concluded that the reference is an error.

An obvious reference for this paper would have been the paper by Marvin B. Hertz, et al., "Human Exposure to Air Pollution in Salt Lake Communities, 1940–1971," however, it is not referenced. Perhaps this was the reference intended. Even so, the ratio 0.159 cannot be obtained from the Hertz paper.

In the Hertz paper, page 2-11, Table 2.1.2, which gives CHESS 1971 Annual Averages for Magna, the suspended sulfate concentration is 9.6 μg/m³ and the total suspended particulate concentration is 53.9, which gives a ratio of 0.178. In Tables 2.1.5 and 2.1.A.16, the following concentrations are given: TSP, 66 μg/m³, SS, 12.4 μg/m³. Here the ratio is 0.188. Other ratios can be determined for various time periods from Tables 2.1.A.4 and 2.1.A.5, but none of these is 0.159.

Note (page 3-11) that the unexplained ratio 0.159 for Magna is used with the 0.063 ratio for East Helena to obtain the ratio 0.111 plus or minus 0.057 that is used to estimate suspended sulfate concentrations for Kellogg, and the 0.11 plus or minus 0.06 ratio for Anaconda (page 3-13).

(Pages 3-8 and 3-9) Particulate emissions for East Helena are given in two tables on pages that face each other. The headings of the second column in Table 3.1.4 should be "Emissions, Tons/year," not "Emissions, Tons/day."

On page 3-7 it is stated that estimates of stack emissions for both particulate and sulfur dioxide for East Helena for the years 1941–1970 were provided by Asarco. Presumably the data in Table 3.1.3 are Asarco data. The source of the data in Table 3.1.4 is not stated.

The Office of Air Programs Publication No. AP-91, Helena Valley, Montana, Area Environmental Pollution Study, gives more information about the industrial complex at East Helena. This study was conducted during the period June 1969 through June 1970. The table below is from this study.

EMISSIONS FROM EAST HELENA INDUSTRIAL COMPLEX

(Tons per day)

Company and operation	Emissions					
	SO₂ production			Particulates production		
	Reduced	Normal	Maximum	Reduced	Normal	Maximum
Asarco:						
Sintering	184 6	315.6	355 1	0.8	0.5	0.5+
Smelting	8.4	14.6	23 2	(¹)	(¹)	(¹)
Miscellaneous	(¹)	(¹)	(¹)	(²)	(²)	(²)
Subtotal	193.0	330.2	378.3	.3	.5	.5+
Anaconda:						
Fuming	13.0	13.0	13.0	(²)	(²)	(²)
Miscellaneous	(⁴)	(⁴)	(⁴)	1.0	1.0	1.0
Subtotal	13 0	13.0	13 0	1.0	1.0	1.0
American Chemet: Pigment production	(¹)	(¹)	(¹)	(¹)	(¹)	(¹)
Total	206.0	343 2	391.3	1.3	1.5	1.5+

¹ Negligible.
² The outside storage of concentrates contributes a significant but undetermined amount of particulates.
³ Emissions also occur during the slag charging and the coal mill, but no estimates have been made.
⁴ Emissions occur when slag is dumped, but no estimate of their quantity has been made.
⁵ Emissions are controlled by cyclones and bag filters with high collection efficiencies.

It may be noted that ASARCO is only one of several particulate sources for the East Helena area. Fuming and other slag processing activities of the Anaconda Co. are estimated to produce 1.0 tons per day of particulates, resulting in a normal total of 1.⬛ tons per day, not a rate in the neighborhood of 0.3 tons per day as Table 3.1.3 suggests. Further, the total normal sulfur dioxide emission rate in the preceding table is 343.2 tons per day, a considerably higher rate than is given in Table 3.1.2. (i.e., 1969: 221 tons/day; 1970: 239 tons/day).

On page 3-7, right hand side, is given an explanation of how the data in Table 3.1.4 were used to obtain a ratio of total suspended particulate concentration to tons of particulate emitted per day for East Helena. However, after giving this explanation, the estimates of TSP in Table 3.1.5, that were used to make the suspended sulfate estimates were *not* obtained by means of this ratio. They seem to have been obtained from the particulate emission data in Table 3.1.3, using the factor 3S3.22 $(\mu g/m^3)/(tons/day)$. The derivation of this factor is not explained. The ratio that is explained never seems to have been used. The suspended sulfate estimates are obtained by multiplying the total suspended particulate concentrations by the factor 0.063, which is explained on page 3-8.

Both observed and estimated suspended particulate concentrations are given in Table 3.1.4 and 3.1.5. It may be noted that the estimated TSP values are used to estimate the suspended sulfate concentrations and not the observed values for the years 1966 through 1969. In 1966, the observed value was 87 $\mu g/m^3$, whereas the estimated value is 114.2 $\mu g/m^3$. No explanation is given for rejecting the observed values.

Data for Magna during the period January 1971-June 1972 indicated an average ratio of suspended sulfate concentration to total suspended particulate of 0.159. The available data for East Helena indicated a suspended sulfate to total suspended particulate ratio of 0.063 ± 0.022 $\mu g/m^3$. For Kellogg, the assumption has been made that the ratio of suspended sulfate to total suspended particulate is the average of these values, or 0.111 ± 0.057. For Anaconda, this value was rounded to 0.11 ± 0.06. It is multiplied by the estimated concentrations of total suspended particulate listed in Table 3.1.7, to obtain the suspended sulfate values for each year.

The following table has been prepared from the Helena Valley study, June through October 1969.

Station	Location [1]		Suspended particulate	Particulate sulfate	Ratio
	Degrees	Miles			
1.................................	34	0.8	108	3.5	0.032
2.................................	105	2.5	74	3.7	.05
3.................................	112	.4	59	4.4	.069
4.................................	274	4.5	62	2.9	.047
Average........................			76	3.6	.050

[1] With respect to the smelter stack.

The data from stations 1 and 3, the stations nearest the stack, were used to obtain a ratio range (0.037, pages 3–8), but for some curious reason the available ratios from the Helena Valley study were not used. The average ratio for stations 1 and 3 is 0.051.

The ratio chosen for East Helena, 0.063 plus or minus 0.022 ($\mu g/m^3$)/($\mu g/m^3$), is not significantly different from that which might have been obtained had more use been made of the Helena Valley study, but there is no basis for the assumption that the ratio of suspended sulfate to suspended particulate is similar in Magna, East Helena, Helena, and Anaconda.

The dubious nature of using suspended particulate concentrations to estimate suspended sulfate can be seen by comparing Figures 2.4.3 and 2.4.4. In the Low Exposure Community, the sulfate level remains low and nearly constant while the suspended particulate concentrations fluctuate.

In the High Exposure Community, the highest concentration of suspended particulate occurred on the fourth week whereas the peak sulfate value occurred on the third week. On the fourth week, sulfate levels dropped. A corresponding drop in the sulfate levels does not occur until the fifth week. Only during the last seven or eight weeks do suspended particulate and suspended sulfate concentrations fluctuate together. There may be some situations where suspended particulate and suspended sulfate concentrations are well correlated. Justification for assuming correlation in the Salt Lake Basin and the Rocky Mountain communities is inadequately supported by scientific evidence presented in the CHESS Monograph.

Further, the 7.2 $\mu g/m^3$ suspended sulfate estimate for Anaconda is based on an estimate that comes from another estimate of suspended particulate values based on rates of emission from the smelter. During the period 1961–1962, the annual total suspended particulate concentration was found to be 84.5 $\mu g/m^3$. In 1971, the average suspended particulate level was observed to be 52 $\mu g/m^3$. By comparing the observed total suspended particulate concentration with the particulate emitted from the Anaconda plant, a ratio of 9.1 ± 2.3 ($\mu g/m^3$)/(ton/day) was determined. This ratio was multiplied by the particulate emission for Anaconda shown in Table 3.1.3 to estimate the total suspended particulate concentrations for the years 1940–1970. This ratio cannot be actually obtained from the data presented in the report because particulate emissions for the year 1971 are not given, i.e., they are not listed in Table 3.1.3.

The basis for this ratio is unfounded since there are sources for the suspended particulate other than the smelter emissions.

Although there are no actual sulfate observations from the Anaconda area included in the CHESS report there are some actual observations of suspended sulfate versus total suspended particulate available for the year 1971, that were obtained from the Montana State Department of Health and Environmental Sciences. These suggest that annual average suspended sulfate levels in Anaconda are in the neighborhood of 4 or 5 $\mu g/m^3$, even less than the estimated value (7.2 $\mu g/m^3$).

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There are also pronounced seasonal effects, with much higher values in winter than in summer. The months of February and April had values of 7 and 9 $\mu g/m^3$ whereas the months of July and August have values of less than 1 ug/m³. Local heating emissions and relative humidity may be significant factors determining the measured concentration as well as the smelter emissions.

5. ESTIMATES OF SUSPENDED PARTICULATE, SALT LAKE BASIN STUDY

On page 2-23 it is stated that "the number of sulfric acid plants utilizing sulfur recovered from emissions have increased from one in 1940 to seven in 1971, and that air pollution control devices in the form of baghouses, scrubbers, cyclones, and mist eliminators have been installed. Such changes in the smelter operations would greatly effect the ratio of suspended particulate to tons of copper produced. Therefore, aside from the fact that there would be differences from year to year because of meteorology, the procedure described in the first paragraph, right hand column, page 2-24, for estimating suspended particulate from copper production in tons for 1971, is highly questionable.

6. ESTIMATES IN THE CHIGACO AND NEW YORK STUDIES

In the Chicago and New York studies suspended sulfate concentrations were estimated from suspended particulate concentrations. In Chicago, the estimates were used to fill in data for some years when no data were available. In the New York study measured values for suspended sulfates for 1956–1970 were available from the Manhattan 121st Street station, and these values were used as citywide values. The observed annual ratios of suspended sulfate to dustfall for New York City were used to estimate the suspended sulfate levels in Queens and Bronx. In Table 5.3.1 suspended sulfate levels for the Low Community (Riverhead) are listed as about 10 $\mu g/m^3$ for the years 1961 through 1970. The basis for this estimate is not given, although it was probably determined from the 1971 concentration, which was 10.2 $\mu g/m^3$.

In summary, it appears that some values, on which are based important conclusions that sulfates may be harmful to health, are estimated values.

C. Use of Mathematical Dispersion Models

The dispersion model shown in Figure 2.1.16 is incorrectly applied. It was used in the Salt Lake Basin study to determine sulfur dioxide contours around the smelter source and to show that annual exposure estimates obtained from the ratio of 1971 observed air quality to 1971 emissions were not unreasonably high or low. First, the contours are incorrect because the model used does not take into account the elevation of the terrain and the wind direction frequencies for the Salt Lake City airport, which were used are different from those affecting the smelter plume, which originates at the base of the Oquirrh Mountains. Second, a dispersion model is based on numerous assumptions and applied in this way might be off by a factor of two, or more. It does not make sense to use a model to check observations.

The usual application is to apply observational data to calibrate, or verify, a model. A model such as the one used might have been applied to show some sort of relative distribution of concentrations across the Salt Lake Valley, however, it should not have been used to justify estimates of concentrations over the period 1940–1970. (See Tables 2.1.A.14 and 2.1.A.16). Further, during this review of the CHESS report it was discovered that smelter emissions used for the model estimates were tons of sulfur, not tons of sulfur dioxide. Therefore, the model estimate is only half what it should have been. Doubling the emission rate and reducing the wind direction frequency somewhat with respect to Magna might result in an estimated concentration near that measured, which was 61 $\mu g/m^3$.

Apparently the dispersion model was run only once and then the ratio between the emission at the smelter for 1971 and the calculated concentration was applied to emission values for the other years in order to obtain the other listed concentrations in the column headed "Diffusion Model". No account is taken of the fact that meteorological conditions, or perhaps stack conditions, were not the same for all years. More information should have been included in this report on exactly what meteorological data were used in the model. The model requires the use of the STAR program, which is obtained from the National Climate Center. Frequently the results of running this program are based on data for the year 1964, which is the only year when wind directions were punched on data cards to the nearest 10 degrees each hour rather than each 3-hours. Therefore, the model is likely to have incorporated meteorological data for some year other than 1971, the year of the emission data. No attempts is made to show that the year (or period) of the meteorological data is average, good or bad. Similarly there is no attempt to show that 1971 was an average year, yet all of the estimates are based on this assumption.

Considering how the model estimates for the years 1940–1970 were obtained it is misleading to include them in the table, and they serve little purpose since the ratio for the year 1970 is repeated throughout.

On page 2–43, bottom of right hand column, the following statements appear: "Estimates of sulfur dioxide, total suspended particulates, and suspended sulfate concentrations in the High exposure community for 1940–1970 and the Intermediate II exposure community for 1950–1970 were obtained by a mathematical dispersion model, which utilized emissions from the industrial source and extensive local meteorological data, and by observed relationships among pollutants. Observed suspended particulate, suspended sulfate, and sulfur dioxide concentrations for 1970–1971 were used to calibrate the models used to estimate exposure levels for previous years." This is an overstatement. The estimates were obtained from simple ratios and the application of a regression equation. See page 2–39. The model was only applied once to demonstrate that annual exposure estimates obtained from a ratio were not unreasonably high or low.

In the Chicago study, another attempt was made to apply a dispersion model (Figure 4.1.10). This model gives a false picture of pollution conditions that prevailed in the study area because it is based only on pollution sources within the city limits of Chicago, omitting effects of adjoining large industrial sources in Indiana and of some suburban communities to the southwest of the Loop area, which have considerable air pollution.

Maps recently published by the Chicago Department of Environment Control, for the years 1970 and 1975 clearly show that pollution concentrations are not simply concentric around the urban core as the model indicates.

On page 4-8, it is stated Measured data from the City network, from which the exposure estimates were made, were best supported by the Mitre model. It is not clear why a greater use was not made of the available actual measurements instead of the model estimates. Also, it is not sufficiently clear why the model happens to be for the year 1968.

SUMMARY ASSESSMENT--METEOROLOGY AND POLLUTION MEASURES

The Investigative Report (1976, 99-102) cited the following problems with the environmental measures:

1. superficial and perfunctory treatment of meteorological information;

2. insufficient exploration of possible relationships between meteorological conditions and asthma attack rates;

3. failure to consider peak and episode concentrations;

4. use of a single monitoring station to determine the exposure of a community;

5. failure to establish similarity of exposure and stress factors between communitites in the same study, excluding the exposure to specific pollutants;

6. impreciseness of monitoring station locations;

7. inexact locations of residences of individuals studied.

APPENDIX 14-B

ANALYSIS OF TEMPERATURE
EFFECTS ON MORTALITY

(Appendix materials to be inserted)

APPENDIX 14-C

WHO TASK GROUP ON ENVIRONMENTAL
HEALTH CRITERIA FOR SULFUR OXIDES
AND SUSPENDED PARTICULATE MATTER

AND

TASK GROUP CONSIDERATION OF
HOLLAND REPORT

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR SULFUR OXIDES AND SUSPENDED PARTICULATE MATTER

Participants

Members [a]

Professor K. Biersteker, Medical Research Division, Municipal Health Department, Rotterdam, Netherlands (*Vice-Chairman*).

Professor K. A. Buštueva, Department of Community Hygiene, Central Institute for Advanced Medical Training, Moscow, USSR

Dr P. Camner, Department of Environmental Hygiene, The Karolinska Institute, Stockholm, Sweden

Professor L. Friberg, Department of Environmental Hygiene, The Karolinska Institute, Stockholm, Sweden (*Chairman*)

Mrs M. Fugaš, Laboratory for Environmental Hygiene, Institute for Medical Research and Occupational Health, Zagreb, Yugoslavia

Dr R. J. M. Horton, Health Effects Research Laboratory, US Environmental Protection Agency, Research Triangle Park, NC, USA

Professor S. Maziarka, National Institute of Hygiene, Warsaw, Poland

Dr B. Prinz, State Institute for Protection of Air Quality and Land Usage, Essen, Federal Republic of Germany

Dr H. P. Ribeiro, Laboratory of Pulmonary Function, Santa Casa de Misericordia de São Paulo, São Paulo, Brazil

Dr T. Suzuki, Institute of Public Health, Tokyo, Japan

Mr G. Verduyn, Institut d'Hygiene et d'Epidemiologie, Brussels, Belgium

Mr R. E. Waller, Medical Research Council, Air Pollution Unit, St Bartholomew's Hospital Medical College, London, England (*Rapporteur*)

Mr D. A. Williams, Surveillance Division, Air Pollution Control Directorate, Environment Canada, Ottawa, Ontario, Canada

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[a] Unable to attend:

Professor M. H. Wahdan, High Institute of Public Health, University of Alexandria, Alexandria, Egypt

Representatives of other Organizations

Mr J. Janczak, Environment and Housing Division, United Nations Economic Commission for Europe, Geneva, Switzerland

Mr D. Larré, Division of Geophysics, Global Pollution and Health, United Nations Environmental Programme, Nairobi, Kenya

Dr D. Djordević, Occupational Safety and Health Branch, International Labour Organisation, Geneva, Switzerland

Mr G. W. Kronebach, Technical Supporting Services Branch, World Meteorological Organization, Geneva, Switzerland

Dr A. Berlin, Health Protection Directorate, Commission of the European Communities, Luxembourg

Mr J. A. Bromley, Environmental Directorate, Organization for Economic Co-operation and Development, Paris, France

Secretariat

Professor B. G. Ferris, Jr, Department of Physiology, Harvard University School of Public Health, Boston, MA, USA (*Temporary Adviser*)

Dr Y. Hasegawa, Medical Officer, Control of Environmental Pollution and Hazards, World Health Organization, Geneva, Switzerland (*Secretary*)

Dr H. W. de Koning, Scientist, Control of Environmental Pollution and Hazards, World Health Organization, Geneva, Switzerland

Dr B. Marschall, Medical Officer, Occupational Health, World Health Organization, Geneva, Switzerland

Dr R. Masironi, Scientist, Cardiovascular Diseases, World Health Organization, Geneva, Switzerland

Dr S. I. Muravieva, Institute of Industrial Hygiene and Occupational Diseases, Academy of Medical Sciences of the USSR, Moscow, USSR (*Temporary Adviser*)

Dr V. B. Vouk, Chief, Control of Enviromental Pollution and Hazards, World Health Organization, Geneva, Switzerland

ENVIRONMENTAL HEALTH CRITERIA FOR SULFUR OXIDES AND SUSPENDED PARTICULATE MATTER

A WHO Task Group on Environmental Health Criteria for Sulfur Oxides and Suspended Particulate Matter met in Geneva from 6 to 12 January 1976. The meeting was opened by Dr B. H. Dieterich, Director, Division of Environmental Health, who welcomed the participants and the representatives of other international organizations on behalf of the Director-General. Dr Dieterich briefly outlined the history and purpose of the WHO Environmental Health Criteria Programme and the progress made in its implementation, thanks to the active collaboration of WHO Member States and the support of the United Nations Environment Programme (UNEP).

The Task Group reviewed and revised the second draft criteria document and made an evaluation of the health risks from exposure to these substances.

The first and second drafts were prepared by Professor B. G. Ferris, Jr, Harvard University School of Public Health, USA. The comments on which the second draft was based were received from the national focal points collaborating in the WHO Environmental Health Criteria Programme in Belgium, Bulgaria, Canada, Czechoslovakia, the Federal Republic of Germany, Greece, Japan, New Zealand, Poland, Sweden, USA, USSR and from the Food and Agriculture Organization of the United Nations (FAO), the United Nations Eduational Scientific and Cultural Organization (UNESCO), the United Nations Industrial Development Organization (UNIDO), the World Meteorological Organization (WMO), the International Atomic Energy Agency (IAEA), and the Commission of European Communities (CEC). Comments were also received from Professor H. Antweiler and Dr B. Prinz (Federal Republic of Germany), Professor K. Biersteker and Dr R. van der Lende (Netherlands), Professor F. Sawicki (Poland), and Professor W. W. Holland and Professor P. J. Lawther (United Kingdom).

The collaboration of these national institutions, international organizations and individual experts is gratefully acknowledged. The Secretariat also wishes to thank Professor B. G. Ferris, Jr and Mr R. E. Waller for their invaluable assistance in the final stages of the preparation of the document.

In view of the substantial amendments made to the document (particularly within sections 2 to 5) since the meeting of the Task Group, a revised version was circulated to all members in February 1978. At the same time, copies of a newly-produced review of the health effects of particulate pollution (Holland et al., in press), that had been submitted for consideration, were distributed to the members. Comments were sought on the draft of the criteria document itself, and on any amendments or additions considered necessary in light of the new report. These comments, together with others received from the International Petroleum Industry Environmental Conservation Association, and the International Iron and Steel Institute, were then considered by a small group consisting of the Chairman of the Task Group meeting, the Rapporteur and some members of the Secretariat. The alterations suggested (mainly within section 9) were circulated again to the original members of the Task Group prior to publication.

The document has been based, primarily, on original publications listed in the reference section. However, several recent reviews of health aspects of sulfur oxides and suspended particulate matter have also been used including those by Katz (1969), Committee on the Challenges of Modern Society (1971), Organization for Economic Cooperation and Development (1965), Rall (1974), Task Group on Lung Dynamics (1966), Task Group on Metal Accumulation (1973), US Department of Health, Education and Welfare (1969a), US Environmental Protection Agency (1974), World Health Organization (1976a), and World Meteorological Organization (1974).

The purpose of this document is to review and evaluate available information on the biological effects of sulfur oxides and suspended particulate matter including suspended sulfates and sulfuric acid aerosols, and to provide a scientific basis for decisions aimed at the protection of human health from the adverse consequences of exposure to these substances in both occupational and general environments. Although there are various routes of exposure, such as inhalation, ingestion (World Health Organization, 1971, 1974) and contact with skin, attention in this report has been concentrated upon the effects of inhalation of these substances, since this is the most important route of exposure. The discussion has also been limited to sulfur dioxide, sulfur trioxide, sulfate ions, and particulate matter primarily resulting from the combustion of fossil fuels. The sulfate ion has been considered in the variety of forms in which it occurs in the atmosphere, e.g., sulfuric acid and various sulfate salts.

The vast literature on these pollutants has been carefully evaluated and selected according to its validity and relevance for assessing human exposure, for understanding the mechanisms of the biological action of the pollutants and for establishing environmental health criteria, i.e., exposure-effect/response relationships in man. Environmental considerations have been limited to elucidating the pathways leading from the natural and man-made sources of these substances to the sites of toxic action in the human organism. The non-human targets (plants, animals, ecosystems) have not been considered unless the effects of their contamination were judged to be of direct relevance to human health. For similar reasons, much of the published information on the effects of these pollutants on experimental animals has not been included.

Details concerning the WHO Environmental Health Criteria Programme

GLOSSARY

$AaDO_2$: Alveolar-arterial difference or gradient of the partial pressure of oxygen. An overall measure of the efficiency of the lung as a gas exchanger. In healthy subjects, the gradient is 5 to 15 mm Hg (torr).

A/PR/8 virus: A type of virus capable of causing influenza in laboratory animals; also, A/PR/8/34.

Abscission: The process whereby leaves, leaflets, fruits, or other plant parts become detached from the plant.

Absorption coefficient: A quantity which characterizes the attenuation with distance of a beam of electromagnetic radiation (like light) in a substance.

Absorption spectrum: The spectrum that results after any radiation has passed through an absorbing substance.

Abstraction: Removal of some constituent of a substance or molecule.

Acetaldehyde: CH_3CHO; an intermediate in yeast fermentation of carbohydrate and in alcohol metabolism; also called acetic aldehyde, ethaldehyde, ethanal.

Acetate rayon: A staple or filament fiber made by extrusion of cellulose acetate. It is saponified by dilute alkali whereas viscose rayon remains unchanged.

Acetylcholine: A naturally-occurring substance in the body which can cause constriction of the bronchi in the lungs.

Acid: A substance that can donate hydrogen ions.

Acid dyes: A large group of synthetic coal tar-derived dyes which produce bright shades in a wide color range. Low cost and ease of application are features which make them the most widely used dyes for wool. Also used on nylon. The term acid dye is derived from their precipitation in an acid bath.

Acid mucopolysaccharide: A class of compounds composed of protein and polysaccharide. Mucopolysaccharides comprise much of the substance of connective tissue.

Acid phosphatase: An enzyme (EC 3.1.3.2) which catalyzes the disassociation of phosphate (PO_4) from a wide range of monoesters of orthophosphoric acid. Acid phosphatase is active in an acidic pH range.

Acid rain: Rain having a pH less than 5.6, the minimum expected from atmospheric CO_2.

Acrolein: $CH_2=CHCHO$; a volatile, flammable, oily liquid, giving off
    irritant vapor. Strong irritant of skin and mucuous membranes. Also
    called acrylic aldehyde, 2-propenal.

Acrylics (plastics): Plastics which are made from acrylic acid and are
    light in weight, have great breakage resistance, and a lack of
    odor and taste. Not resistant to scratching, burns, hot water,
    alcohol or cleaning fluids. Examples include Lucite and Plexiglass.
    Acrylics are thermoplastics and are softened by heat and hardened
    into definite shapes by cooling.

Acrylic fiber: The generic name of man-made fibers derived from acrylic
    resins (minimum of 85 percent acrylonitrite units).

Actinic: A term applied to wavelengths of light too small to affect
    one's sense of sight, such as ultraviolet.

Actinomycetes: Members of the genus Actinomyces; nonmotile, nonspore-
    forming, anaerobic bacteria, including both soil-dwelling saprophytes
    and disease-producing parasites.

Activation energy: The energy required to bring about a chemical reaction.

Acute respiratory disease: Respiratory infection, usually with rapid
    onset and of short duration.

Acute toxicity: Any poisonous effect produced by a single short-term
    exposure, that results in severe biological harm or death.

Acyl: Any organic radical or group that remains intact when an organic
    acid forms an ester.

Adenoma: An ordinarily benign neoplasm (tumor) of epithelial tissue;
    usually well circumscribed, tending to compress adjacent tissue rather
    than infiltrating or invading.

Adenosine monophosphate (AMP): A nucleotide found amoung the hydrolysis
    products of all nucleic acids; also called adenylic acid.

Adenosine triphosphatase (ATPase): An enzyme (EC 3.6.1.3) in muscle
    and elsewhere that catalyzes the release of the high-energy, ter-
    minal phosphate group of adenosine triphosphate.

Adrenalectomy: Removal of an adrenal gland. This gland is located near
    or upon the kidney and is the site of origin of a number of hormones.

Adsorption: Adhesion of a thin layer of molecules to a liquid or solid sur-
    face.

Advection: Horizontal flow of air at the surface or aloft; one of the
    means by which heat is transferred from one region of the earth
    to another.

Aerodynamic diameter: Expression of aerodynamic behavior of an irregularly shaped particle in terms of the diameter of a sphere of unit density having identical aerodynamic behavior to the particle in question.

Aerosol: Solid particles or liquid droplets which are dispersed or suspended in a gas.

Agglutination: The process by which suspended bacteria, cells or similar particles adhere and form into clumps.

Airborne pathogen: A disease-causing microorganism which travels in the air or on particles in the air.

Air pollutant: A substance present in the ambient atmosphere, resulting from the activity of man or from natural processes, which may cause damage to human health or welfare, the natural environment, or materials or objects.

Airway conductance: Inverse of airway resistance.

Airway resistance (R_{aw}): The pressure difference between the alveoli and the mouth required to produce an air flow of 1 liter per second.

Alanine aminotransferase: An enzyme (EC 2.6.1.2) transferring amino groups from L-alanine to 2-ketoglutarate. Also known as alanine transaminase.

Albumin: A type of simple, water-soluble protein widely distributed throughout animal tissues and fluids, particularly serum.

Aldehyde: An organic compound characterized by the group $-\overset{\text{O}}{\underset{}{\overset{\|}{\text{C}}}}\text{-H}$.

Aldolase: An enzyme (EC 4.1.2.7) involved in metabolism of fructose which catalyzes the formation of two 3-carbon intermediates in the major pathway of carbohydrate metabolism.

Algal bloom: Sudden spurt in growth of algae which can affect water quality adversely.

Alkali: A salt of sodium or potassium capable of neutralizing acids.

Alkaline phosphatase: A phosphatase (EC 3.1.3.1) with an optimum pH of 8.6, present ubiquitously.

Allergen: A material that, as a result of coming into contact with appropriate tissues of an animal body, induces a state of sensitivity resulting in various reactions; generally associated with idiosyncratic hypersensitivities.

Alpha-hydroxybutyrate dehydrogenase: An enzyme (EC 1.1.1.30), present mainly in mitochondria, which catalyzes the conversion of hydroxybutyrate to acetoacetate in intermediate biochemical pathways.

Alpha rhythm: A rhythmic pulsation obtained in brain waves exhibited in the sleeping state of an individual.

Alveolar capillary membrane: Finest portion of alveolar capillaries, where gas transfer to and from blood takes place.

Alveolar macrophages (AM): Large, mononuclear, phagocytic cells found on the alveolar surface, responsible for the sterility of the lung.

Alveolar oxygen partial pressure (PAO_2): Partial pressure of oxygen in the air contained in the air sacs of the lungs.

Alveolar septa: The tissue between two adjacent pulmonary alveoli, consisting of a close-meshed capillary network covered on both surfaces by thin alveolar epithelial cells.

Alveolus: An air cell; a terminal, sac-like dilation in the lung. Gas exchange (O_2/CO_2) occurs here.

Ambient: The atmosphere to which the general population may be exposed. Construed here not to include atmospheric conditions indoors, or in the workplace.

Amine: A substance that may be derived from ammonia (NH_3) by the replacement of one, two or three of the hydrogen (H) atoms by hydrocarbons or other radicals (primary, secondary or tertiary amines, respectively).

Amino acids: Molecules consisting of a carboxyl group, a basic amino group, and a residue group attached to a central carbon atom. Serve as the building blocks of proteins.

p-Aminohippuric acid (PAH): A compound used to determine renal plasma flow.

Aminotriazole: A systemic herbicide, $C_2H_4N_4$, used in areas other than croplands, that also possesses some antithyroid activity; also called amitrole.

Ammonification: Decomposition with production of ammonia or ammonium compounds, esp. by the action of bacteria on nitrogenous organic matter.

Ammonium: Anion (NH_4^+) or radical (NH_4) derived from ammonia by combination with hydrogen. Present in rainwater, soils and many commercial fertilizers.

Amnestic: Pertains to immunologic memory: upon receiving a second dose of antigen, the host "remembers" the first dose and responds faster to the challenge.

Anaerobic: Living, active or occurring in the absence of free oxygen.

Anaerobic bacteria: A type of microscopic organism which can live in an environment not containing free oxygen.

Anaphylactic dyspneic attack: Difficulty in breathing associated with a systemic allergic response.

Anaphylaxis: A term commonly used to denote the immediate, transient kind of immunological (allergic) reaction characterized by contraction of smooth muscle and dilation of capillaries due to release of pharmacologically active substances.

Angiosperm: A plant having seeds enclosed in an ovary; a flowering plant.

Angina pectoris: Severe constricting pain in the chest which may be caused by depletion of oxygen delivery to the heart muscle; usually caused by coronary disease.

Angstrom $\overset{o}{A}$: A unit (10^{-8} cm) used in the measurement of the wavelength of light.

Anhydride: A compound resulting from removal of water from two molecules of a carboxylic (-COOH) acid. Also, may refer to those substances (anhydrous) which do not contain water in chemical combination.

Anion: A negatively charged atom or radical.

Anorexia: Diminished appetite; aversion to food.

Anoxic: Without or deprived of oxygen.

Anthraquinone: A yellow crystalline ketone, $C_{14}H_8O_2$, derived from anthracene and used in the manufacture of dyes.

Anthropogenic: Of, relating to or influenced by man. An anthropogenic source of pollution is one caused by man's actions.

Antibody: Any body or substance evoked by the stimulus of an antigen and which reacts specifically with antigen in some demonstrable way.

Antigen: A material such as a foreign protein that, as a result of coming in contact with appropriate tissues of an animal, after a latent period, induces a state of sensitivity and/or the production of antibody.

Antistatic agent: A chemical compound applied to fabrics to reduce or eliminate accumulation of static electricity.

Arachidonic acid: Long-chain fatty-acid which serves as a precursor of prostaglandins.

Area source: In air pollution, any small individual fuel combustion or other pollutant source; also, all such sources grouped over a specific area.

Aromatic: Belonging to that series of carbon-hydrogen compounds in which the carbon atoms form closed rings containing unsaturated bonds (as in benzene).

Arterial partial pressure of oxygen (PaO$_2$): Portion of total pressure of dissolved gases in arterial blood as measured directly from arterial blood.

Arterialized partial pressure of oxygen: The portion of total pressure of dissolved gases in arterial blood attributed to oxygen, as measured from non-arterial (e.g., ear-prick) blood.

Arteriosclerosis: Commonly called hardening of the arteries. A condition that exists when the walls of the blood vessels thicken and become infiltrated with excessive amounts of minerals and fatty materials.

Artifact: A spurious measurement produced by the sampling or analysis process.

Ascorbic acid: Vitamin C, a strong reducing agent with antioxidant properties.

Aspartate transaminase: Also known as aspartate aminotransferase (EC 2.6.1.1). An enzyme catalyzing the transfer of an amine group from glutamic acid to oxaloacetic, forming aspartic acid in the process. Serum level of the enzyme is increased in myocardial infarction and in diseases involving destruction of liver cells.

Asphyxia: Impaired exchange of oxygen and carbon dioxide, excess of carbon dioxide and/or lack of oxygen, usually caused by ventilatory problems.

Asthma: A term currently used in the context of bronchial asthma in which there is widespread narrowing of the airways of the lung. It may be aggravated by inhalation of pollutants and lead to "wheezing" and shortness of breath.

Asymptomatic: Presenting no subjective evidence of disease.

Atmosphere: The body of air surrounding the earth. Also, a measure of pressure (atm.) equal to the pressure of air at sea level, 14.7 pounds per square inch.

Atmospheric deposition: Removal of pollutants from the atmosphere onto land, vegetation, water bodies or other objects, by absorption, sedimentation, Brownian diffusion, impaction, or precipitation in rain.

Atomic absorption spectrometry: A measurement method based on the absorption of radiant energy by gaseous ground-state atoms. The amount of absorption depends on the population of the ground state which is related to the concentration of the sample being analyzed.

Atropine: A poisonous white crystalline alkaloid, $C_{17}H_{23}NO_3$, from belladonna and related plants, used to relieve spasms and to dilate the pupil of the eye.

Autocorrelation: Statistical interdependence of variables being analyzed; produces problems, for example, when observations may be related to previous measurements or other conditions.

Autoimmune disease: A condition in which antibodies are produced against the subject's own tissues.

Autologous: A term referring to cellular elements, such as red blood cells and alveolar macrophage, from the same organism; also, something natually and normally ocurring in some part of the body.

Autotrophic: A term applied to those microorganisms which are able to maintain life without an exogenous organic supply of energy, or which only need carbon dioxide or carbonates and simple inorganic nitrogen.

Autotrophic bacteria: A class of microorganisms which require only carbon dioxide or carbonates and a simple inorganic nitrogen compound for carrying on life processes.

Auxin: An organic substance that causes lengthening of the stem when applied in low concentrations to shoots of growing plants.

Awn: One of the slender bristles that terminate the glumes of the spikelet in some cereals and other grasses.

Azo dye: Dyes in which the azo group is the chromophore and joins benzene or napthalene rings.

Background measurement: A measurement of pollutants in ambient air due to natural sources; usually taken in remote areas.

Bactericidal activity: The process of killing bacteria.

Barre: Bars or stripes in a fabric, caused by uneven weaving, irregular yarn or uneven dye distribution.

Basal cell: One of the innermost cells of the deeper epidermis of the skin.

Benzenethiol: A compound of benzene and a hydrosulfide group.

Beta (b)-lipoprotein: A biochemical complex or compound containing both lipid and protein and characterized by having a large molecular weight, rich in cholesterol. Found in certain fractions of human plasma.

Bilateral renal sclerosis: A hardening of both kidneys of chronic inflammatory origin.

Biomass: That part of a given habitat consisting of living matter.

Biosphere: The part of the earth's crust, waters and atmosphere where living organisms can subsist.

Biphasic: Having two distinct successive stages.

Bleb: A collection of fluid beneath the skin; usually smaller than bullae or blisters.

Blood urea: The chief end product of nitrogen metabolism in mammals, excreted in human urine in the amount of about 32 grams (1 oz.) a day.

Bloom: A greenish-gray appearance imparted to silk and pile fabrics either by nature of the weave or by the finish; also, the creamy white color observed on some good cottons.

Blue-green algae: A group of simple plants which are the only N_2-fixing organisms which photosynthesize as do higher plants.

Brightener: A compound such as a dye, which adheres to fabrics in order to provide better brightness or whiteness by converting ultraviolet radiation to visible light. Sometimes called optical bleach or whitening agent. The dyes used are of the florescent type.

Broad bean: The large flat edible seed of an Old World upright vetch (Vicia faba), or the plant itself, widely grown for its seeds and for fodder.

Bronchi: The first subdivisions of the trachea which conduct air to and from the bronchioles of the lungs.

Bronchiole: One of the finer subdivisions of the bronchial (trachea) tubes, less than 1 mm in diameter, and having no cartilage in its wall.

Bronchiolitis: Inflammation of the smallest bronchial tubes.

Bronchiolitis fibrosa obliterans syndrome: Obstruction of the bronchioles by fibrous granulation arising from an ulcerated mucosa; the condition may follow inhalation of irritant gases.

Bronchitis: Inflammation of the mucous membrane of the bronchial tubes. It may aggravate an existing asthmatic condition.

Bronchoconstrictor: An agent that causes a reduction in the caliber (diameter) of a bronchial tube.

Bronchodilator: An agent which causes an increase in the caliber (diameter) of a bronchus or bronchial tube.

Bronchopneumonia: Acute inflammation of the walls of the smaller bronchial tubes, with irregular area of consolidation due to spread of the inflammation into peribronchiolar alveoli and the alveolar ducts.

Brownian diffusion: Diffusion by random movement of particles suspended in liquid or gas, resulting from the impact of molecules of the fluid surrounding the particles.

Buffer: A substance in solution capable of neutralizing both acids and bases and thereby maintaining the original pH of the solution.

Buffering capacity: Ability of a body of water and its watershed to neutralize introduced acid.

Butanol: A four-carbon, straight-chain alcohol, C_4H_9OH, also known as butyl alcohol.

Butylated hydroxytoluene (BHT): A crystalline phenolic antioxidant.

Butylated hydroxyanisol (BHA): An antioxidant.

^{14}C labeling: Use of a radioactive form of carbon as a tracer, often in metabolic studies.

^{14}C-proline: An amino acid which has been labeled with radioactive carbon.

Calcareous: Resembling or consisting of calcium carbonate (lime), or growing on limestone or lime-containing soils.

Calorie: Amount of heat required to raise temperature of 1 gram of water at $15^{\circ}C$ by 1 degree.

Cannula: A tube that is inserted into a body cavity, or other tube or vessel, usually to remove fluid.

Capillary: The smallest type of vessel; resembles a hair. Usually in reference to a blood or lymphatic capillary vessel.

Carbachol: A chemical compound (carbamoylcholine chloride, $C_6H_{15}ClN_2O_2$) that produces a constriction of the bronchi; a parasympathetic stimulant used in veterinary medicine and topically in glaucoma.

Carbon monoxide: An odorless, colorless, toxic gas with a strong affinity for hemoglobin and cytochrome; it reduces oxygen absorption capacity, transport and utilization.

Carboxyhemoglobin: A fairly stable union of carbon monoxide with hemoglobin which interferes with the normal transfer of carbon dioxide and oxygen during circulation of blood. Increasing levels of carboxyhemoglobin result in various degrees of asphyxiation, including death.

Carcinogen: Any agent producing or playing a stimulatory role in the formation of a malignancy.

Carcinoma: Malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and giving rise to metastases.

Cardiac output: The volume of blood passing through the heart per unit time.

Cardiovascular: Relating to the heart and the blood vessels or the circulation.

Carotene: Lipid-soluble yellow-to-orange-red pigments universally present the photosynthetic tissues of higher plants, algae, and the photosynthetic bacteria.

Cascade impactor: A device for measuring the size distribution of particulates and/or aerosols, consisting of a series of plates with orifices of graduated size which separate the sample into a number of fractions of decreasing aerodynamic diameter.

Catabolism: Destructive metabolism involving the release of energy and resulting in breakdown of complex materials in the organism.

Catalase: An enzyme (EC 1.11.1.6) catalyzing the decomposition of hydrogen peroxide to water and oxygen.

Catalysis: A modification of the rate of a chemical reaction by some material which is unchanged at the end of the reaction.

Catalytic converter: An air pollution abatement device that removes organic contaminants by oxidizing them into carbon dioxide and water.

Catecholamine: A pyrocatechol with an alkalamine side chain, functioning as a hormone or neurotransmitter, such as epinephrine, morepinephrine, or dopamine.

Cathepsins: Enzymes which have the ability to hydrolyze certain proteins and peptides; occur in cellular structures known as lysosomes.

Cation: A positively charged ion.

Cellular permeability: Ability of gases to enter and leave cells; a sensitive indicator of injury to deep-lung cells.

Cellulose: The basic substance which is contained in all vegetable fibers and in certain man-made fibers. It is a carbohydrate and constitutes the major substance in plant life. Used to make cellulose acetate and rayon.

Cellulose acetate: Commonly refers to fibers or fabrics in which the cellulose is only partially acetylated with acetate groups. An ester made by reacting cellulose with acetic anhydride with SO_4 as a catalyst.

Cellulose rayon: A regenerated cellulose which is chemically the same as cellulose except for physical differences in molecular weight and crystallinity.

Cellulose triacetate: A cellulose fiber which is completely acetylated. Fabrics of triacetate have higher heat resistance than acetate and may be safely ironed at higher temperature. Such fabrics have improved ease-of-care characteristics because after heat treatment during manufacture, a change in the crystalline structure of the fiber occurs.

Cellulosics: Cotton, viscose rayon and other fibers made of natural fiber raw materials.

Celsius scale: The thermometric scale in which freezing point of water is 0 and boiling point is 100.

Central hepatic necrosis: The pathologic death of one or more cells, or of a portion of the liver, involving the cells adjacent to the central veins.

Central nervous system (CNS): The brain and the spinal cord.

Centroacinar area: The center portion of a grape-shaped gland.

Cerebellum: The large posterior brain mass lying above the pons and medulla and beneath the posterior portion of the cerebrum.

Cerebral cortex: The layer of gray matter covering the entire surface of the cerebral hemisphere of mammals.

Chain reaction: A reaction that stimulates its own repetition.

Challenge: Exposure of a test organism to a virus, bacteria, or other stress-causing agent, used in conjunction with exposure to a pollutant of interest, to explore possible susceptibility brought on by the pollutant.

Chamber study: Research conducted using a closed vessel in which pollutants are reacted or substances exposed to pollutants.

Chemiluminescence: A measurement technique in which radiation is produced as a result of chemical reaction.

Chemotactic: Relating to attraction or repulsion of living protoplasm by chemical stimuli.

Chlorophyll: A group of closely related green photosynthetic pigments occurring in leaves, bacteria, and organisms.

Chloroplast: A plant cell inclusion body containing chlorophyll.

Chlorosis: Discoloration of normally green plant parts that can be caused by disease, lack of nutrients, or various air pollutants, resulting in the failure of chlorophyll to develop.

Cholesterol: A steroid alcohol $C_{27}H_{45}OH$; the most abundant steroid in animal cells and body fluids.

Cholinesterase (CHE): One (EC 3.1.1.8) of a family of enzymes capable of catalyzing the hydrolysis of acylcholines.

Chondrosarcoma: A malignant neoplasm derived from cartilage cells, occurring most frequently near the ends of long bones.

Chromatid: Each of the two strands formed by longitudinal duplication of a chromosome that becomes visible during an early stage of cell division.

Chromophore: A chemical group that produces color in a molecule by absorbing near ultraviolet or visible radiation when bonded to a nonabsorbing, saturated residue which possesses no unshared, nonbonding valence electrons.

Chromosome: One of the bodies (46 in man) in the cell nucleus that is the bearer and carrier of genetic information.

Chronic respiratory disease (CRD): A persistent or long-lasting intermittent disease of the respiratory tract.

Cilia: Motile, often hairlike extensions of a cell surface.

Ciliary action: Movements of cilia in the upper respiratory tract, which move mucus and foreign material upward.

Ciliogenesis: The formation of cilia.

Citric acid (Krebs) cycle: A major biochemical pathway in cells, involving terminal oxidation of fatty acids and carbohydrates. It yields a major portion of energy needed for essential body functions and is the major source of CO_2. It couples the glycolytic breakdown of sugar in the cytoplasm with those reactions producing ATP in the mitochondria. It also serves to regulate the synthesis of a number of compounds required by a cell.

Clara cell: A nonciliated mammalian cell.

Closing volume (CV): The lung volume at which the flow from the lower parts of the lungs becomes severely reduced or stops during expiration, presumably because of airway closure.

Codon: A sequence of three nucleotides which encodes information required to direct the synthesis of one or more amino acids.

Coefficient of haze (COH): A measurement of visibility interference in the atmosphere.

Cohort: A group of subjects included in a test or experiment; usually characterized by age, class or other characteristic.

Collagen: The major protein of the white fibers of connective tissue, cartilage, and bond. Comprises over half the protein of the mammal.

Collisional deactivation: Reduction in energy of excited molecules caused by collision with other molecules or other objects such as the walls of a container.

Colorimetric: A chemical analysis method relying on measurement of the degree of color produced in a solution by reaction with the pollutant of interest.

Community exposure: A situation in which people in a sizeable area are subjected to ambient pollutant concentrations.

Compliance: A measure of the change in volume of an internal organ (e.g. lung, bladder) produced by a unit of pressure.

Complement: Thermolabile substance present in serum that is destructive to certain bacteria and other cells which have been sensitized by specific complement-fixing antibody.

Compound: A substance with its own distinct properties, formed by the chemical combination of two or more elements in fixed proportion.

Concanavalin-A: One of two crystalline globulins occurring in the jack bean; a potent hemagglutinin.

Conifer: A plant, generally evergreen, needle-leafed, bearing naked seeds singly or in cones.

Converter: See catalytic converter.

Coordination number: The number of bonds formed by the central atom in a complex.

Copolymer: The product of the process of polymerization in which two or more monomeric substances are mixed prior to polymerization. Nylon is a copolymer.

Coproporphyrin: One of two porphyrin compounds found normally in feces as a decomposition product of bilirubin (a bile pigment). Porphyrin is a widely-distributed pigment consisting of four pyrrole nuclei joined in a ring.

Cordage: A general term which includes banding, cable, cord, rope, string, and twine made from fibers. Synthetic fibers used in making cordage include nylon and dacron.

Corrosion: Destruction or deterioration of a material because of reaction with its environment.

Corticosterone: A steroid obtained from the adrenal cortex. It induces some deposition of glycogen in the liver, sodium conservation, and potassium excretion.

Cosmopolitan: In the biological sciences, a term denoting worldwide distribution.

Coulometric: Chemical analysis performed by determining the amount of a substance released in electrolysis by measuring the number of coulombs used.

Coumarin: A toxic white crystalline lactone ($C_9H_6O_2$) found in plants.

Coupler: A chemical used to combine two others in a reaction, e.g. to produce the azo dye in the Griess-Saltzman method for NO_2.

Crevice corrosion: Localized corrosion occurring within crevices on metal surfaces exposed to corrosives.

Crosslink: To connect, by an atom or molecule, parallel chains in a complex chemical molecule, such as a polymer.

Cryogenic trap: A pollutant sampling method in which a gaseous pollutant is condensed out of sampled air by cooling (e.g. traps in one method for nitrosamines are maintained below $-79°C$, using solvents maintained at their freezing points).

Cuboidal: Resembling a cube in shape.

Cultivar: An organism produced by parents belonging to different species or to different strains of the same species, originating and persisting under cultivation.

Cuticle: A thin outer layer, such as the thin continuous fatty film on the surface of many higher plants.

Cyanosis: A dark bluish or purplish coloration of the skin and mucous membrane due to deficient oxygenation of the blood.

Cyclic GMP: Guanosine 5'-phosphoric acid.

Cytochrome: A class of hemoprotein whose principal biological function is electron and/or hydrogen transport.

Cytology: The anatomy, physiology, pathology and chemistry of the cell.

Cytoplasm: The substance of a cell exclusive of the nucleus.

Dacron: The trade name for polyester fibers made by E.I. du Pont de Nemours and Co., Inc., made from dimethyl terephthalate and ethylene glycol.

Dark adaptation: The process by which the eye adjusts under reduced illumination and the sensitivity of the eye to light is greatly increased.

Dark respiration: Metabolic activity of plants at night; consuming oxygen to use stored sugars and releasing carbon dioxide.

Deciduous plants: Plants which drop their leaves at the end of the growing season.

Degradation (textiles): The decomposition of fabric or its components or characteristics (color, strength, elasticity) by means of light, heat, or air pollution.

Denitrification: A bacterial process occurring in soils, or water, in which nitrate is used as the terminal electron acceptor and is reduced primarily to N_2. It is essentially an anaerobic process; it can occur in the presence of low levels of oxygen only if the microorganisms are metabolizing in an anoxic microzone.

De novo: Over again.

Deoxyribonucleic acid (DNA): A nucleic acid considered to be the carrier of genetic information coded in the sequence of purine and pyrimidine bases (organic bases). It has the form of a double-stranded helix of a linear polymer.

Depauperate: Falling short of natural development or size.

Derivative spectrophotometer: An instrument with an increased capability for detecting overlapping spectral lines and bands and also for suppressing instrumentally scattered light.

Desorb: To release a substance which has been taken into another substance or held on its surface; the opposite of absorption or adsorption.

Desquamation: The shedding of the outer layer of any surface.

Detection limit: A level below which an element or chemical compound cannot be reliably detected by the method or measurement being used for analysis.

Detritus: Loose material that results directly from disintegration.

DeVarda alloy: An alloy of 50 percent Cu, 45 percent Al, 5 percent Zn.

Diastolic blood pressure: The blood pressure as measured during the period of filling the cavities of the heart with blood.

Diazonium salt: A chemical compound (usually colored) of the general structure ArN_2Cl^-, where Ar refers to an aromatic group.

Diazotizer: A chemical which, when reacted with amines (RNH_2, for example), produces a diazonium salt (usually a colored compound).

Dichotomous sampler: An air-sampling device which separates particulates into two fractions by particle size.

Differentiation: The process by which a cell, such as a fertilized egg, divides into specialized cells, such as the embryonic types that eventually develop into an entire organism.

Diffusion: The process by which molecules or other particles intermingle as a result of their random thermal motion.

Diffusing capacity: Rate at which gases move to or from the blood.

Dimer: A compound formed by the union of two like radicals or molecules.

Dimerize: Formation of dimers.

1,6-diphosphofructose aldolase: An enzyme (EC 4.1.1.13) cleaving fructose 1,6-bisphosphate to dihydroxyacetone phosphate and glyceraldehyde-3-phosphate.

D-2,3-diphosphoglycerate: A salt or ester of 2,3-diphosphoglyceric acid, a major component of certain mammalian erythrocytes involved in the release of O_2 from HbO_2. Also a postulated intermediate in the biochemical pathway involving the conversion of 3- to 2-phosphoglyceric acid.

Diplococcus pneumoniae: A species of spherical-shaped bacteria belonging to the genus Streptococcus. May be a causal agent in pneumonia.

Direct dye: A dye with an affinity for most fibers; used mainly when color resistance to washing is not important.

Disperse dyes: Also known as acetate dyes; these dyes were developed for use on acetate fabrics, and are now also used on synthetic fibers.

Distal: Far from some reference point such as median line of the body, point of attachment or origin.

Diurnal: Having a repeating pattern or cycle 24 hours long.

DL_{CO}: The diffusing capacity of the lungs for carbon monoxide. The ability of the lungs to transfer carbon monoxide from the alveolar air into the pulmonary capillary blood.

Dorsal hyphosis: Abnormal curvative of the spine; hunch-back.

Dose: The quantity of a substance to be taken all at one time or in fractional amounts within a given period; also the total amount of a pollutant delivered or concentration per unit time times time.

Dose-response curve: A curve on a graph based on responses occurring in a system as a result of a series of stimuli intensities or doses.

Dry deposition: The processes by which matter is transferred to ground from the atmosphere, other than precipitation; includes surface absorption of gases and sedimentation, Brownian diffusion and impaction of particles.

Dyeing: A process of coloring fibers, yarns, or fabrics with either natural or synthetic dyes.

Dynamic calibration: Testing of a monitoring system using a continuous sample stream of known concentration.

Dynamic compliance (C_{Ldyn}): Volume change per unit of transpulmonary pressure minus the pressure of pulmonary resistance during airflow.

Dynel: A trademark for a modacrylic staple fiber spun from a copolymer of acrylonitrile and vinyl chloride. It has high strength, quick-drying properties, and resistance to alkalies and acids.

Dyspepsia: Indigestion, upset stomach.

Dyspnea: Shortness of breath; difficulty or distress in breathing; rapid breathing.

Ecosystem: The interacting system of a biological community and its environment.

Eddy: A current of water or air running contrary to the main current.

Edema: Pressure of excess fluid in cells, intercellular tissue or cavities
    of the body.

Elastomer: A synthetic rubber product which has the physical properties
    of natural rubber.

Electrocardiogram: The graphic record of the electrical currents that
    initiate the heart's contraction.

Electrode: One of the two extremities of an electric circuit.

Electrolyte: A non-metallic electric conductor in which current is carried
    by the movement of ions; also a substance which displays these qualities
    when dissolved in water or another solvent.

Electronegativity: Measure of affinity for negative charges or electrons.

Electron microscopy: A technique which utilizes a focused beam of electrons
    to produce a high-resolution image of minute objects such as particu-
    late matter, bacteria, viruses, and DNA.

Electronic excitation energy: Energy associated in the transition of
    electrons from their normal low-energy orbitals or orbitals of higher
    energy.

Electrophilic: Having an affinity for electrons.

Electrophoresis: A technique by which compounds can be separated from a
    complex mixture by their attraction to the positive or negative
    pole of an applied electric potential.

Eluant: A liquid used in the process of elution.

Elute: To perform an elution.

Elution: Separation of one material from another by washing or by dissolving
    one in a solvent in which the other is not soluble.

Elutriate: To separate a coarse, insoluble powder from a finer one by
    suspending them in water and pouring off the finer powder from the
    upper part of the fluid.

Emission spectrometry: A rapid analytical technique based on measurement
    of the characteristic radiation emitted by thermally or electrically
    excited atoms or ions.

Emphysema: An anatomic alteration of the lung, characterized by abnormal
    enlargement of air spaces distal to the terminal bronchioles, due
    to dilation or destructive changes in the alveolar walls.

Emphysematous lesions: A wound or injury to the lung as a result of
    emphysema.

Empirical modeling: Characterization and description of a phenomena based on experience or observation.

Encephalitis: Inflammation of the brain.

Endoplasmic reticulum: An elaborate membrane structure extending from the nuclear membrane or eucaryotic cells to the cytoplasmic membrane.

Endothelium: A layer of flat cells lining especially blood and lymphatic vessels.

Entropy: A measure of disorder or randomness in a system. Low entropy is associated with highly ordered systems.

Enzyme: Any of numerous proteins produced by living cells which catalyze biological reactions.

Enzyme Commission (EC): The International Commission on Enzymes, established in 1956, developed a scheme of classification and nomenclature under which each enzyme is assigned an EC number which identifies it by function.

Eosinophils: Leukocytes (white blood cells) which stain readily with the dye, eosin.

Epidemiology: A study of the distribution and determinants of disease in human population groups.

Epidermis: The outermost living layer of cells of any organism.

Epididymal fat pads: The fatty tissue located near the epididymis. The epididymis is the first convoluted portion of the excretory duct of the testis.

Epiphyte: A plant growing on another plant but obtaining food from the atmosphere.

Epithelial: Relating to epithelium, the membranous cellular layer which covers free surfaces or lines tubes or cavities of an animal body, which encloses, protects, secretes, excretes and/or assimilates.

Erosion corrosion: Acceleration or increase in rate of deterioration or attack on a metal because of relative movement between a corrosive fluid and the metal surface. Characterized by grooves, gullies, or waves in the metal surface.

Erythrocyte: A mature red blood cell.

Escherichia coli: A short, gram-negative, rod-shaped bacteria common to the human intestinal tract. A frequent cause of infections in the urogenital tract.

Esophageal: Relating to the portion of the digestive tract between the pharynx and the stomach.

Estrus: That portion or phase of the sexual cycle of female animals characterized by willingness to permit coitus.

Estrus cycle: The series of physiologic uterine, ovarian and other changes that occur in higher animals.

Etiolation: Paleness and/or altered development resulting from the absence of light.

Etiology: The causes of a disease or condition; also, the study of causes.

Eucaryotic: Pertaining to those cells having a well-defined nucleus surrounded by a double-layered membrane.

Euthrophication: Elevation of the level of nutrients in a body of water, which can contribute to accelerated plant growth and filling.

Excited state: A state of higher electronic energy than the ground state, usually a less stable one.

Expiratory (maximum) flow rate: The maximum rate at which air can be expelled from the lungs.

Exposure level: Concentration of a contaminant to which an individual or a population is exposed.

Extinction coefficient: A measure of the space rate of diminution, or extinction, of any transmitted light, thus, it is the attenuation coefficient applied to visible radiation.

Extramedullary hematopoiesis: The process of formation and development of the various types of blood cells and other formed elements not including that occurring in bone marrow.

Extravasate: To exclude from or pass out of a vessel into the tissues; applies to urine, lymph, blood and similar fluids.

Far ultraviolet: Radiation in the range of wavelengths from 100 to 190 nanometers.

Federal Reference Method (FRM): For NO_2, the EPA-approved analyzers based on the gas-phase chemiluminescent measurement principle and associated calibration procedures; regulatory specifications prescribed in Title 40, Code of Federal Regulations, Part 50, Appendix F.

Fenestrae: Anatomical aperatures often closed by a membrane.

Fiber: A fine, threadlike piece, as of cotton, jute, or asbestos.

Fiber-reactive dye: A water-soluble dyestuff which reacts chemically with the cellulose in fibers under alkaline conditions; the dye contains two chlorine atoms which combine with the hydroxyl groups of the cellulose.

Fibrin: A white insoluble elastic filamentous protein derived from fibrinogen by the action of thrombin, especially in the clotting of blood.

Fibroadenoma: A benign neoplasm derived from glandular epithelium, involving proliferating fibroblasts, cells found in connective tissue.

Fibroblast: An elongated cell with cytoplasmic processes present in connective tissue, capable of forming collagen fibers.

Fibrosis: The formation of fibrous tissue, usually as a reparative or reactive process and not as a normal constituent of an organ or tissue.

Flocculation: Separation of material from a solution or suspension ؛ reaction with a flocculant to create fluffy masses containing ؟ ؏ material to be removed.

Fly ash: Fine, solid particles of noncombustible ash carried out of a bed of solid fuel by a draft.

Folded-path optical system: A long (e.g. 8-22 m) chamber with multiple mirrors at the ends which can be used to reflect an infrared beam through an ambient air sample many times; a spectrometer can be used with such a system to detect trace pollutants at very low levels.

Forced expiratory flow (FEF): The rate at which air can be expelled from the lungs; see expiratory flow rate.

Forced expiratory volume (FEV): The maximum volume of air that can be expired in a specific time interval when starting from maximal inspiration.

Forced vital capacity (FVC): The greatest volume of air that can be exhaled from the lungs under forced conditions after a maximum inspiration.

Fractional threshold concentration: The portion of the concentration at which an event or a response begins to occur, expressed as a fraction.

Free radical: Any of a variety of highly-reactive atoms or molecules characterized by having an unpaired electron.

Fritted bubbler: A porous glass device used in air pollutant sampling systems to introduce small bubbles into solution.

Functional residual capacity: The volume of gas remaining in the lungs
     at the end of a normal expiration. It is the sum of expiratory
     reserve volume and residual volume.

Gas exchange: Movement of oxygen from the alveoli into the pulmonary
     capillary blood as carbon dioxide enters the alveoli from the blood.

Gas chromatography (GC): A method of separating and analyzing mixtures
     of chemical substances. A flow of gas causes the components of a
     mixture to migrate differentially from a narrow starting zone in a
     special porous, insoluble sorptive medium. The pattern formed by
     zones of separated pigments and of colorless substances in this
     process is called a chromatogram, and can be analyzed to obtain the
     concentration of identified pollutants.

Gas-liquid chromatography: A method of separating and analyzing volatile
     organic compounds, in which a sample is vaporized and swept through
     a column filled with solid support material covered with a nonvolatile
     liquid. Components of the sample can be identified and their con-
     centrations determined by analysis of the characteristics of their
     retention in the column, since compounds have varying degrees of
     solubility in the liquid medium.

Gastric juice: A thin watery digestive fluid secreted by glands in the
     mucous membrane of the stomach.

Gastroenteritis: Inflammation of the mucous membrane of stomach and
     intestine.

Genotype: The type of genes possessed by an organism.

Geometric mean: An estimate of the average of a distribution. Specifically,
     the nth root of the product of n observations.

Geometric standard deviation: A measure of variability of a distribution.
     It is the antilogarithm of the standard deviation of the logarithms
     of the observations.

Globulins (a, b, q): A family of proteins precipitated from plasma (or
     serum) by half-saturation with ammonium sulfate, or separable by
     electrophoresis. The main groups are the a, b, q fractions, differ-
     ing with respect to associated lipids and carbohydrates and in their
     content of antibodies (immunoglobulins).

Glomular nephrotic syndrome: Dysfunction of the kidneys characterized
     by excessive protein loss in the urine, accumulation of body fluids
     and alteration in albumin/globulin ratio.

Glucose: A sugar which is a principal source of energy for man and other
     organisms.

Glucose-6-phosphate dehydrogenase: An enzyme (EC 1.1.1.49) catalyzing
     the dehydrogenation of glucose-6-phosphate to 6-phosphogluconolactone.

Glutamic-oxaloacetic transaminase (SGOT): An enzyme (EC 2.6.1.1) whose serum level increases in myocardial infarction and in diseases involving destruction of liver cells. Also known as aspartate aminotransferase.

Glutamic-pyruvic transaminase (SGPT): Now known as alanine aminotransferase (EC 2.6.1.2), the serum levels of this enzyme are used in liver function tests.

Glutathione (GSH): A tripeptide composed of glycine, cystine, and glutamic acid.

Glutathione peroxidase: An enzyme (EC 1.11.1) which catalyzes the destruction of hydroperoxides formed from fatty acids and other substances. Protects tissues from oxidative damage. It is a selenium-containing protein.

Glutathione reductase: The enzyme (EC 1.6.4.2) which reduces the oxidized form of glutathione.

Glycolytic pathway: The biochemical pathway by which glucose is converted to lactic acid in various tissues, yielding energy as a result.

Glycoside: A type of chemical compound formed from the condensation of a sugar with another chemical radical via a hemiacetal linkage.

Goblet cells: Epithelial cells that have been distended with mucin and when this is discharged as mucus, a goblet-shaped shell remains.

Golgi apparatus: A membrane system involved with secretory functions and transport in a cell. Also known as a dictyosome.

Grana: The lamellar stacks of chlorophyll-containing material in plant chloroplasts.

Griege carpet: A carpet in its unfinished state, i.e. before it has been scoured and dyed. The term also is used for woven fabrics in the unbleached and unfinished state.

Ground state: The state of minimum electronic energy of a molecule or atom.

Guanylate cyclase (GC): An enzyme (EC 4.6.2.1) catalyzing the transformation of guanosine triphosphate to guanosine 3':5'-cyclic phosphate.

H-Thymidine: Thymine deoxyribonucleoside: One of the four major nucleosides in DNA. ^{3}H-thymidine has been uniformly labeled with tritium, a radioactive form of hydrogen.

Haze: Fine dust, smoke or fine vapor reducing transparency of air.

Hemagglutination: The agglutination of red blood cells. Can be used as as a measurement of antibody concentration.

Hematocrit: The percentage of the volume of a blood sample occupied by cells.

Hematology: The medical specialty that pertains to the blood and blood-forming tissues.

Hemochromatosis: A disease characterized by pigmentation of the skin possibly due to inherited excessive absorption of iron.

Hemoglobin (Hb): The red, respiratory protein of the red blood cells, hemoglobin transports oxygen from the lungs to the tissues as oxy-hemoglobin (HbO_2) and returns carbon dioxide to the lungs as hemoglobin carbamate, completing the respiratory cycle.

Hemolysis: Alteration or destruction of red blood cells, causing hemoglobin to be released into the medium in which the cells are suspended.

Hepatectomy: Complete removal of the liver in an experimental animal.

Hepatic: Relating to the liver.

Hepatocyte: A liver cell.

Heterogeneous process: A chemical reaction involving reactants of more than one phase or state, such as one in which gases are absorbed into aerosol droplets, where the reaction takes place.

Heterologous: A term referring to donor and recipient cellular elements from different organisms, such as red blood cells from sheep and alveolar macrophage from rabbits.

Hexose monophosphate shunt: Also called the phosphogluconate oxidative pathway of glucose metabolism which affords a total combustion of glucose independent of the citric acid cycle. It is the important generator of NADPH necessary for synthesis of fatty acids and the operation of various enzymes. It serves as a source of ribose and 4- and 7-carbon sugars.

High-volume sampler (Hi-vol): Device for taking a sample of the particulate content of a large amount of air, by drawing air through a fiber filter at a typical rate of 2,000 m^3/24 hr (1.38 m^3/min), or as high as 2,880 m^3/24 hr (2 m^3/min).

Histamine: An amine derived from the amino acid, histidine. It is a powerful stimulant of gastric secretion and a constrictor of bronchial smooth muscle. It is a vasodilator and causes a fall in blood pressure.

Homogenate: Commonly refers to tissue ground into a creamy consistency in which the cell structure is disintegrated.

Host defense mechanism: Inherent means by which a biologic organism protects itself against infection, such as antibody formation, macrophage action, ciliary action, etc.

Host resistance: The resistance exhibited by an organism, such as man, to an infecting agent, such as a virus or bacteria.

Humoral: Relating to the extracellular fluids of the body, blood and lymph.

Hybrid: An organism descended from parents belonging to different varieties or species.

Hydrocarbons: A vast family of compounds containing carbon and hydrogen in various combinations; found especially in fossil fuels. Some contribute to photochemical smog.

Hydrolysis: Decomposition involving splitting of a bond and addition of the H and OH parts of water to the two sides of the split bond.

Hydrometeor: A product of the condensation of atmospheric water vapor (e.g. fog, rain, hail, snow).

Hydroxyproline: An amino acid found among the hydrolysis products of collagen.

Hygroscopic: Pertaining to a marked ability to accelerate the condensation of water vapor.

Hyperplasia: Increase in the number of cells in a tissue or organ excluding tumor formation.

Hyperplastic: Relating to hyperplasia; an increase in the number of cells.

Hypertrophy: Increase in the size of a tissue element, excluding tumor formation.

Hypertension: Abnormally elevated blood pressure.

Hypolimnia: Portions of a lake below the thermocline, in which water is stagnant and uniform in temperature.

Hypoxia: A lower than normal amount of oxygen in the air, blood or tissues

Immunoglobulin (Ig): A class of structurally related proteins consist-
     ing of two pairs of polypeptide chains. Antibodies are Ig's and
     all Ig's probably function as antibodies.

Immunoglobulin A (IgA): A type of antibody which comprises approximately
     10 to 15 percent of the total amount of antibodies present in normal
     serum.

Immunoglobulin G (IgG): A type of antibody which comprises approximately
     80 percent of the total amount of antibodies present in normal serum.
     Subfractions of IgG are fractions G_1, and G_2.

Immunoglobulin M (IgM): A type of antibody which comprises approximately
     5 to 10 percent of the total amount of antibodies present in normal
     serum.

Impaction: An impinging or striking of one object against another; also,
     the force transmitted by this act.

Impactor: An instrument which collects samples of suspended particulates
     by directing a stream of the suspension against a surface, or into a
     liquid or a void.

Index of proliferation: Ratio of promonocytes to polymorphic monocytes
     in the blood.

Infarction: Sudden insufficiency of arterial or venous blood supply
     due to emboli, thrombi, or pressure.

Infectivity model: A testing system in which the susceptibility of
     animals to airborne infectious agents with and without exposure to air
     pollutants is investigated to produce information related to the
     possible effects of the pollutant on man.

Inflorescence: The arrangement and development of flowers on an axis;
     also, a flower cluster or a single flower.

Influenza A_2/Taiwan Virus: An infectious viral disease, believed to
     have originated in Taiwan, characterized by sudden onset, chills,
     fevers, headache, and cough.

Infrared: Light invisible to the human eye, between the wavelengths
     of 7×10^{-7} and 10^{-3} m (7000 and 10,000,000 A).

Infrared laser: A device that utilizes the natural oscillations of atoms
     or molecules to generate coherent electromagnetic radiation in the
     infrared region of the spectrum.

Infrared spectrometer: An instrument for measuring the relative amounts
     of radiant energy in the infrared region of the spectrum as a function
     of wavelength.

Ingestion: To take in for digestion.

In situ: In the natural or original position.

Instrumental averaging time: The time over which a single sample or measurement is taken, resulting in a measurement which is an average of the actual concentrations over that period.

Insult: An injury or trauma.

Intercostal: Between the ribs, especially of a leaf.

Interferant: A substance which a measurement method cannot distinguish completely from the one being measured, which therefore can cause some degree of false response or error.

Interferon: A macromolecular substance produced in response to infection with active or inactivated virus, capable of inducing a state of resistance.

Intergranular corrosion: A type of corrosion which takes place at and adjacent to grain boundaries, with relatively little corrosion of the grains.

Interstitial edema: An accumulation of an excessive amount of fluids in a space within tissues.

Interstitial pneumonia: A chronic inflammation of the interstitial tissue of the lung, resulting in compression of air cells.

Intraluminal mucus: Mucus that collects within any tubule.

Intraperitoneal injection: An injection of material into the serous sac that lines the abdominal cavity.

In utero: Within the womb; not yet born.

In vitro: Refers to experiments conducted outside the living organism.

In vivo: Refers to experiments conducted within the living organism.

Irradiation: Exposure to any form of radiation.

Ischemia: Local anemia due to mechanical obstruction (mainly arterial narrowing) of the blood supply.

Isoenzymes: Also called isozymes. One of a group of enzymes that are very similar in catalytic properties, but may be differentiated by variations in physical properties, such as isoelectric point or electrophoretic mobility. Lactic acid dehydrogenase is an example of an enzyme having many isomeric forms.

Isopleth: A line on a map or chart connecting points of equal value.

Jacobs-Hochheiser method: The original Federal Reference Method for NO_2, currently unacceptable for air pollution work.

Klebsiella pneumoniae: A species of rod-shaped bacteria found in soil, water, and in the intestinal tract of man and other animals. Certain types may be causative agents in pneumonia.

Kyphosis: An abnormal curvature of the spine, with convexity backward.

Lactate: A salt or ester of lactic acid.

Lactic acid (lactate) dehydrogenase (LDH): An enzyme (EC 1.1.1.27) with many isomeric forms which catalyzes the oxidation of lactate to pyruvate via transfer of H to NAD. Isomeric forms of LDH in the blood are indicators of heart damage.

Lamellar bodies: Arranged in plates or scales. One of the characteristics of Type II alveolar cells.

Lavage fluid: Any fluid used to wash out hollow organs, such as the lung.

Lecithin: Any of several waxy hygroscopic phosphatides that are widely distributed in animals and plants; they form colloidal solutions in water and have emulsifying, wetting and hygroscopic properties.

Legume: A plant with root nodules containing nitrogen fixing bacteria.

Lesion: A wound, injury or other more or less circumscribed pathologic change in the tissues.

Leukocyte: Any of the white blood cells.

Lewis base: A base, defined in the Lewis acid-base concept, is a substance that can donate an electron pair.

Lichens: Perennial plants which are a combination of two plants, an alga and a fungus, growing together in an association so intimate that they appear as one.

Ligand: Those molecules or anions attached to the central atom in a complex.

Light-fastness: The ability of a dye to maintain its original color under natural or indoor light.

Linolenic acid: An unsaturated fatty acid essential in nutrition.

Lipase: An enzyme that accelerates the hydrolysis or synthesis of fats or the breakdown of lipoproteins.

Lipids: A heterogeneous group of substances which occur widely in bio-
logical materials. They are characterized as a group by their
extractability in nonpolar organic solvents.

Lipofuscin: Brown pigment granules representing lipid-containing residues
of lysosomal digestion. Proposed to be an end product of lipid
oxidation which accumulates in tissue.

Lipoprotein: Complex or protein containing lipid and protein.

Loading rate: The amount of a nutrient available to a unit area of body
of water over a given period of time.

Locomotor activity. Movement of an organism from one place to another
of its own volition.

Long-pathlength infrared absorption: A measurement technique in which a
system of mirrors in a chamber is used to direct an infrared beam
through a sample of air for a long distance (up to 2 km); the amount
of infrared absorbed is measured to obtain the concentrations of
pollutants present.

Lung compliance (C_l): The volume change produced by an increase in a
unit change in pressure across the lung, i.e., between the pleural
surface and the mouth.

Lycra: A spandex textile fiber created by E. I. du Pont de Nemours & Co.,
Inc., with excellent tensile strength, a long flex life and high
resistance to abrasion and heat degradation. Used in brassieres,
foundation garments, surgical hosiery, swim suits and military and
industrial uses.

Lymphocytes: White blood cells formed in lymphoid tissue throughout the
body, they comprise about 22 to 28 percent of the total number of
leukocytes in the circulating blood and function in immunity.

Lymphocytogram: The ratio, in the blood, of lymphocyte with narrow
cytoplasm to those with broad cytoplasm.

Lysosomes: Organelles found in cells of higher organisms that contain
high concentrations of degradative enzymes and are known to destroy
foreign substances that cells engulf by pinocytosis and phyocytosis.
Believed to be a major site where proteins are broken down.

Lysozymes: Lytic enzymes destructive to cell walls of certain bacteria.
Present in some body fluids, including tears and serum.

Macaca speciosa: A species of monkeys used in research.

Macrophage: Any large, ameboid, phagocytic cell having a nucleus without
many lobes, regardless of origin.

Malaise: A feeling of general discomfort or uneasiness, often the first
    indication of an infection or disease.

Malate dehydrogenase: An enzyme (EC 1.1.1.37) with at least six isomeric
    forms that catalyze the dehydrogenation of malate to oxaloacetate
    or its decarboxylation (removal of a CO_2 group) to pyruvate. Malate,
    oxaloacetate, and pyruvate are intermediate components of biochemical
    pathways.

Mannitol: An alcohol derived from reduction of the sugar, fructose.
    Used in renal function testing to measure glomerular (capillary)
    filtration.

Manometer: An instrument for the measurement of pressure of gases or
    vapors.

Mass median diameter (MMD): Geometric median size of a distribution of
    particles based on weight.

Mass spectrometry (MS): A procedure for identifying the various kinds of
    particles present in a given substance, by ionizing the particles
    and subjecting a beam of the ionized particles to an electric or
    magnetic field such that the field deflects the particles in angles
    directly proportional to the masses of the particles.

Maximum flow (V_{max}): Maximum rate or expiration, usually expressed at
    50 or 25 percent of vital capacity.

Maximum mid-expiratory flow rate (MMFR): The mean rate of expiratory gas
    flow between 25 and 75 percent of the forced expiratory vital capacity.

Mean (arithmetic): The sum of observations divided by sample size.

Median: A value in a collection of data values which is exceeded in
    magnitude by one-half the entries in the collection.

Mesoscale: Of or relating to meteorological phenomena from 1 to 100
    kilometers in horizontal extent.

Messenger RNA: A type of RNA which conveys genetic information encoded
    in the DNA to direct protein synthesis.

Metaplasia: The abnormal transformation of an adult, fully differentiated
    tissue of one kind into a differentiated tissue of another kind.

Metaproterenol: A bronchodilator used for the treatment of bronchial
    asthma.

Metastases: The shifting of a disease from one part of the body to another;
    the appearance of neoplasms in parts of the body remote from the seat
    of the primary tumor.

Meteorology: The science that deals with the atmosphere and its phenomena.

Methemoglobin: A form of hemoglobin in which the normal reduced state of iron (Fe^{2+}) has been oxidized to Fe^{3+}. It contains oxygen in firm union with ferric (Fe^{3+}) iron and is not capable of exchanging oxygen in normal respiratory processes.

Methimazole: An anti-thyroid drug similar in action to propylthiouracil.

Methyltransferase: Any enzyme transferring methyl groups from one compound to another.

Microcoulometric: Capable of measuring millionths of coulombs used in electrolysis of a substance, to determine the amount of a substance in a sample.

Microflora: A small or strictly localized plant.

Micron: One-millionth of a meter.

Microphage: A small phagocyte; a polymorphonuclear leukocyte that is phagocytic.

Millimolar: One-thousandth of a molar solution. A solution of one-thousandth of a mole (in grams) per liter.

Minute volume: The minute volume of breathing; a product of tidal volume times the respiratory frequency in one minute.

Mitochondria: Organelles of the cell cytoplasm which contain enzymes active in the conservation of energy obtained in the aerobic part of the breakdown of carbohydrates and fats, in a process called respiration.

Mobile sources: Automobiles, trucks and other pollution sources which are not fixed in one location.

Modacrylic fiber: A manufactured fiber in which the fiber-forming substance is any long chain synthetic polymer composed of less than 85 percent but at least 35 percent by weight of acrylonitrite units.

Moeity: One of two or more parts into which something is divided.

Mole: The mass, in grams, numerically equal to the molecular weight of a substance.

Molecular correlation spectrometry: A spectrophotometric technique which is used to identify unknown absorbing materials and measure their concentrations by using preset wavelengths.

Molecular weight: The weight of one molecule of a substance obtained by adding the gram-atomic weights of each of the individual atoms in the substance.

Monocyte: A relatively large mononuclear leukocyte, normally constituting 3 to 7 percent of the leukocytes of the circulating blood.

Mordant: A substance which acts to bind dyes to a textile fiber of fabric.

Morphological: Relating to the form and structure of an organism or any of its parts.

Moving average: A procedure involving taking averages over a specific period prior to and including a year in question, so that successive averaging periods overlap; e.g. a three-year moving average would include data from 1967 through 1969 for the 1969 average and from 1968 through 1970 for 1970.

Mucociliary clearance: Removal of materials from the upper respiratory tract via ciliary action.

Mucociliary transport: The process by which mucus is transported, by ciliary action, from the lungs.

Mucosa: The mucous membrane; it consists of epithelium, lamina propria and, in the digestive tract, a layer of smooth muscle.

Mucous membrane: A membrane secreting mucus which lines passages and cavities communicating with the exterior of the body.

Murine: Relating to mice.

Mutagen: A substance capable of causing, within an organism, biological changes that affect potential offspring through genetic mutation.

Mutagenic: Having the power to cause mutations. A mutation is a change in the character of a gene (a sequence of base pairs in DNA) that is perpetuated in subsequent divisions of the cell in which it occurs.

Myocardial infarction: Infarction of any area of the heart muscle usually as a result of occlusion of a coronary artery.

Nares: The nostrils.

Nasopharyngeal: Relating to the nasal cavity and the pharynx (throat).

National Air Surveillance Network (NASN): Network of monitoring stations for sampling air to determine extent of air pollution; established jointly by federal and state governments.

Near ultraviolet: Radiation of the wavelengths 2000-4000 Angstroms.

Necrosis: Death of cells that can discolor areas of a plant or kill the entire plant.

Necrotic: Pertaining to the pathologic death of one or more cells, or of a portion of tissue or organ, resulting from irreversible damage.

Neonate: A newborn.

Neoplasm: An abnormal tissue that grows more rapidly than normal; synonymous with tumor.

Neoplasia: The pathologic process that results in the formation and growth of a tumor.

Neutrophil: A mature white blood cell formed in bone marrow and released into the circulating blood, where it normally accounts for 54 to 65 percent of the total number of leukocytes.

Ninhydrin: An organic reagent used to identify amino acids.

Nitramine: A compound consisting of a nitrogen attached to the nitrogen of amine.

Nitrate: A salt or ester of nitric acid (NO_3^-).

Nitrification: The principal natural source of nitrate in which ammonium (NH_4^+) ions are oxidized to nitrites by specialized microorganisms. Other organisms oxidize nitrites to nitrates.

Nitrite: A salt or ester of nitrous acid ($NO_2^=$).

Nitrocellulose: Any of several esters of nitric acid formed by its action on cellulose, used in explosives, plastics, varnishes and rayon; also called cellulose nitrate.

Nitrogen cycle: Refers to the complex pathways by which nitrogen-containing compounds are moved from the atmosphere into organic life, into the soil, and back to the atmosphere.

Nitrogen fixation: The metabolic assimilation of atmospheric nitrogen by soil microorganisms, which becomes available for plant use when the microorganisms die; also, industrial conversion of free nitrogen into combined forms used in production of fertilizers and other products.

Nitrogen oxide: A compound composed of only nitrogen and oxygen. Components of photochemical smog.

Nitrosamine: A compound consisting of a nitrosyl group connected to the nitrogen of an amine.

Nitrosation: Addition of a nitrosyl group.

N-Nitroso compounds: Compounds carrying the functional nitrosyl group.

Nitrosyl: A group composed of one oxygen and one nitrogen atom (-N=O).

Nitrosylhemoglobin (NOHb): The red, respiratory protein of erythrocytes to which a nitrosyl group is attached.

N/P Ratio: Ratio of nitrogen to phosphorous dissolved in lake water, important due to its effect on plant growth.

Nucleolus: A small spherical mass of material within the substance of the nucleus of a cell.

Nucleophilic: Having an affinity for atomic nuclei; electron-donating.

Nucleoside: A compound that consists of a purine or pyrimidine base combined with deoxyribose or ribose and found in RNA and DNA.

5'-Nucleotidase: An enzyme (EC 3.1.3.5) which hydrolyzes nucleoside 5'-phosphates into phosphoric acid (H_3PO_4) and nucleosides.

Nucleotide: A compound consisting of a sugar (ribose or deoxyribose), a base (a purine or a pyrimidine), and a phosphate; a basic structural unit of RNA and DNA.

Nylon: A generic name chosen by E. I. du Pont de Nemours & Co., Inc. for a group of protein-like chemical products classed as synthetic linear polymers; two main types are Nylon 6 and Nylon 66.

Occlusion: A point which an opening is closed or obstructed.

Olefin: An open-chain hydrocarbon having at least one double bond.

Olfactory: Relating to the sense of smell.

Olfactory epithelium: The inner lining of the nose and mouth which contains neural tissue sensitive to smell.

Oligotrophic: A body of water deficient in plant nutrients; also generally having abundant dissolved oxygen and no marked stratification.

Oribitals: Areas of high electron density in an atom or molecule.

Orlon: An acrylic fiber produced by E. I. du Pont de Nemours and Co., Inc., based on a polymer of acrylonitrite; used extensively for outdoor uses, it is resistant to chemicals and withstands high temperatures.

Osteogenic osteosarcoma: The most common and malignant of bone sarcomas (tumors). It arises from bone-forming cells and affects chiefly the ends of long bones.

Ovarian primordial follicle: A spheroidal cell aggregation in the ovary in which the primordial oocyte (immature female sex cell) is surrounded by a single layer of flattened follicular cells.

Oxidant: A chemical compound which has the ability to remove electrons from another chemical species, thereby oxidizing it; also, a substance containing oxygen which reacts in air to produce a new substance, or one formed by the action of sunlight on oxides of nitrogen and hydrocarbons.

Oxidation: An ion or molecule undergoes oxidation by donating electrons.

Oxidative deamination: Removal of the NH_2 group from an amino compound by reaction with oxygen.

Oxidative phosphorylation: The mitochondrial process by which "high-energy" phosphate bonds form from the energy released as a result of the oxidation of various substrates. Principally occurs in the tri-carboxylic acid pathway.

Oxyhemoglobin: Hemoglobin in combination with oxygen. It is the form of hemoglobin present in arterial blood.

Ozone layer: A layer of the stratosphere from 20 to 50 km above the earth's surface characterized by high ozone content produced by ultra-violet radiation.

Ozone scavenging: Removal of O_3 from ambient air or plumes by reaction with NO, producing NO_2 and O_2.

Paired electrons: Electrons having opposite intrinsic spins about their own axes.

Parenchyma: The essential and distinctive tissue of an organ or an ab-normal growth, as distinguished from its supportive framework.

Parenchymal: Referring to the distinguishing or specific cells of a gland or organ.

Partial pressure: The pressure exerted by a single component in a mixture of gases.

Particulates: Fine liquid or solid particles such as dust, smoke, mist, fumes or smog, found in the air or in emissions.

Pascal: A unit of pressure in the International System of Units. One pascal is equal to 7.4×10^{-3} torr. The pascal is equivalent to one newton per square meter.

Pathogen: Any virus, microorganism, or other substance causing disease.

Pathophysiological: Derangement of function seen in disease; alteration in function as distinguished from structural defects.

Peptide bond: The bond formed when two amino acids react with each other.

Percentiles: The percentage of all observations exceeding or preceding some point; thus, 90th percentile is a level below which will fall 90 percent of the observations.

Perfusate: A liquid, solution or colloidal suspension that has been passed over a special surface or through an appropriate structure.

Perfusion: Artificial passage of fluid through blood vessels.

Permanent-press fabrics: Fabrics in which applied resins contribute to the
     easy care and appearance of the fabric and to the crease and seam
     flat-
     ness by reacting with the cellulose on pressing after garment
     manufacture.

Permeation tube: A tube which is selectively porous to specific gases.

Peroxidation: Refers to the process by which certain organic compounds
     are converted to peroxides.

Peroxyacetyl nitrate (PAN): Pollutant created by action of sunlight on
     hydrocarbons and NO_x in the air; an ingredient of photochemical smog.

pH: A measure of the acidity or alkalinity of a material, liquid, or solid.
     pH is represented on a scale of 0 to 14 with 7 being a neutral state,
     0 most acid, and 14 most alkaline.

Phagocytosis: Ingestion, by cells such as macrophages, of other cells,
     bacteria, foreign particles, etc.; the cell membrane engulfs solid or
     liquid particles which are drawn into the cytoplasm and digested.

Phenotype: The observable characteristics of an organism, resulting from
     the interaction between an individual genetic structure and the
     environment in which development takes place.

Phenylthiourea: A crystalline compound, $C_7H_8N_2S$, that is bitter or tasteless
     depending on a single dominant gene in the tester.

Phlegm: Viscid mucus secreted in abnormal quantity in the respiratory passages

Phosphatase: Any of a group of enzymes that liberate inorganic phosphate
     from phosphoric esters (E.C. sub-subclass 3.1.3).

Phosphocreatine kinase: An enzyme (EC 2.7.3.2) catalyzing the formation of
     creatine and ATP, its breakdown is a source of energy in the contraction
     of muscle; also called creatine phosphate.

Phospholipid: A molecule consisting of lipid and phosphoric acid group(s).
     An example is lecithin. Serves as an important structural factor
     in biological membranes.

Photochemical oxidants: Primary ozone, NO_2, PAN with lesser amounts of
     other compounds formed as products of atmospheric reactions involving
     organic pollutants, nitrogen oxides, oxygen, and sunlight.

Photochemical smog: Air pollution caused by chemical reaction of various
     airborne chemicals in sunlight.

Photodissociation: The process by which a chemical compound breaks down into
     simpler components under the influence of sunlight or other radiant energy.

Photolysis: Decomposition upon irradiation by sunlight.

Photomultiplier tube: An electron multiplier in which electrons released by photoelectric emission are multiplied in successive stages by dynodes that produce secondary emissions.

Photon: A quantum of electromagnetic energy.

Photostationary: A substance or reaction which reaches and maintains a steady state in the presence of light.

Photosynthesis: The process in which green parts of plants, when exposed to light under suitable conditions of temperature and water supply, produce carbohydrates using atmospheric carbon dioxide and releasing oxygen.

Phytotoxic: Poisonous to plants.

Phytoplankton: Minute aquatic plant life.

Pi π bonds: Bonds in which electron density is not symmetrical about a line joining the bonded atoms.

Pinocytotic: Refers to the cellular process (pinocytosis) in which the cytoplasmic membrane forms invaginations in the form of narrow channels leading into the cell. Liquids can flow into these channels and the membrane pinches off pockets that are incorporated into the cytoplasm and digested.

Pitting: A form of extremely localized corrosion that results in holes in the metal. One of the most destructive forms of corrosion.

Pituary: A stalk-like gland near the base of the brain which is attached to the hypothalmus. The anterior portion is a major repository for for hormones that control growth, stimulate other glands, and regulate the reproductive cycle.

Placenta: The organ in the uterus that provides metabolic interchange between the fetus and mother.

Plasmid: Replicating unit, other than a nucleus gene, that contains nucleoprotein and is involved in various aspects of metabolism in organisms; also called paragenes.

Plasmolysis: The dissolution of cellular components, or the shrinking of plant cells by osmotic loss of cytoplasmic water.

Plastic: A plastic is one of a large group of organic compounds synthesized from cellulose, hydrocarbons, proteins or resins and capable of being cast, extruded, or molded into various shapes.

Plasticizer: A chemical added to plastics to soften, increase malleability or to make more readily deformable.

Platelet (blood): An irregularly-shaped disk with no definite nucleus; about one-third to one-half the size of an erythrocyte and containing no hemoglobin. Platelets are more numerous than leukocytes, numbering from 200,000 to 300,000 per cu. mm. of blood.

Plethysmograph: A device for measuring and recording changes in volume of a part, organ or the whole body; a body plethysmograph is a chamber apparatus surrounding the entire body.

Pleura: The serous membrane enveloping the lungs and lining the walls of the chest cavity.

Plume: Emission from a flue or chimney, usually distributed stream-like downwind of the source, which can be distinguished from the surrounding air by appearance or chemical characteristics.

Pneumonia (interstitial): A chronic inflammation of the interstitial tissue of the lung, resulting in compression of the air cells. An acute, infectious disease.

Pneumonocytes: A nonspecific term sometimes used in referring to types of cells characteristic of the respiratory part of the lung.

Podzol: Any of a group of zonal soils that develop in a moist climate, especially under coniferous or mixed forest.

Point source: A single stationary location of pollutant discharge.

Polarography: A method of quantitative or qualitative analysis based on current-voltage curves obtained by electrolysis of a solution with steadily increasing voltage.

Pollution gradient: A series of exposure situations in which pollutant concentrations range from high to low.

Polyacrylonitrile: A polymer made by reacting ethylene oxide and hydrocyanic acid. Dynel and Orlon are examples.

Polyamides: Polymerization products of chemical compounds which contain amino ($-NH_2$) and carboxyl ($-COOH$) groups. Condensation reactions between the groups.form amides ($-CONH_2$). Nylon is an example of a polyamide.

Polycarbonate: Any of various tough transparent thermoplastics characterized by high impact strength and high softening temperature.

Polycythemia: An increase above the normal in the number of red cells in the blood.

Polyester fiber: A man-made or manufactured fiber in which the fiber-forming substance is any long-chain synthetic polymer composed of at least 85 percent by weight of an ester of a dihydric alcohol and terephthalic acid. Dacron is an example.

Polymer: A large molecule produced by linking together many like molecules.

Polymerization: In fiber manufacture, converting a chemical monomer (simple molecule) into a fiber-forming material by joining many like molecules into a stable, long-chain structure.

Polymorphic monocyte: Type of leukocyte with a multi-lobed nucleus.

Polymorphonuclear leukocytes: Cells which represent a secondary non-specific cellular defense mechanism. They are transported to the lungs from the bloodstream when the burden handled by the alveolar macrophages is too large.

Polysaccharides: Polymers made up of sugars. An example is glycogen which consists of repeating units of glucose.

Polystyrene: A thermoplastic plastic which may be transparent, opaque, or translucent. It is light in weight, tasteless and odorless, it also is resistant to ordinary chemicals.

Polyurethane: Any of various polymers that contain NHCOO linkages and are used especially in flexible and rigid foams, elastomers and resins.

Pores of Kohn: Also known as interalveolar pores; pores between air cells. Assumed to be pathways for collateral ventilation.

Precipitation: Any of the various forms of water particles that fall from the atmosphere to the ground, rain, snow, etc.

Precursor: A substance from which another substance is formed; specifically, one of the anthropogenic or natural emissions or atmospheric constituents which reacts under sunlight to form secondary pollutants comprising photochemical smog.

Probe: In air pollution sampling, the tube or other conduit extending into the atmosphere to be sampled, through which the sample passes to treatment, storage and/or analytical equipment.

Proline: An amino acid, $C_5H_9NO_2$, that can be synthesized from glutamate by animals.

Promonocyte: An immature monocyte not normally seen in the circulating blood.

Proteinuria: The presence of more than 0.3 gm of urinary protein in a 24-hour urine collection.

Pulmonary: Relating to the lungs.

Pulmonary edema: An accumulation of excessive amounts of fluid in the lungs.

Pulmonary lumen: The spaces in the interior of the tubular elements of the lung (bronchioles and alveolar ducts).

Pulmonary resistance: Sum of airway resistance and viscous tissue resistance.

Purine bases: Organic bases which are constituents of DNA and RNA, including adenine and guanine.

Purulent: Containing or forming pus.

Pyrimidine bases: Organic bases found in DNA and RNA. Cytosine and thymine occur in DNA and cytosine and uracil are found in RNA.

QRS: Graphical representation on the electrocardiogram of a complex of three distinct waves which represent the beginning of ventricular contraction.

Rainout: Removal of particles and/or gases from the atmosphere by their involvement in cloud formation (particles act as condensation nuclei, gases are absorbed by cloud droplets), with subsequent precipitation.

Rayleigh scattering: Coherent scattering in which the intensity of the light of wavelength g, scattered in any direction making an angle r with the incident direction, is directly proportional to $1 + \cos^2 r$ and inversely proportional to g^4.

Reactive dyes: Dyes which react chemically with cellulose in fibers under alkaline conditions. Also called fiber reactive or chemically reactive dyes.

Reduction: Acceptance of electrons by an ion or molecule.

Reference method (RM): For NO_2, an EPA-approved gas-phase chemiluminescent analyzer and associated calibration techniques; regulatory specifications are described in Title 40, Code of Federal Regulations, Part 50, Appendix F. Formerly, Federal Reference Method.

Residual capacity: The volume of air remaining in the lungs after a maximum expiratory effort; same as residual volume.

Residual volume (RV): The volume of air remaining in the lungs after a maximal expiration. RV = TLC - VC

Resin: Any of various solid or semi-solid amorphous natural organic substances, usually derived from plant secretions, which are soluble in organic solvents but not in water; also any of many synthetic substances with similar properties used in finishing fabrics, for permanent press shrinkage control or water repellency.

Ribosomal RNA: The most abundant RNA in a cell and an integral constituent of ribosomes.

Ribosomes: Discrete units of RNA and protein which are instrumental in the synthesis of proteins in a cell. Aggregates are called polysomes.

Runoff: Water from precipitation, irrigation or other sources that flows over the ground surface to streams.

Sclerosis: Pathological hardening of tissue, especially from overgrowth of fibrous tissue or increase in interstitial tissue.

Selective leaching: The removal of one element from a solid alloy by corrosion processes.

Septa: A thin wall dividing two cavities or masses of softer tissue.

Seromucoid: Pertaining to a mixture of watery and mucinous material such as that of certain glands.

Serum antiprotease: A substance, present in serum, that inhibits the activity of proteinases (enzymes which destroy proteins).

Sigma (s) bonds: Bonds in which electron density is symmetrical about a line joining the bonded atoms.

Silo-filler's disease: Pulmonary lesion produced by oxides of nitrogen produced by fresh silage.

Single breath nitrogen elimination rate: Percentage rise in nitrogen fraction per unit of volume expired.

Single breath nitrogen technique: A procedure in which a vital capacity inspiration of 100 percent oxygen is followed by examination of nitrogen in the vital capacity expirate.

Singlet state: The highly-reactive energy state of an atom in which certain electrons have unpaired spins.

Sink: A reactant with or absorber of a substance.

Sodium arsenite: Na_3AsO_3, used with sodium hydroxide in the absorbing solution of a 24-hour integrated manual method for NO_2.

Sodium dithionite: A strong reducing agent (a supplier of electrons).

Sodium metabisulfite: $Na_2S_2O_5$, used in absorbing solutions of NO_2 analysis methods.

Sorb: To take up and hold by absorption or adsorption.

Sorbent: A substance that takes up and holds another by absorption or adsorption.

Sorbitol dehydrogenase: An enzyme that interconverts the sugars, sorbitol and fructose.

Sorption: The process of being sorbed.

Spandex: A manufactured fiber in which the fiber forming substance is a long chain synthetic elastomer composed of at least 85 percent of a segmented polyurethane.

Spectrometer: An instrument used to measure radiation spectra or to determine wavelengths of the various radiations.

Spectrophotometry: A technique in which visible, UV, or infrared radiation is passed through a substance or solution and the intensity of light transmitted at various wavelengths is measured to determine the spectrum of light absorbed.

Spectroscopy: Use of the spectrometer to determine concentrations of an air pollutant.

Spermatocytes: A cell destined to give rise to spermatozoa (sperm).

Sphingomyelins: A group of phospholipids found in brain, spinal cord, kidney and egg yolk.

Sphygomenometer: An apparatus, consisting of a cuff and a pressure gauge, which is used to measure blood pressure.

Spirometry: Also called pneometry. Testing the air capacity of the lungs with a pneometer.

Spleen: A large vascular organ located on the upper left side of the abdominal cavity. It is a blood-forming organ in early life. It is a storage organ for red corpuscles and because of the large number of macrophages, acts as a blood filter.

Sputum: Expectorated matter, especially mucus or mucopurulent matter expectorated in diseases of the air passages.

Squamous: Scale-like, scaly.

Standard deviation: Measure of the dispersion of values about a mean value. It is calculated as the positive square root of the average of the squares of the individual deviations from the mean.

Standard temperature and pressure: 0^oC, 760 mm mercury.

Staphylococcus aureus: A spherically-shaped, infectious species of bacteria found especially on nasal mucous membrane and skin.

Static lung compliance ($C_{L,stat}$): Measure of lung's elastic recoil (volume change resulting from change in pressure) with no or insignificant air-flow.

Steady state exposure: Exposure to air pollutants whose concentration remains constant for a period of time.

Steroids: A large family of chemical substances comprising many hormones and vitamins and having large ring structures.

Stilbene: An aromatic hydrocarbon $C_{14}H_{12}$ used as a phosphor and in making dyes.

Stoichiometric factor: Used to express the conversion efficiency of a non-quantitative reaction, such as the reaction of NO_2 with azo dyes in air monitoring methods.

Stoma: A minute opening or pore (plural is stomata).

Stratosphere: That region of the atmosphere extending from 11 km above the surface of the earth to 50 km. At 50 km above the earth temperature rises to a maximum of 0^oC.

Streptococcus pyogenes: A species of bacteria found in the human mouth, throat and respiratory tract and in inflammatory exudates, blood stream, and lesions in human diseases. It causes formation of pus or even fatal septicemias.

Stress corrosion cracking: Cracking caused by simultaneous presence of tensile stress and a specific corrosive medium. The metal or alloy is virtually unattached over most of its surface, while fine cracks progress through it.

Strong interactions: Forces or bond energies holding molecules together. Thermal energy will not disrupt the formed bonds.

Sublobular hepatic necrosis: The pathologic death of one or more cells, or of a portion of the liver, beneath one or more lobes.

Succession: The progressive natural development of vegetation towards a climax, during which one community is gradually replaced by others.

Succinate: A salt of succinic acid involved in energy production in the citric acid cycle.

Sulfadiazine: One of a group of sulfa drugs. Highly effective against pneumococcal, staphlococcal, and streptococcal infections.

Sulfamethazine: An antibacterial agent of the sulfonamide group, active against homolytic streptococci, staphytococci, pneumococci and meningococci

Sulfanilimide: A crystalline sulfonamide ($C_6H_8N_2O_2S$), the amide of sulfanilic acid and parent compound of most sulfa drugs.

Sulfhydryl group: A chemical radical consisting of sulfur and hydrogen
    which confers reducing potential to the chemical compound to which it is
    attached (-SH).

Sulfur dioxide (SO_2): Colorless gas with pungent odor released primarily from
    burning of fossil fuels, such as coal, containing sulfur.

Sulfur dyes: Used only on vegetable fibers, such as cottons. They are
    insoluble in water and must be converted chemically in order to be
    soluble. They are resistant (fast) to alkalies and washing and fairly
    fast to sunlight.

Supernatant: The clear or partially clear liquid layer which separates
    from the homogenate upon centrifugation or standing.

Surfactant: A substance capable of altering the physiochemical nature of
    surfaces, such as one used to reduce surface tension of a liquid.

Symbiotic: A close association between two organisms of different species in
    which at least one of the two benefits.

Synergistic: A relationship in which the combined action or effect of two
    or more components is greater than that of the components acting separately.

Systolic: Relating to the rhythmical contraction of the heart.

Tachypnea: Very rapid breathing.

Terragram (Tg): One million metric tons, 10^{12} grams.

Teratogenesis: The disturbed growth processes resulting in a deformed
    fetus.

Teratogenic: Causing or relating to abnormal development of the fetus.

Threshold: The level at which a physiological or psychological effect begins
    to be produced.

Thylakoid: A membranous lamella of protein and lipid in plant chloroplasts
    where the photochemical reactions of photosynthesis take place.

Thymidine: A nucleoside ($C_{10}H_{14}N_2O_5$) that is composed of thymine and
    deoxyribose; occurs as a structural part of DNA.

Tidal volume (V_T): The volume of air that is inspired or expired in a single
    breath during regular breathing.

Titer: The standard of strength of a volumetric test solution. For example,
    the titration of a volume of antibody-containing serum with another
    volume containing virus.

Tocopherol: a-d-tocopherol is one form of Vitamin E prepared synthetically. The a form exhibits the most biological activity. It is an antioxidant and retards rancidity of fats.

Torr: A unit of pressure sufficient to support a 1 mm column of mercury; 760 torr = 1 atmosphere.

Total lung capacity (TLC): The sum of all the compartments of the lung, or the volume of air in the lungs at maximum inspiration.

Total suspended particulates (TSP): Solid and liquid particles present in the atmosphere.

Trachea: Commonly known as the windpipe, a cartilaginous air tube extending from the larnyx (voice box) into the thorax (chest) where it divides, serving as the entrance to each of the lungs.

Transaminase: Aminotransferase; an enzyme transferring an amino group from an a-amino acid to the carbonyl carbon atom of an a-keto acid.

Transmissivity (UV): The percent of ultraviolet radiation passing through a a medium.

Transmittance: The fraction of the radiant energy entering an absorbing layer which reaches the layer's further boundary.

Transpiration: The process of the loss of water vapor from plants.

Triethanolamine: An amine, $(HOCH_2CH_2)_3N$, used in the absorbing solution of one analytical method for NO_2^-.

Troposphere: That portion of the atmosphere in which temperature decreases rapidly with altitude, clouds form, and mixing of air masses by convection takes place. Generally extends to about 7 to 10 miles above the earth's surface.

Type 1 epithelial cells: Squamous cells which provide a continuous lining to the alveolar surface.

Type I pneumonocytes: Pulmonary surface epithelial cells.

Type II pneumonocytes: Great alveolar cells.

Ultraviolet: Light invisible to the human eye of wavelengths between $4x10^{-7}$ and $5x10^{-9}$ m (4000 to 50A).

Urea-formaldehyde resin: A compound composed of urea and formaldehyde in an arrangement that conveys thermosetting properties.

Urobilinogen: One of the products of destruction of blood cells; found in the liver, intestines and urine.

Uterus: The womb; the hollow muscular organ in which the impregnated ovum (egg) develops into the fetus.

Vacuole: A minute space in any tissue.

Vagal: Refers to the vagus nerve. This mixed nerve arises near the medulla oblongata and passes down from the cranial cavity to supply the larynx, lungs, heart, esophagus, stomach, and most of the abdominal viscera.

Valence: The number of electrons capable of being bonded or donated by an atom during bonding.

Van Slyke reactions: Reaction of primary amines, including amino acids, with nitrous acid, yielding molecular nitrogen.

Variance: A measure of dispersion or variation of a sample from its expected value; it is usually calculated as the square root a sum of squared deviations about a mean divided by the sample size.

Vat dyes: Dyes which have a high degree of resistance to fading by light, NO_x and washing. Widely used on cotton and viscose rayon. Colors are brilliant and of almost any shade. The name was originally derived from their application in a vat.

Venezuelan equine encephalomyelitis: A form of equine encephalomyelitis found in parts of South America, Panama, Trinidad, and the United States, and caused by a virus. Fever, diarrhea, and depression are common. In man, there is fever and severe headache after an incubation period of 2 to 5 days.

Ventilatory volume (V_E): The volume of gas exchanged between the lungs and the atmosphere that occurs in breathing.

Villus: A projection from the surface, especially of a mucous membrane.

Vinyl chloride: A gaseous chemical suspected of causing at least one type of cancer. It is used primarily in the manufacture of polyvinyl chloride, a plastic.

Viscose rayon: Filaments of regenerated cellulose coagulated from a solution of cellulose xanthate. Raw materials can be cotton linters or chips of spruce, pine, or hemlock.

Visible region: Light between the wavelengths of 4000-8000 $\overset{\circ}{A}$.

Visual range: The distance at which an object can be distinguished from background.

Vital capacity: The greatest volume of air that can be exhaled from the lungs after a maximum inspiration.

Vitamin E: Any of several fat-soluble vitamins (tocopherols), essential in nutrition of various vertibrates.

Washout: The capture of gases and particles by falling raindrops.

Weak interactions: Forces, electrostatic in nature, which bind atoms and/or molecules to each other. Thermal energy will disrupt the interaction. Also called van der Waal's forces.

Wet deposition: The process by which atmospheric substances are returned to earth in the form of rain or other precipitation.

Wheat germ lipase: An enzyme, obtained from wheat germ, which is capable of cleaving a fatty acid from a neutral fat; a lipolytic enzyme.

X-ray fluorescence spectrometry: A nondestructive technique which utilizes the principle that every element emits characteristic x-ray emissions when excited by high-energy radiation.

Zeolites: Hydrous silicates analogous to feldspars, occurring in lavas and various soils.

Zooplankton: Minute animal life floating or swimming weakly in a body of water.