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Epidemiological studies of the respiratory effects of air pollution

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ABSTRACT: Environmental epidemiological studies of the health effects of air pollution have been major contributors to the understanding of such effects. The chronic effects of atmospheric pollutants have been studied, but, except for the known respiratory effects of particulate matter (PM), they have not been studied conclusively. There are ongoing studies of the chronic effects of certain pollutant classes, such as ozone, acid rain, airborne toxics, and the chemical form of PM (including diesel exhaust).

Acute effects on humans due to outdoor and indoor exposures to several gases/fumes and PM have been demonstrated in epidemiological studies. However, the effects of these environmental factors on susceptible individuals are not known conclusively. These acute effects are especially important because they increase the human burden of minor illnesses, increase disability, and are thought to decrease productivity. They may be related to the increased likelihood of chronic disease as well. Further research is needed in this latter area, to determine the contributions of the time-related activities of individuals in different microenvironments (outdoors, in homes, in transit). Key elements of further studies are the assessment of total exposure to the different pollutants (occurring from indoor and outdoor sources) and the interactive effects of pollutants.

Major research areas include determination of the contributions of indoor sources and of vehicle emissions to total exposure, how to measure such exposures, and how to measure human susceptibility and responses (including those at the cellular and molecular level). Biomarkers of exposures, doses and responses, including immunochemicals, biochemicals and deoxyribonucleic acid (DNA) adducts, are beginning to promote some basic knowledge of exposure-response, especially the mechanisms. These will be extremely useful additions to standard physiological, immunological, and clinical instruments, and the understanding of biological plausibility. The outcomes of all this work will be the management of risks and the prevention of respiratory diseases related to air pollution.
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Previously published reviews of this series
1. Sandström T. Respiratory effects of air pollutants: experimental studies in humans. *Eur Respir J* 1995; 8: 976–995.
2. Chitano P, Hosselet JJ, Mapp CE, Fabbri LM. Effects of oxidant air pollutants on the respiratory system: insights from experimental animal research. *Eur Respir J* 1995; 8: 1357–1371.
3. Heyder J, Takenaka S. Long-term canine exposure studies with ambient air pollutants. *Eur Respir J* 1996; 9: 571–584.

This review of epidemiological studies of the respiratory effects of exposures to air pollutants follows excellent reviews of experimental studies in animals and humans that have recently appeared in the Journal [1–3]. It has relied both on prior reviews of the topic and on the extensive literature of the major research reports. It includes, as requested, evaluations of the exposure-response relationships for different respiratory effects and some risk assessment, and also attempts to look at the important issues and hypotheses awaiting further research.

Historically, the clearest evidence for an association between air pollution and health outcomes in populations was from acute mortality epidemics. There were a number of well-known acute air pollution episodes [4–10]. These episodes had greatly increased concentrations of sulphur oxides (SO_2) and particulate matter (PM), and often increased acidity, usually due to unfavourable meteorological conditions and air stagnation. A very significant increase in daily mortality occurred, primarily among persons with prior cardiac and respiratory disease. These epidemics led to the subsequent epidemiological investigations of environmental health effects.

Some guidelines for epidemiological investigations

In order to understand exposures to contaminants and the resulting health impacts, it has been suggested [11, 12] that one needs to evaluate: 1) the type of viable and nonviable particles; 2) the various sources of contaminants and the physicochemical factors leading to exposures; 3) the chemical nature of the complex mixtures in the air and the atmospheric physical (including meteorological) interactions; 4) the nature and mechanisms of the morbidity effects associated with the contaminants, including the range and distribution of sensitivity in the population; and 5) the methods of evaluation. Epidemiological methods provide the opportunity to study pollutants and interactions in complex environments within this framework. Assessments differ with the different

mechanisms (allergic, infective or irritant/toxic). Epidemiological investigators can study effects of real-life exposures in various population subgroups, even though it may be difficult to attribute the specific adverse health effects observed to concentrations of any one pollutant. Epidemiology also needs to resolve the methodological problems relating to the measures of exposure, the measures of effect (and avoidance of bias), and the use of covariables and confounding variables [4–6, 12–14].

Without adequate exposure data, epidemiological studies may be of little use in studying such refined issues [8, 15, 16]. Personal exposure factors, including time-activity patterns, may cause a given subject to experience pollution levels very different from those measured at a nearby fixed monitoring station [8, 12, 15]. For instance, exposure to sources of indoor pollution may be critical, given that the majority of time is spent indoors, and those exposures may have deleterious respiratory health effects, as will be discussed [8, 10, 16].

The epidemiological evaluation of the pathogenesis and natural history of respiratory diseases requires examination of human susceptibility and sensitivity of specific subgroups to air pollution [4, 5, 7, 11–15, 17–24]. Susceptibility may have been innate (*e.g.* genetic) and/or induced by events/exposures (infectious, allergenic and/or irritant); physiological and immunological markers of susceptibility and sensitization continue to be found. Those who are susceptible usually hyperrespond when exposed. Asthmatics are excellent examples of individuals who were susceptible to air pollutants; and once sensitized or inflicted with the disease, they are susceptible to the effects of many environmental (and nonenvironmental) triggers. Furthermore, differences between smokers and nonsmokers suggest that smokers are less responsive than nonsmokers. Smokers have altered lung function and an increase in mucus, both of which could influence dose in the different regions of the lung. They also have smaller airway calibre, predisposing them to bronchial responsiveness. Age also determines susceptibility; children appear to be more susceptible. The elderly may be more susceptible, due mainly to existing disease. Pre-existing conditions are often manifestations of susceptibility, which typically implies that the individual is endowed with some physiological or biochemical characteristic that may lead to an enhanced response. The underlying characteristic is not usually idiosyncratic, but shared by others, usually a small fraction of the population. Likewise, it is possible that some subgroups have host characteristics that protect them or permit them to adapt to exposures. Also, factors associated with lower socioeconomic status, including crowding and nutrition, may predispose individuals or increase risk. Even without obvious susceptibility, approximately 10–20% of healthy subjects will have symptomatic or lung function responses to irritants [5, 13, 14].

Pollutant factors of importance

The deposition of gaseous pollutants depends on their reactivity, whether they are freely gaseous or adsorbed on particles, and whether they are inhaled through the nose or mouth. Highly reactive-hydroscopic gases (*e.g.* SO_2) are absorbed almost entirely in the nose during normal nasal breathing; on the other hand, ozone (O_3) readily can reach the alveoli. Exercise during exposure increases the pollutant effect on ventilatory function. Deposition also depends on enlargement of aerosols and any neutralization that occurs in the airways. Metabolism will also determine the fate of some gaseous pollutants [8, 10, 14, 25]. Deposition of PM and associated effects depend on the size of particles as well as on the type of breathing; tracheobronchial deposition occurs with a fraction of 0.14–0.36 for 10 µm aerodynamic diameter (D_{ae}) particles, 0.09–0.27 for 12 µm D_{ae}; it is 0.12 under maximally deep inhalation of 16.4 µm D_{ae}. "... there can be a significant deposition of particles >10 µm D_{ae}" [5]. Lesser deposition can occur even with larger particles, including pollen [26].

Short-term exposures and acute effects

Mortality

Acute mortality responses appear to occur in nonepidemic conditions as well as epidemic. Table 1 provides a compendium of the studies of short-term mortality associated with air pollutants and meteorology.

Sulphur oxides and particulates. The best-known episode of mortality associated with sulphur oxides (SO_x) and PM was the London fog of December 1952. About 4,000 excess deaths occurred, predominantly attributed to bronchitis/pneumonia [4, 5, 10]. Subsequent episodes in London were also documented (table 1), and multiple reanalyses have occurred and been reviewed [5, 10, 29, 30, 42, 50]. Some analyses indicate that acidic sulphur may have played a role [10] (Environmental Protection Agency (EPA), in press). A study of the Donora episode of 1948 also found excess mortality in those with existing disease [51]. There may also have been effects in children (*op cit.* [18]).

In New York City, excess deaths were also found in some episodes, mostly among persons 45 yrs of age and older, due to influenza, pneumonia and cardiopulmonary causes; these studies, negative studies, and reanalyses have been presented and reviewed [4–6, 9, 10, 32]. Similar analyses have been conducted at other times in other cities under conditions of lower pollution; the quantitative studies are presented in table 1 and the qualitative studies have been reviewed previously [53]. Episodes of the duration and intensity reported before the early 1960s no longer seem to occur in the cities of the United States and Western Europe, but probably occur in Eastern Europe.

As noted above, not all quantitative studies agree on results even with the same or similar data bases for the same locations. This occurred even with inclusion of weather variables, lag effects, and controls for effects of other pollutants in the analyses of the death certificate files. Some studies, as noted, have found PM to be the remaining significant pollutant, whilst others have found SO_x to be more important; some have found sulphate (the particulate SO_x) to be the key pollutant [53]; and conflicting results concerning the effects of acidity continue to appear [46, 54]. Some qualitative studies using

Table 1. – Quantitative relationship of short-term exposure to daily mortality

First author	Year	[Ref]	Location	24 h exposure $\mu g \cdot m^{-3}$				Results
				SO_2	Smoke	TSP	PM10	
LOGAN	1953	[27]	London, UK 1952	>1000	>1000			Threefold increase during 5 day fog*
Ministry Health	1954	[28]						
MARTIN	1960	[29]	London, UK 1958–1960	500**	500**			Significant increase when exceeding limits shown*
LAWTHER	1963	[30]	London, UK 1958–1959	710	750			1.25 fold increase
BUECHLEY	1973	[31]	New York, USA 1962–1966	500				Correlation; 2% excess at level shown* COHs NS
POPE	1992	[32]	Salt Lake City, UT, USA	low			47–297	Significant increase in mortality (50–100 $\mu g \cdot m^{-3}$) - 7.5% in respiratory deaths (6.3-day⁻¹) - 8% in total deaths; NS in summer or with other pollutants in model
LYON	1995	[33]	Salt Lake City, USA	low			47–297	No significant increase overall; some increase in the elderly
SCHWARTZ	1992	[34]	Philadelphia, PA, USA	Med=47		<380		7% increase in total mortality per 100 $\mu g \cdot m^{-2}$ increase in TSP; weather, season, SO_2 in models
LI	1995	[35]	Philadelphia, PA, USA	Med=47		<380		No significant increase
SCHWARTZ	1992	[34]	Steubenville, OH, USA	<7->55		<36->209		4% increase in total mortality per 100 $\mu g \cdot m^{-3}$ increase in TSP; weather, season, SO_2 in models
HATZAKIS	1986	[36]	Athens, Greece	≥80	55–250			Small significant effect of SO_2 (not smoke) on mortality in the elderly
KATSOUYANNI	1993	[37]	Athens and 14 Greek Cities	≥80	55–250			No independent effect of either SO_2 or smoke; independent effect of temp. (>30°C) and some interaction of high temp. and high SO2; effect of O_3 NS
TOULOUMI	1994	[38]	Athens				78–306	Significant 3.4% increase (50–100 $\mu g \cdot m^{-3}$) in total mortality, 3 day lag; NS with SO_2, CO in model
FAIRLEY	1990	[39]	San Jose, CA, USA	low			<150·day⁻¹	0.12% increase in mortality per increase of 10 $\mu g \cdot m^{-3}$ PM10
SHUMWAY	1988	[40]	Los Angeles, CA, USA	low			>100#	1.1% increase in mortality per increase of 10 $\mu g \cdot m^{-3}$ PM10
ABBEY	1995	[41]	Los Angeles and other CA areas	low		>200	>100	No increase in total or cause-specific mortality
KINNEY	1995	[42]	Los Angeles and other CA areas	low			58–177	No increase in total or cause-specific mortality
DOCKERY	1992	[43]	St. Louis, MO, USA	<34 $\mu g \cdot m^{-3}$			28–97	Significant 8% increase in total mortality (50–100 $\mu g \cdot m^{-3}$); NS with O_3 in model†
SCHWARTZ	1993	[44]	Kingston, TN, USA	<34 $\mu g \cdot m^{-3}$			30–67	No significant increase in mortality†
			Birmingham, AL, USA	?			48–163	Significant 5% increase (50–100 $\mu g \cdot m^{-3}$) in total mortality, 3 day lag; no other AP in model†
OZKAYNAK	1994	[45]	Toronto, Canada	?			40–96	Significant 2.5% increase (50–100 $\mu g \cdot m^{-3}$) in total mortality; no other AP in model†
ITO	1995	[46]	Chicago, IL, USA	?			38–128	Significant 2.5% increase (50–100 $\mu g \cdot m^{-3}$) in total mortality, CO in model, ≤3 day lag†
STYER	1995	[47]	Chicago, IL, USA	?			37–365	No significant increase in total mortality; 3 day lag†
OSTRO	1995	[48]	Santiago, Chile	?			115–367	Significant 2.6–7% increase in total mortality; 50–100 $\mu g \cdot m^{-3}$), ≤4 day lag, other AP in models†
XU	1994	[49]	Beijing, China	Annual x̄=93 – 390		Annual x̄=108 vs 350		Significant doubling of respiratory disease mostly related to SO_2 and TSP; only SO_2 significant for other mortality and in winter; other factors in models

*: multiple reanalysis performed; other studies of a lesser quantitative nature generally confirmatory, including one in The Netherlands (EPA, 1982 [5]); acid may also have been involved (WHO 1987 [10]; ATS 1978 [4]; Ito et al. 1995 [46]); **: thresholds according to WHO (1987); ‡: adjusted value <150 $\mu g \cdot m^{-3}$; #: from Ostro & Abbey; †: from EPA PM Criteria Document (1995). EPA: Environmental Protection Agency; WHO: World Health Organization; ATS: American Thoracic Society; NS: nonsignificant; PM10: particulate matter with aerodynamic diameter <10 μm; TSP: total suspended particulates; temp: temperature; x̄: mean; AP: air pollutant; COH: coefficient of haze; Med: median.

Table 2. – PM10-acute respiratory and cardiovascular mortality effects studies based on various PM measures*

Health outcome	Location	Original PM measurement (lag)	Mean equivalent PM10	% change per 10 µg·m⁻³ PM10 equivalent	95% CI
Respiratory mortality	Birmingham, AL, USA	PM10 (3 day)	48	1.5	-5.8–9.4
	Utah Valley, UT, USA	PM10 (5 day)	47	3.7	0.7–6.7
	Philadelphia, PA, USA	TSP (2 day)	40	3.3	0.1–6.6
	Santa Clara, CA, USA	COH	35	3.5	1.5–5.6
Cardiovascular mortality	Birmingham, AL, USA	PM10 (3 day)	48	1.6	-1.5–3.7
	Utah Valley, UT, USA	PM10 (5 day)	47	1.8	0.4–3.3
	Philadelphia, PA, USA	TSP (2 day)	40	1.7	1.0–2.4
	Santa Clara, CA, USA	COH	35	0.8	0.1–1.6

*: EPA Summary, unpublished, 1995. PM: particulate matter; PM10: particulate matter with aerodynamic diameter ≤10 µm; 95% CI: 95% confidence interval; TSP: total suspended particulates; COH: hydrocarbon; EPA: Environmental Protection Agency; lag: number of days between air pollution and increase in mortality.

different general linear models (GLMs) also demonstrate some disagreement of results for the same cities, though most are in agreement when PM or SO_2 concentrations are above the World Health Organization (WHO)/European (EURO) [10] lower limits of such effects, shown in table 1, which are similar to those shown by EPA [4]. However, current estimates include estimates below the current standards and guidelines (table 2), which deserve further discussion.

The studies by certain groups using Poisson & GEE statistical methods appear to give consistent estimates of mortality excesses related to exposure to PM, as seen in table 2. The use of these methods as well as other GLMs in theoretically similar data sets which did not yield similar results (table 1), has raised questions about the use of certain models [42]. Disagreements have also arisen as to the biological plausibility of the results as well as aspects of causality [55–57], and the appropriateness of the exposure assessments. Current discussions have favoured the likelihood that the elderly, cardiopulmonary cases are the most likely to be affected.

The associations may not be simple linear relationships, and other determinants of day-to-day changes in mortality make it difficult to specify a pollutant concentration at which excess deaths begin to occur [4, 12, 57]. Many intervening factors, such as temperature extremes, influenza epidemics, holiday weekends, and season of the year, have strong effects on the day-to-day number of deaths and may enhance or minimize the effect of air pollution [12, 31, 57–60]. Thus, there is still no agreement as to how many deaths may be attributed specifically to the air pollutants [4, 5, 61]. There is little disagreement that the effects of temperature still predominate.

Ozone/oxidants, nitrogen dioxide and carbon monoxide. Temporal analyses of mortality associated with ozone (O_3) or total oxidants (O_x) have been less frequent, though ozone has been incorporated in some of the PM studies. In these latter studies, the effect of ozone is often as strong as that of PM [52]. Studies in various locales have found high temperatures to be the primary source of mortality, though O_3 is sometimes concurrent in linear model solutions with temperature and other pollutants [10, 13, 37, 41, 62]. There has been a study in Los Angeles that showed significant associations both of O_3

and nitrogen dioxide (NO_2) with total and cause-specific mortality [42]; PM was not significant. No lowest observed effect levels (LOELs) have been defined for acute mortality associated with O_3 or NO_2.

Two studies have shown associations of carbon monoxide (CO) with mortality in the Los Angeles area; both controlled for temperature and other pollutants. The first [63] showed only the effect of CO on cardiovascular mortality. The second [40] showed effects both of CO and PM on total and cardiovascular mortality.

Summary of current knowledge. Air pollutants together with temperature can cause increases in short-term mortality. The issues of such mortality increases have been discussed frequently in the past few years (*e.g.* [52]). Recent findings have generated hypotheses, and there has been agreement that further studies are needed using appropriate exposure and response measures, and that statistical analyses have to be replicated using the same data sets as used in the prior analyses and investigations. The major statistical issues addressed have indicated that none of the methods utilized were invalid *per se*. Use of any of the methods needs to include their appropriate use, the nature and number of variables and of cases, and the nature of temporal trends. Independence and colinearity of observations and confounding need to be addressed further, as should testing of assumptions, heterogeneity, and "sensitivity" (*ibid.*). As prior differences in results could be related to any of these factors (*ibid.*, [6, 55–57]), reanalyses are underway to examine such factors; preliminary results differ quantitatively but not qualitatively from prior results [64]. New study designs should have the ability to explore nonlinear threshold models [55]. Evaluation continues of mortality effects in those (especially the elderly) with existing cardiopulmonary diseases; it is likely that some small shortening of life (or increased morbidity and disability) could occur under the circumstances described in studies showing significant associations.

Interpretations have too often depended on data from stationary monitors when individuals' exposures are not reflected by such measurements. Furthermore, the size and species of the particulate should be critical aspects of the exposure measurements, especially as different particles produce different physiological and pathological responses. It was concluded that one needed epidemiological studies that utilized appropriate monitors (with

respect to simplicity, reliability and quality of data) for personal exposure assessments within studies designed to focus on the dose-response nature of the PM and other pollutant effects [52, 56].

Exacerbations of chronic respiratory diseases

PM/SO$_x$ and chronic obstructive pulmonary disease (COPD). Some studies of the daily symptom status of patients with COPD show relationships between disease status and air pollution concentrations at relatively high concentrations of sulphur dioxide and particulates [4, 5, 65–68], as seen in table 3. Low temperatures can exert a greater effect than air pollution [98]. An extensive series of studies on the effects of air pollution on bronchitic patients was conducted in the UK between 1955 and 1970 [65–68]. They showed that exacerbations of disease were associated with high concentrations of smoke (>250 µg·m^{-3}) and SO$_2$ (>500 µg·m^{-3}), although they were associated with relative increases rather than absolute concentrations. Furthermore, in the UK, examination of sickness absence records, of rates of physician consultation and of daily records of hospital admissions through the emergency service, showed associations with periods of heavy air pollution [4, 5]. With decreasing concentrations of pollutants in the UK, it has been difficult (since 1969) to relate bronchitics' symptom status to variations in air pollution (Waller, personal communication).

In Barcelona (Spain), SUNYER *et al.* [99] demonstrated that patients with COPD had significantly increased frequencies of visits to emergency rooms related to PM and SO$_2$ during winter, and SO$_2$ predominantly in summer; the increases in visits related to 25 µg·m^{-3} SO$_2$ were 6 and 9%, respectively; other variables were controlled in analyses, and the reliability of diagnoses was confirmed. In Ontario (Canada), BURNETT *et al.* [100] found increases for respiratory hospital admissions in those aged over 65 yrs of 2.8–3.2%, related to 13 µg·m^{-3} increases in sulphate, after controlling for O$_3$, temperature and season. (A reliability study of COPD hospital admissions in nearby Quebec [101] found a 75.5% correspondence with national health insurance data). Only studies covering an entire catchment area are considered to show an accurate relationship between admission rates and air pollution, and clinical studies in general do not appear to represent events in an entire community. The reliability of the diagnosis in USA hospitals is usually considered to be less than elsewhere [5, 13].

Higher annual sulphate levels in the USA have also been associated with increased symptoms in cardiopulmonary patients, and symptoms of acute and chronic respiratory diseases in children and adults [102]. Children with chronic respiratory disease symptomatology in The Netherlands had decreased peak flow, increased wheeze and increased bronchodilator use associated with total suspended particulates (TSP) >110 µg·m^{-3} in winter [89–90].

PM/O$_3$ and COPD. Various studies in the USA of respiratory disease hospital admissions have shown relationships with particulate matter with an aerodynamic diameter ≤10 µm (PM10) and often with O$_3$ after controlling for temperature; increases ranged 1.2–13% in the elderly per 50 µg·m^{-3} PM10, and 3.5–57% for COPD per 100 µg·m^{-3} PM10 [103–106]; the lack of known catchment areas for the hospitals weaken such findings (see below). In a field study of adults with symptoms of COPD [21], O$_3$ was significantly related to peak expiratory flow (PEF) after adjustment was made for smoking, relative humidity, TSP, and gas-stove use, as was TSP after all adjustments; and there was an substantial O$_3$-TSP interaction.

Asthma. Asthmatics appear to be more susceptible to short-term peak concentration of air pollutants, although there is a broad range of sensitivity [4, 17, 107, 108]. Oral breathing produces larger and quicker effects, as does exercise. Air pollution may also enhance the asthmatic patient's reactivity to other stimuli. Recent studies have reported a pollutant-induced enhancement of the effect of pharmacological bronchoconstricting agents at relatively low concentrations of NO$_2$, O$_3$, and SO$_x$, alone or together (*ibid*; [11, 85, 109]). Sulphate, sulphuric acid and nitrate affect asthmatics more in experimental studies, especially as potentiators of exercise or bronchoconstrictor challenges; other chemicals may also act as potentiators. In addition, these pollutants may act as potentiators for exposure to allergens and their effects in allergic asthmatics [8, 11, 85, 110, 111]. Thus, the sensitivity of asthmatics to external stimuli, indicates that various air pollutants, allergens, and weather conditions are important classes of the many that can precipitate attacks.

PM/SO$_x$ and asthma. In Donora, during the 1948 air pollution episode, 88% of those persons with asthma reported respiratory symptoms during the episode, a rate twice that of the general population [51]. Increased hospitalization was found to be related to SO$_2$ in Vancouver, Canada [112]. In Seattle, PM was found to be similarly related [44], but not in Detroit [105]. SAMET *et al.* [113] also found very little effect of air pollutants on asthma Emergency Room (ER) visits. Other studies have recorded increased ER visits for persons with asthma during air pollution episodes and during other times of increased air pollution concentrations ([4, 5].

Increased rates of asthma attacks and reduced lung function were noted in epidemiological studies during episodes, or days of higher levels of sulphur oxides/PM (tables 3 and 4). Lagged effects of outdoor PM and temperature in asthmatics have been seen in various locales. Sulphates are more likely than sulphur dioxide alone to be responsible for many of the adverse health effects typically associated with SO$_2$, even after rates were adjusted for temperature. The studies conducted in several US cities suggest that even 8–15 µg·m^{-3} (for 24 h) is associated with the acute effects [102]. COHEN *et al.* [73] found such relationships for asthma attack rates (reported and confirmed) in all physician diagnosed asthmatics in one town. Temperature and pollutants also had a synergistic relationship to attacks. Suspended sulphate showed the strongest relationship; however, suspended nitrate, SO$_2$ and TSP individually, as well as in combination, explained a significant portion of the residual. MOSEHOLM *et al.* [147] also reported the effects of NO$_2$, SO$_2$ and weather in Denmark; medication use was also

Table 3. – Acute symptoms associated with air pollutants

First author	Year	[Ref]	Location	SO₂	TSP	PM2.5/BS	PM10	O₃*	NO₂	Results
						Exposures µg·m⁻³#				
HAMMER	1976	[69]	New York, USA	286 LOEL†	145 LOEL	RSP annual x̄ 28–43 [SO₄ 10–14]				Increase in LRI in children with increases above these levels
LOVE	1981	[70]	Salt Lake City, USA	low			11–195	low	low	Significant 20% increase in URI in nonasthmatic children; LRI NS; temp. in model (winter)
POPE	1991	[71]								
POPE	1992	[72]	Salt Lake City, UT, USA	low			7–251	low	low	Significant 20% increase in LRI, 29% increase in cough in symptomatic children; winter; temp. but not other AP in models (NS in asymptomatic children)
COHEN	1972	[73]	Cumberland, WV, USA	200 LOEL†	150 LOEL	[SO₄]			[NO₃]	Increase in asthma attacks when these levels exceeded interaction with low temp; SO₄ and NO₃ effects also
HAMMER	1977	[74]	Birmingham, AL, USA	26 LOEL† x̄=8	180–220 LOEL x̄=73.1 (20–148)					Increase in LRI in children with increases above these levels
ZAGRANISKI	1979	[75]	New Haven, CT, USA	?		[SO₄ x̄=12.5; 1.5–35.7]		8–461		Significant increase in symptoms in asthma/allergy and smoking adults related to O₃ and pH of TSP, not related to SO₄
OSTRO	1991	[76]	Denver, CO, USA	?		0.5–73		?	?	No significant increase in cough in adult asthmatics†
OSTRO	1993	[53]	Southern CA, USA	?	(SO₄: 2–36) (6 day)	COH: 4–26		20–549	?	Significant 48% increase (50–100 µg·m⁻³ SO₄ and/or 0.1 ppm O₃) in LRI in nonsmoking adults; no significant increase in URI: temp; other AP, stoves NS
SCHWARTZ	1994	[77]	6 cities in USA 1984–1988	Median =10.5 90th%=47		Median =18 90th%=37	Median =30 90th%=53	Median =36.9 90th%=54	Median =24.4 90th%=45	Significant 51% increase in cough and 103% increase in LRI in PM and 2 AP models; temp., city included in model; 22% increase in cough with 30 ppb increase in ozone
HAMMER	1974	[78]	Los Angeles, CA, USA		?			78–980	?	Significant increase in cough, increased chest discomfort, in young adults related to O₃ but not to NO₂, TSP, CO†
SCHWARTZ	1989	[79]								
SCHWARTZ	1990	[80]								
WHITTMORE	1980	[81]	Los Angeles, CA, USA		x̄ 51–121			59–294		Significant increase in asthma attacks in juvenile–adult asthmatics; SO₂ and NOₓ highly correlated with TSP
MARGOLIS	1994	[82]	Orange County, CA, USA	<79	Median= SO₄ 5.7; ≤10			0.05–0.30 ppb 6 h <29	Upper third ≥150	Significantly increased symptoms (and decreased PEF) in adult asthmatics related to SO₄ and NO₂, controlling for other AP, temp., season, medications, pollen and fungi
KRZYZANOWSKI	1992	[83]	Tucson, AZ, USA			Median= <81 75th%=<105	≤187 (x̄=42)	29–181 ppb, 1 h 18–161 ppb 8 h	25.1± 10.2	Increase in allergic and irritant symptoms and ARIs above 56 ppb O₃ independently and interactive with temp. and with PM10 >50 µg·m⁻³ indoor AP, and covariates; independent increase in symptoms with PM10; PEF decrease (3.8% per 100 ppb) also significant (with no threshold)
QUACKENBOSS	1991	[84]								
LEBOWITZ	1992	[85]								

see next page for definitions.

Table 3. – Cont.......

First author	Year	[Ref]	Location	Exposures µg·m⁻³#						Results
				SO$_2$	TSP	PM$_{2.5}$/BS	PM$_{10}$	O$_3$*	NO$_2$	
Lebowitz Lebowitz Lebowitz Lebowitz	1984 1985 1985 1987	[21] [23] [86] [87]	Tucson, AZ, USA	(SO$_4$ annual= 3.39–4.69)	57–389			180–239	319–413 (1 h)	Wheeze and cough increase related to TSP, O$_3$ and NO$_2$, independently in adult asthmatics, controlling for significant effects of temp., RH, indoor AP, pollen; interactions with temp. usually significant; NS in normals; increased rhinitis, cough, sore throat in allergies seen with TSP; time in/out included
Vedal	1987	[88]	Chestnut Ridge, PA, USA,	≤176 (1 h)		COH ≤1.3 units (1 h)		≤129		No significant relationship with symptoms (or PEF)
Lawther	1970	[65]	London, UK 1954–1964	500–600		BS=250–500			?	Increase in bronchitics' symptoms with these levels; temp. important
Hoek	1993	[89]	Wageningen, NL	≤105	≤110				≤127	ARI NS; temp. in model (winter)
Roemer	1993	[90]	Wageningen, NL		>110					Significant increase in cough in symptomatic children in winter related to TSP
Dusseldorf	1994	[91]	Netherlands	?			4–137		?	No significant increase in cough in adults near steel mill†
Makino Mizoguchi	1975 1977	[92] [93]	Tokyo, Japan	-266	? high			≤45 O$_x$	≤207*	Significant increase in symptoms in children independently related to O$_x$, SO$_2$, TSP and temp.
Shimizu	1976	[94]	Osaka, Japan	<1596*				<373 O$_x$	<226*	Significant increase in symptoms in children related to SO$_2$, TSP; weather in models
Schwartz	1991	[95]	5 German Communities 1983–1985	Median= 9–48	Median= 17–56 90th%= 41–118				Median= 14–>50	Significant 26% increase in ARI in children; TSP NS with NO$_2$ in model; weather in model
von Mutius	1995	[96]	Leipzig, Germany	20–90	40–250				NO$_x$: 40–500	Significant increase in URI in children related to SO$_2$, NO$_x$, TSP, controlling for temp., ETS; with possible interactions
Forsberg	1993	[97]	Pitea, Sweden	1.3–12.9		BS= 1.0–21.4			7.4–55.8	Significant increase in dyspnoea in asthmatics related to BS; temp. and RH in model

#: 24 h, unless otherwise noted; *: 1 h daily maximum values unless otherwise stated; †: from EPA Criteria Documents; LOEL: lowest observed effect level; x̄: mean; TSP: total suspended particulates; PM$_{2.5}$: particulate matter with aerodynamic diameter ≤2.5 µm; BS: black smoke; RSP: respirable suspended particulate (~PM$_{3.5}$); COH: coefficient of haze; PM$_{10}$: particulate matter with aerodynamic diameter ≤10 µm; LRI: lower respiratory illness; URI: upper respiratory illness; NS: nonsignificant; temp: temperature; AP: air pollutant; ppb: parts per billion; PEF: peak expiratory flow; ARI: acute respiratory infection; RH: relative humidity; ETS: environmental tobacco smoke.

Table 4. – Acute pulmonary function changes associated with air pollution

First author	Year	[Ref]	Location	Exposures µg·m⁻³						Results
				SO_2	TSP	PM2.5/BS	PM10	O_3*	NO_2	
SPECKTOR	1988	[114]	Tuxedo, NY, USA	?		H_2SO_4 ≤9	?	41–243	?	Significant decrease in spirometry and PEF related only to O_3 in acute healthy exercising nonsmoking adults
SPECKTOR SPECKTOR	1988 1991	[115] [116]	Rural NJ, USA	?		H_2SO_4 <19 (12 h)	?	78–294	?	Significant decreases in lung function in children related to O_3 (1 day lag), but not to H_2SO_4
THURSTON	1993	[117]	Rural CT, USA	?		H^+ ≤110 nM	?	137–314	?	Significant decreases in PEF in asthmatic children related to O_3; (effect of AP seen as symptoms also), medication, temp. RH in models†
LIPPLAM LIPPMAN BOCK LIOY	1983 1985 1985 1985	[118] [119] [120] [121]	Rural PA and NJ, USA	?	≤66	[H_2SO_4 (6 h) av ≤6]		≤110 ≤216	?	Significant decrease in PEF in children: other AP and temp. sometimes in models; otherwise assumed not confounders
DOCKERY	1982	[122]	Steubenville, OH, USA	280–460	220–455				?	Significant 2–3% decrease in lung function in children; temp. in model
LEBOWITZ	1974	[19]	Tucson, AZ, USA	low	≤150			≤235		Significant decrease in FEV in exercising children with interaction with temp.
LEBOWTIZ	1985	[21]	Tucson, AZ, USA	low	In <69 Out <170 daily	RSP In <50 Out <125 daily		74–235		Significant decreases in daily PEF in children (TSP, O_3), adults with AOD (TSP, temp. gas stoves) controlling for meterology, indoor surrogates, pollen, fungi
QUACKENBOSS KRZYZANOWSKI	1991 1992	[84] [83]	Tucson, AZ, USA	low		Median <81 75th% <105	Out= ≤187 x̄=42 Indoor: ≤212	29–181	Out: mean 15–48 In: median 11–37	Significant decrease in PEF in asthmatic children related independently to O_3, PM and NO_2; temp., weather, t-act., medication in model
NEAS	1995	[123]	Uniontown, PA, USA (summer)	x̄=29.2 max=128.4		x̄=24.5 max=88.1 H^+ x̄=102 nM·m⁻³	x̄=35.6 max=83.4	12 h·day⁻¹ av=98		Children's PEF significantly decreased, by ≥1%, especially in those with symptoms related to O_3, H^+, PM temp. and time spent outdoors in models; cough increased 16% with H^+
SELWYN	1985	[124]	Houston, TX, USA	low		x̄=10		≤265	low	No significant decrease in lung function in healthy adults with temp. and RH in model
JOHNSON HOLGUIN CONTANT	1986 1985 1985	[125] [126] [127]	Houston, TX, USA	low		x̄=10		-249,-412	low	Increased asthma attacks, medication use, and other Sx with O_3, and decreased temp.; also decreased FEV1 and FVC; SO_2 and PM not in models
POPE	1991	[71]	Salt Lake City, UT, USA	low			11–195	low	low	Significant decreases in PEF in asthmatic children related to PM10: temp., but not other AP, in model
POPE	1993	[128]	Salt Lake City, UT, USA	low			≤181	low	low	Significant decrease in FEV in adults related to PM; temp., but not other AP, in model

see next page for definitions.

Table 4. – Cont......

First author	Year	[Ref]	Location	Exposures μg·m⁻³#						Results
				SO₂	TSP	PM2.5/BS	PM10	O₃*	NO₂	
KOENIG	1993	[129]	Seattle, WA, USA	?		5–45		?	?	Significant decrease in spirometry in asthmatic children; temp., but not other AP, in model†
LINN LINN	1980 1983	[130] [131]	Southern CA, USA	x̄=33	x̄=182	(SO₄ x̄=16.5)		≥300† -428	x̄=132	Significant decrease in FEV with exercise in normal and asthmatic adults
HIGGINS GROSS GROSS	1990 1991 1991	[132] [133] [134]	Mountains NE of LA, CA, USA	low		PM2.5 x̄=24	x̄=59	49–481	≤75	Significant decreases in spirometry in children related to O₃; other AP, temp., RH in model; relationship improved at higher O₃ levels
AVOL AVOL	1990 1991	[135] [136]	Foothills SE of LA, CA, USA	low	18–54			118–314	?	No relationship of lung function to AP
RAZIENNE	1987	[137]	Rural Ontario, Canada	?			?	<216	?	Significant decrease in lung function in children: FEV1 with lagged av SO₄, PM2.5, temp., and PEF with O₃, in nonasthmatics. (Studies in girls in another location NS)†
STUDNICKA	1995	[138]	Austria	SO₄ ≤124		[H⁺ 24 h x̄s: 12.2–32.2]	≤20	x̄s (24 h): 45–56		Significant decrease in FEV ≤4 days related to PM10, H⁺ and O₃ in some panels of children; PEF also with O₃; pollen and temp., also significant model
KAGAWA KAGAWA	1975 1976	[139] [140]	Tokyo, Japan	-133	-400			20–590	-414	Significant increase in airway resistance in children with O₃, SO₂, temp. only
VAN DER LENDE	1975	[141]	Vlaardingen, NL 1969–1972	300		BS=140				Decrease in lung function with increases above these levels†
DASSEN	1986	[142]	Netherlands	200–500	200–250	RSP >200				Significant 3–5% increase in lung function in children with RSP
HOEK HOEK ROEMER	1992 1993 1993	[143] [144] [90]	Wageningen, NL	≤105			30–144	7–206	≤127	Significant decrease in PEF in CRD children; NS in all children related to PM10, O₃; temp. and other AP not in model
JAAKKOLA	1990	[145]	3 areas Finland (adults)	0–10 H₂S: 15–100	29–44					Significantly increased prevalence rate of nasal symptoms and increased cough related to AP
JAAKKOLA	1991	[146]	3 cities in Finland (children)	37–83 H₂S max=42.3	73–198				max=48	Significantly increased (60–100%) respiratory infections related to AP; atopy, age, passive smoking, sex, daily contacts taken into account; AP effects not differentiated

*: 1 h max daily (unless otherwise noted); †: from EPA Criteria Documents; FEV: forced expiratory volume; Sx: symptoms; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; CRD: chronic respiratory disease; t-act: time-activity; AOD: airway obstructive disease. In: indoors; Out: outdoors; RH: relative humidity. For further definitions see legends to tables 1 and 3.

considered. WHO environmental health criteria (EHCs) have also documented responses related to metal particulate (especially in those sensitized) and to pesticides.

PM and O_3/NO_2/organics and asthma. BATES and SIZTO [148] found highly significant associations between excess respiratory admissions, especially asthma (and especially in the young), and average maximum hourly SO_4 and O_3 concentrations, and temperature in Southern Ontario. There appeared to be 24–48 h lags for effects. These correlations were consistent in other years. Other studies in the USA confirmed this association with ozone [149–152]. In Helsinki, a combination of temperature and ozone, as well as other gaseous pollutants, was associated with increased asthma admissions to hospitals [153], and a combination of temperature and NO_2 was associated with ER visits in northern Finland [154]. In Birmingham (UK), location near roadways (a surrogate for NO_2) was also associated with hospital admissions for childhood asthma [155]. In Mexico City, ER visits for childhood asthma increased by 43% per 98 µg·m⁻³ (50 ppb) increase in ozone, and by 68% if O_3 exceeded 216 µg·m⁻³ (110 ppb) for two or more days, controlling for other pollutants, weather and other factors [156]. Asthma attendance was also correlated with spore and pollen counts along with weather factors [157].

Increased rates of asthma attacks and reduced lung function were noted in epidemiological studies during episodes, or days of higher levels of photochemical oxidant air pollution (tables 3 and 4). (Experimental studies also show increased bronchial responsiveness with ozone [17]).

WHITTMORE and KORN [81] found significant increases in the probability of asthma attacks in asthmatics in Los Angeles associated with increases of 0.10 ppm (range 0.03–0.15 ppm) in oxidant levels; attacks increased on days with high TSP, and also cooler temperature. ZAGRANISKI *et al.* [75] reported an increased prevalence rate for respiratory symptoms at about 0.08 ppm (range 0.004–0.235 ppm) O_3 in patients with asthma in New Haven.

Studies in Tucson [21, 83, 86] showed effects in asthmatics, related to temperature, O_3 (0.052–0.12 ppm), and the two together (clinically significant reductions of 15–24% in PEF); these were related to time-activity (time spent in/out of doors), controlling for other factors. Medication use confirmed the changes. More severe symptoms usually occurred 1–3 days after significant PEF declines. These time-lag effects of ozone (and temperature) have been shown by some other studies [115, 121], but not all [83]. Both 1 and 8 h concentrations of O_3 have been shown to have significant effects, and to interact with PM10 and temperature in producing reductions in PEF [83]. However, temperature effects were always more important. In addition, the low humidity in some environments probably had a major influence on the effects seen at concentrations below 120 ppb [86]. This general interactive type of relationship has also been seen for outdoor NO_2 and either an indication of gas stove usage or measured indoor NO_2 in asthmatic adults and children, in which time spent outdoors was an important factor, and medication usage did not prevent the effects [84, 87].

Different forms of particulate, including environmental tobacco smoke (ETS) (and ETS-organic compounds) indoors also have effects on symptoms and PEF in asthmatics, especially in children [84, 115, 158–161]. It has also been demonstrated that there were influences of indoor particulate matter with an aerodynamic diameter ≤2.5 µm (PM2.5) and cigarette smoking on morning PEF in asthmatic children when including previous days' asthmatic medications, an inhibitor of adverse effects on physiological status. Thus, nocturnal asthma may well have significant physiological decrements associated with environmental stimuli, for which there can be only partial protection. Indoor formaldehyde (HCHO) exposures have effects on symptoms and PEF in asthmatic children; there also appears to be avoidance of high exposures to HCHO by asthmatics [160]. The impact of bioaerosols (indoors and outdoors) has also been substantial [8, 16, 162–164], as will be discussed further. The effects of other meteorological phenomena have been reviewed previously [17, 165].

Summary. Several studies have shown that daily temperature variations were often more strongly correlated with attack rates, but air pollution still exerted a significant effect even when temperature-adjusted rates were computed. Examination of tables 3 and 4 *vis-a-vis* asthmatics indicates the LOEL for symptoms and significant PEF reductions of: 157 µg·m⁻³ (0.08 ppm) O_3 based on several studies; about 200 µg·m⁻³ SO_2 based on two studies; TSP approximately 80–120 µg·m⁻³ based on four studies; PM10 >50 µg·m⁻³ based on 1–2 studies; PM2.5 >25–75 µg·m⁻³ based on three studies, but less if primarily SO_4 effects (as low as 10 µg·m⁻³ SO_4) based on three other studies. The evidence for NO_2 is too conflicting to determine any LOEL.

The major problems in most studies of exacerbations of asthma have been the lack of information on time-activity patterns, the possible effects of medications, and the absence of records for all days on which symptoms could have occurred. Investigators who have been able to control some of these variables have found consistent effects of O_3 (as well as other pollutants) on asthma and other airway obstructive disease (AOD), though controlled exposure studies have not [13, 17]. However, even the lack of records for all days, and the presence of medication information implying very good management, have not interfered with the occurrence of effects related to air pollutants in asthmatics ([88, 83]; Daumer, personal communication). Experimental evidence suggests a continuum in the dose-response relationship. Peak flow measurements have been shown to be most responsive to pollutant and meteorological exposures as well as to beneficial effects of medications [166], as also described above.

There are some possible long-range effects of bronchial responsiveness (BR) produced by pollutants (and temperature). Several studies [167–169] have shown detrimental longitudinal effects of BR on lung function, either reduced growth or increased decline. The long-range implications of BR and immunological status have also been discussed at length [8, 11, 16, 162, 170–172].

In conclusion, a variety of indoor and outdoor pollutants, including bioaerosols, have been shown to affect lung function in those with pre-existing disease [8, 10, 11, 16, 23, 83–86, 89, 111, 159, 160, 162–164, 166, 173–176] as well as symptoms; PEF appears to be a

more sensitive instrument for detecting such changes [166, 177, 178].

Respiratory infections. Air pollution and impaired resistance to respiratory infection, shown in animals, has also been seen in studies of humans; a greater incidence of acute respiratory illness (ARI) supports a probable association between increased acute lower respiratory tract disease (acute bronchitis, pneumonia, other acute chest illnesses) and air pollution [4, 5, 10, 14]. Although important, excess acute lower respiratory illness rates in children cannot be accounted for by social class or area differences in residential mobility (*ibid.*).

Atopic status appears to be an additional risk factor for respiratory illnesses associated with air pollution [179, 180]. The role of air pollution as adjuvants to altered immunological status, for infections and allergic sensitization, has also been seen in animal models ([181–183]; Kagawa, personal communication).

PM/SO$_x$. Several epidemiological studies have observed the increased incidence of acute respiratory illness (spatially and temporally) in populations living in communities with more sulphur oxides and particulates [4, 6, 69, 102, 184–190]; the quantitative studies are found in table 3. The frequency and severity of acute lower respiratory disease increased with the degree of air pollution (*ibid.*), and appeared to diminish when air quality was improved in the UK [186, 191]. Several recent studies confirm the effect of various outdoor pollutants on respiratory illnesses and symptoms, especially in children: PM effects in children in Switzerland [192] and in the US [71]. Several metals have also been associated with acute respiratory infections (ARIs) [25]. Indoor PM has been shown to be a special problem for such illnesses in the developing world [193].

Environmental tobacco smoke (ETS). Multiple studies have found the relationship between ETS and ARIs [159]. (There have also been numerous studies showing other respiratory effects of ETS in children [159], which are not discussed here).

NO$_2$. Elementary schoolchildren and infants living in a high-exposure community for two or more years also experience increased bronchitis morbidity; this has suggested an adverse effect in areas with average NO$_2$ concentrations of 150–282 µg·m^{-3} (0.08–0.15 ppm), confirmed by subsequent years of study and analyses by EPA [70, 194–197]. In Switzerland, increases in ARIs were found with 24 h exposures to ambient NO$_2$ of 150–282 µg·m^{-3} (NO$_3$ of 3.8 µg·m^{-3}) and no other associated pollutants, adjusting for other factors [192]. QUACKENBOSS *et al.* [84, 176] have found increased respiratory illnesses related to monitored PM and NO$_2$, indoors and outdoors, as well as ETS, controlling for other indoor pollutants and factors. NEES and co-workers [198, 199] found a 40% increase in childhood lower respiratory illnesses (LRIs) per 28 µg·m^{-3} (15 ppb) increase in NO$_2$ in the six city study in the USA. Some studies [200] have not found such effects, though their NO$_2$ concentrations are often lower.

MELIA and co-workers [201, 202] reported a greater incidence of lower respiratory illnesses in British children residing in homes using gas *versus* electricity for cooking, in which NO$_2$ monitoring occurred. Illness rates were adjusted for other significant factors (ETS, age, sex) and other potentially confounding factors. This study and others have led to major re-evaluations of the role of NO$_2$, including a meta-analysis by HASSELBLAD *et al.* [203] confirming the effects in humans [14]; these effects mirror those found in animal studies [4, 14].

Ozone. Respiratory illness effects have been seen in schoolchildren in Mexico City [204], and adults in Los Angeles (together with sulphate but not particulate haze) [53].

Risk assessments. ARIs appear to be increased by 1.5–2.0 times with exposures to PM (including ETS), SO$_2$, NO$_2$. Early childhood LRIs increased by 1.5 (19.4 to 30–34%), 2.5 if from the lower socioeconomic status (SES), related to SO$_4$ and SO$_2$ of 190 µg·m^{-3}, hospitalizations by 1.5–2.8 (0/1.1 to 1.0/1.8% for bronchitis or pneumonia, 1.1–3.1% for LRIs) with similar concentrations. The level of NO$_2$ reported to produce acute respiratory illnesses is about 137 µg·m^{-3} (1 h) [10].

Implications. These relationships are of particular public health significance because infections and allergies of the respiratory tract account for a major portion of total acute illness in the general population and exact a large economic toll in terms of time lost from school or work, visits to doctors, and admissions to hospitals. The sum of the studies supports an association with increased acute lower respiratory illness. The pollutants, or concentrations, which increase risk of acute illness have usually not been established; though some estimates have been made [61]. However, this is difficult given the many environmental and personal factors that contribute to such risk [4]. The other reason for concern is that these illnesses appear to be related to BR, reduced airway calibre, and subsequently to airway obstructive diseases [18, 23, 86, 170, 186, 205–211]. The role of ventilatory impairment, and BR, cannot be underemphasized [22, 167, 169, 170].

Other acute respiratory responses

Nonirritants. The effects of carbon monoxide (CO) stem primarily from its affinity with oxygen-carrying haemoproteins, which causes a leftward shift and steeper slope of the oxyhaemoglobin dissociation curve and decreases the amount of such haemoprotein available for oxygen transport. The ultimate effect is a tissue deficit of oxygen, such that normal function may not be sustained. In the absence of CO exposure, carboxyhaemoglobin (COHb) concentrations are approximately 0.5%. (A pack-per-day cigarette smokers may achieve COHb saturations of 4–7%). For nonsmokers, exposure to CO at a concentration of 10 mg·m^{-3} (9 ppm) for 8 h or to a concentration of 40 mg·m^{-3} (35 ppm) for 1 h (the present US primary air quality standard) is calculated to cause an increase in COHb concentrations to 1.5% during the interval of exposure. At higher elevations, the oxygen dissociation curve shifts further to the left. During heavy muscular exercise, the oxygen consumption rate of the whole body places maximal stress on the oxygen transport system, and the ability of the cardiovascular system

to transport oxygen to exercising muscles is a determinant of the maximal sustained rate of work that a normal person can perform [212]. Thus, CO has been shown to have predictable effects on healthy young men undergoing strenuous exercise; over the range of COHb concentrations of 5–20%, a linear relationship existed between increasing COHb and decreasing maximal oxygen consumption. Respiratory function may suffer. Nitrogen oxides, specifically NO, can also diffuse into the circulatory system, form met-haemoglobin, and by further depriving cells of oxygen, can have similar effects; the relative potency of met-Hb is about one-third that of COHb [213].

Short-term irritant-related symptoms. In Donora, during the 1948 air pollution episode, 43% of the general population reported respiratory symptoms during the episode [51]. Irritation of the nose and throat are the most common outcome of almost all air pollutants; cough can often be induced, and sometimes wheeze [4, 5, 8, 13, 14, 25, 61]. The quantitative studies of effects on acute symptoms are displayed in table 3. Many qualitative studies have been reported (*ibid.*). Symptoms may temporarily impair performance of normal activities even in healthy subjects. Wood smoke, indoors and out, other forms of particulate indoors (especially ETS), and indoor formaldehyde (HCHO) exposures have acute effects on symptoms, especially in children [108, 115, 159, 161, 176, 214].

Short-term irritant-related reductions in function. A wide variety of human airway responses to most of the pollutants has been demonstrated, as seen in table 4. (These reflect findings in controlled exposure studies of most of the pollutants). There is evidence that they can also cause bronchoconstriction (*ibid.*; [107]). In general, these effects are reversible, and do not necessarily constitute a risk of disease in healthy subjects.

Several field studies have also shown more prolonged decreases in pulmonary function during and following pollution episodes, mostly in children, when exposed to relatively high levels of SO_2 [24, 66–68, 122, 139, 140]; these exposures usually occur with the presence of some PM, and temperature can also play an important role. The levels of reduction can be clinically significant (more than 15% decline), but reverse quickly when exercise is stopped or the exposure is removed.

In general, decrements occur in normal children and adults above 110 µg·m^{-3} PM10 (in the presence of SO_2), 3,760 µg·m^{-3} of NO_2 (560 µg·m^{-3} in asthmatics, thus the 1 h Air Quality Guideline (AQG) of 400 µg·m^{-3}) [10, 71]; above 150–200 µg·m^{-3} of ozone for 1 h (above 100–250 for 8 h).

Decrements related to short-term (1 h) and longer (6–8 h) ozone exposure have also been amply demonstrated [4, 13, 61, 215, 216], and recent studies continue to confirm these results (table 5). In general, these acute functional changes in healthy children and young adults occur with 1 h O_3 concentrations of 0.08–0.15 ppm, and less (>0.06 ppm) for the longer (6–8 h) exposures.

Tolerance and/or adaptation. Humans respond physiologically to complex environments containing pollutants (exogenous stimuli which usually produce adverse changes) by adaptive strategies that should be suitable, but may not be under all circumstances. Recovery from irritant exposures in healthy subjects is generally complete within hours, although the recovery period may be longer for subjects with the most severe responses, and some clinically severe responses can occur at higher doses [58]. The susceptibility of the humans so exposed is of critical importance to early responses and adaptability, and influence changes that help determine later physiological responses to the same or similar stimuli. For many of the current pollutants of concern, such as most volatile organic compounds, either as gases or in particle form (such as from solvents, cleaners and maintenance products, and sidestream tobacco smoke), the mechanisms of response are so complex and poorly understood that toxicological and also some controlled exposure studies are required first. Furthermore, some pollutant classes may be well-characterized, but occur in concentrations sufficient for study only in occupational settings (*e.g.* asbestos, some volatile organic compounds, some mineral fibres); the adverse health effects of these pollutant classes are, therefore, best characterized in occupational studies [12, 171].

Although others have found adaptation to ozone in controlled human exposure studies, no such changes have been seen in epidemiological or physiological studies in the field. This is probably due to prolonged exposure to ambient ozone and/or other pollutants, and lagged effects on lung function (*supra vida*). The studies described do show some relative adaptation has occurred to high temperatures and low relative humidity.

Sometimes, active smokers appear to have adapted to the effects of irritants, as seen in their lesser reactivity to ozone in chamber studies [5]. It may occasionally be the case for passive smoking as well, since it appears to inhibit the effects of ozone in children [121].

Chronic respiratory diseases

Mortality

Sulphur oxides and particulate matter. Non-time series analyses of geographic differences in mortality have favoured an association of sulphur oxides (including sulphates) and PM with mortality, although there has been no general agreement from such studies [4, 5, 10, 25]. The nature of ecological analyses, and their fallacies and biases, have been reviewed elsewhere [4, 8, 12, 25, 52, 279].

A recent study of childhood mortality in different regions of the Czech Republic [280] found a 3.16 excess related to TSP, a 5.41 excess related to SO_2, and a 2.73 excess related to NO_2. A significant correlation between bronchitis mortality and the acidity of precipitation (pH) has been found in the UK [281]. A recent analysis of longitudinal data on large populations in six US cities in which individuals' data were utilized [54] found that total and cause-specific mortality in the different cities was related to the PM concentrations in those cities after adjusting for personal factors. The consistency of the findings for PM is significant, in spite of the fact that other factors might have accounted for some of the

Table 5. – Relationship of chronic term exposures to specific pollutants to chronic respiratory disease (annual measurements unless otherwise stated)

First author	Year	[Ref]	Location (population)	Exposures µg·m⁻³# SO₂	TSP	PM2.5/BS	PM10	O₃*	NO₂	Results
CHAPMAN HAMMER	1973 1976	[217] [69]	Urban Areas USA (adults)	286 (24 h) (≤617)	145 (24 h) (≤244)	SO₄ ≤50			low	Increased prevalence rates of chronic bronchitis, smoking, other factors in models
CHAPMAN HAMMER	1976 1977	[218] [74]	Birmingham, AL USA (children)	26 (24 h)	180–220 (24 h)	RSP ≥45 LOEL			(NOx low)	Increased prevalence rates of symptoms and decreased FEV related to PM; other factors in models
SHY	1973	[219]	USA (children)	69–160	72–114				86–166	Decreased FEV with TSP/sulphate; other covariates in model NO₂ NS
SCHWARTZ	1989	[220]	USA (children)	?	?			<78 LOEL 16–231	~150	Decreased lung function related to NO₂, O₃, (45 mL/28.3 µg·m⁻³ NO₂); other factors in models†
SPEIZER WARE DOCKERY NEAS NEAS	1980 1984 1989 1990 1991	[221] [222] [223] [198] [199]	6 City Study, USA (children)	90th%= 55 ppb Stubenville	39–114		PM15 20–59	?	Est. 7–49 indoor (33 excess if gas stove)	Marginally significant increases in respiratory illnesses under age 2 yrs and decreases in lung function; combined symptoms significantly increased by 47%; other factors in models
WARE WARE DOCKERY NEAS	1984 1986 1989 1994	[224] [222] [225] [226]	6 Cities, USA (children)	90th%= 55 ppb	39–114		PM15 20–59		<42.5	Very large, significant increases in LRIs, cough and bronchitis with TSP, PM15 (not PM2.5), age, sex, SES, maternal smoking in models; other AP NS; bronchitis and LRI increased 13–18%
CHAPMAN	1985	[227]	Utah, USA (children)	11–115	39–108	SO₄ 5–14			NO₃ 0.9–3.5	75–95% increased chronic respiratory symptoms related to SO₂; smoking in model
DODGE DODGE LINN	1980 1983 1976	[228] [229] [230]	Arizona, USA (children) LA vs SF, CA USA (nonsmoking adults)	4–86 ?	37–72 ?			low ?	low 65–130	Significant lower lung function with TSP; SO₂, NS; other factors in models. No significant difference in lung function; no indoor measurements; complicated outdoor exposures
DETELS DETELS DETELS TASHKIN	1981 1987 1991 1994	[231] [232] [233] [234]	Southern CA, USA (adults)	low SO₄ 4.5–13.5 (x̄ of 24 h)	76–133 (x̄ of 24 h)			78–392	53–226*	Increased symptoms and some evidence of decreased lung function, but only smoking controlled for and specific AP not determined and high refusal rates in follow-up exams
ABBEY ABBEY ABBEY	1993 1993 1995	[41] [235] [236]	California (nonsmoking adults)	<57–>400	<60–>200	[SO₄ <6–>15]		<196–>491	<94–>376	Prevalence and incidence rates of chronic bronchitis and asthma significantly related to TSP and ozone; other AP NS; time-activity, ex-smoking, passive smoking, SES, age, gender, occupational exposure in models
PEARLMAN PEARLMAN LOVE	1971 1971 1982	[194] [195] [70]	Chattanooga, TN, USA (children)	low	?				x̄ ≤286 up to 1971 NO₃ ≤4.1 HNO₂=? 1972: 43–91	Significant increased respiratory symptoms in 1972, not in 1973 (22–40 µg·m⁻³ NO₂)

see end of table for definitions

Table 5. – Cont.........

First author	Year	[Ref]	Location (population)	Exposures μg·m⁻³#						Results
				SO₂	TSP	PM2.5/BS	PM10	O₃*	NO₂	
MOSTARDI	1981	[237]	Ohio, USA (children)	21–77	x̄ (9 mo): 51–55	(SO₄ x̄ 9 mo): 11–12			x̄=54 (27+) (NO₃ 4–5)	Significant increase in respiratory symptoms; small decrements in lung function; no indoor measurements; confounders in models
MOSTARDI	1981	[238]								
KRZYZANOWSKI	1990	[160]	Tucson, AZ, USA	low		In medians: 8.9–35.7 75th% 77.8 (weekly)	In medians: 17.5–80.8 Out <60 75th% 105 (weekly)	<235	In medians: 11.5–36.8 75th% 17.7–47.2 Out: 34–48	TWA with time-activities and actual measurements of PM; PM-ETS, HCHO-ETS, NO₂, pollen associated with significant increase in prevalence rates of bronchial responsiveness; HCHO-ETS also associated with asthma and chronic bronchitis; SES, medication, all AP, meteorology, age, sex in models
QUACKENBOSS	1989	[84]								
QUACKENBOSS	1991	[176]								
LEBOWITZ	1990	[85]								
LEBOWITZ	1992	[161]								
LEBOWITZ	1993	[175]								
NERI	1975	[239]	Ontario, Canada	<850 x̄=46–52	<500 x̄=90–93 (LOEL)					Decreased lung function and increased prevalence rates of chronic bronchitis
BECKLAKE	1975	[240]	Montreal, Canada (adults)	15–123	84–131					No differences between areas in lung function after smoking controlled
AUBRY	1979	[241]	Montreal (children)	?	?				Personal 1->28	Increased prevalence rate of asthma; SES and ETS in models
INFANTE-RIVARD	1993	[242]								
STERN	1994	[243]	Canada (children)	low		SO₄ 1.9 vs 6.6	x̄=18–23	>156	low	No increase in chronic symptoms; lower function in more polluted communities
LAMBERT	1970	[244]	Britain (children) (adults)	90 >100		BS=70 >100				Increased prevalence rates of LRIs; increased bronchitis prevalence rates and lower lung function
LUNN	1967	[187]	Britain	181–275		BS=230–301				Increased prevalence rates of symptoms and function; no effects seen
LUNN	1970	[245]	Britain (children)	94–253		48–169				
MELIA	1977	[201]	England (children)	19–145		BS=12–73			16–530 Indoors	Increased prevalence rates of respiratory disease; most confounders controlled
MELIA	1981	[202]	Netherlands (children)							
KERREBIJN	1975	[246]	Netherlands (children)	150 (LOEL)		BS <30				Increased cough, but lung function NS
FISCHER	1985	[247]	Netherlands	?		?			15–300	Decreased lung function related to NO₂ in models
FISCHER	1986	[248]	(adult female nonsmokers)							
REMIJN	1985	[249]								
DIJKSTRA	1990	[250]	Netherlands (children)	?		?		?	22–42 23–72	No increased respiratory symptoms or lung function decline
HOUTHUIJS	1987	[251]								
BRUNEKREEF	1990	[252]								
SAWICKI	1969	[253]	Cracow, Poland	x̄=45, 125	x̄=90, 170					Increased COPD; other factors in model; later, Jedrychowski (communication) showed relation to modelled acid; larger ventilatory declines thought related to occupational and environmental exposures and smoking habits. (KRAZYZANOWSKI et al., 1990 [284])
SAWICKI	1977	[254]	(adults)							
RUDNIK	1978	[255]	Near Cracow	148–180		BS 150–227				Increased respiratory symptoms in boys

see end of table for definitions

Table 5. – Cont.........

First author	Year	[Ref]	Location (population)	Exposures µg·m⁻³#						Results
				SO$_2$	TSP	PM2.5/BS	PM10	O$_3$*	NO$_2$	
PAARC	1982	[256]	France (adults)	?		?			12–16	No effects; no indoor measurements†
PAARC	1983	[257]								
RAMACIOTTI	1977	[258]	Geneva, Switzerland (adult men)	10–60	?					Increased chronic bronchitis, prevalence rates and decreased PEF with SO$_2$ and smoking
BRAUN-FAHRLANDER	1989	[259]	Switzerland (children)	?		?		?	25–52 (Out) 6–91 (In)	Increased respiratory symptoms with NO$_2$ ≥30 µ·m⁻³ outdoors†
GSCHWEND-EIGENMANN	1989	[260]	Switzerland (children)	?		?		?	x̄ 26.2 vs 36.2	Bronchial reactivity increased in nonasthmatic children†
SCHMITZBERGER	1993	[261]	Austrian Alps (children)	12–20			? (probably high)	200–286	15–33	Decreased lung function and increased asthma (O$_3$); SES, indoor surrogates, age, sex in models
KUEHR	1991	[262]	Southern Germany (children)	?	?			?	I/O measurements	Increased prevalence rate of asthma with higher indoor NO$_2$ indexed to gas stoves: ETS in model†
VON MUTTUS	1992	[263]	Leipzig and Munich, Germany (children)	<350 (24 h) <25 (monthly)	<280 (24 h) <70 (light scatter)			186 236 (30 min)	x̄ 39 58	Significantly increased prevalence rates of chronic bronchitis in Leipzig and of asthma in Munich; other factors controlled
ZAPLETAL	1973	[264]	Czechoslovakia (children)	>240 (24 h)	>240 (24 h)					Decreased pulmonary function (flows)
SPINACI	1985	[265]	Turin, Italy (children)	60–200 50–110	110–150 80–110					Initially, lower function with higher pollution data; later, no difference; adjusted for ETS, SES
AROSSA	1987	[266]								
PETRILL	1966	[267]	Genoa, Italy (adults)	53–404 (24 h)	80–850 (24 h)				high	Significantly increased chronic bronchitis with SO$_2$; weather, other AP and other factors in models; all low SES
SARIC	1981	[268]	Croatia (children)	≤550 (24 h)	x̄=200 (24 h)–360	[SO$_4$=3–42] (24 h)				Significant decrease in lung function and increased symptoms with TSP >130, SO$_2$ >60 annual av; indoor, and other factors in model
PERSHAGEN	1984	[269]	Helsinki, Finland (adults)	?	?				5–70	COPD correlates with NO$_2$; temp. in model; no covariates†
GOREN	1988	[270]	Israel (children)	?	?			?	x̄= 23 vs 62	Increased respiratory symptoms; confounders controlled†
SPEKTOR	1991	[115]	Cubata, Brazil (children)	?			64–104	?	?	Lung function measures significantly decreased related to PM10 (about 100 mL·s⁻¹ per 50 µg·m⁻³)†
TSUNETOSHI	1971	[271]	Osaka, Japan (adults)	0.5–4.6 µg·100 cm⁻² daily	dust fall					SO$_2$ significantly related to chronic bronchitis (not dust fall); smoking, other factors in model
YOSHIDA	1976	[272]	Japan	110–120 LOEL						Increased prevalence rates of asthma
SUZUKI	1978	[273]	Japan (adult females)	58–97	122–434	SO$_4$ 40–120				Increased chronic respiratory symptoms, also related to age

see end of table for definitions

Table 5. – Cont.........

First author	Year	[Ref]	Location (population)	Exposures µg·m⁻³#						Results
				SO₂	TSP	PM2.5/BS	PM₁₀	O₃*	NO₂	
YANO	1990	[274]	Japan (adult females)	?	119–341 (winter) 64–77					No increase in chronic symptoms†
NIITTA	1993	[275]	Tokyo, Japan (adult females)						24 h: 45–130 (NOₓ= 97–126 ppb)	Significant increase of ≥35% in chronic respiratory symptoms at higher NO₂ levels; models included age, smoking, duration of residence, SES, home heating; other AP not included
HE	1993	[276]	Wuhan, China (adults)	8–245	36–648	51–207			NOₓ 4–244	3.8% lower FEV1 associated with AP, as were symptoms; effects of specific AP not differentiated
XU	1991	[277]	Beijing, China (adults)	18–128	261–449					Significantly reduced lung function related to SO₂ or TSP, and indoor heating; other factors in models
TAM	1994	[278]	2 districts of Hong Kong (children)	4–177	43–133	RSP 30–68			15–49	Significantly increased bronchial responsiveness, especially in nonwheezing; nonasthmatics, mostly in boys; adjusted for SES, house type, passive smoking; effects of different AP not determined

*: mean of daily maximum 1 h unless otherwise stated; †: from EPA Criteria Documents. SES: Socioeconomic status; TWA: time-weighted average; HCHO: formaldehyde; ETS: environmental tobacco smoke; COPD: chronic obstructive pulmonary disease; RH: relative humidity; I/O: Indoor/Outdoor ratio. For further definitions see legends to tables 1, 2 and 4.

observed association. In contrast to the six city study, in the longitudinal study in California with data on individuals, including individual estimates of exposure [41], no association was found with all cause or cause-specific mortality (table 1).

Though previous reviews did not conclude that air pollution could cause lung cancer [4, 5, 12], two recent studies have indicated an association [50, 282], raising the issue once again.

Chronic respiratory morbidity

Only PM is definitely known to produce chronic respiratory disease, for which AQGs have been written [61, 39], but there is evidence that ozone [13], and NO₂ [10] may also produce such diseases. Table 5 presents the quantitative results concerning chronic effects, as obtained when available from the multiple studies mentioned below. It should be noted that the role of the indoor environmental contaminants, especially due to combustion products and bioaerosols (including allergens), is also considered quite substantial by itself [8, 16].

PM/SO$_x$. Respiratory symptoms and deterioration in lung function in populations (studied cross-sectionally or longitudinally), and longitudinal changes, are greater in those that reside in polluted areas than those residing in cleaner areas [4, 6, 8, 9, 12, 13, 15, 25, 41, 61, 102, 179, 186, 215, 218, 223–225, 228, 229, 235, 244, 263, 283–288]. The pollutant mix invariably contains PM but also often contains SO₂, NO₂, or O₃. The effects of specific species of PM have not been delineated, though SO₄ and H₂SO₄ have been implicated specifically in chronic obstructive lung disease (COPD) [10, 236, 243, 289].

Childhood chronic bronchitis was more associated with typical SO₂ and PM pollution in Germany [263], as had been found in the UK [4, 5, 191, 244]. It is thought that this may be the case in the parts of Central and Eastern Europe that are still polluted primarily by PM and SO₂. Chronic lung conditions in children and adults in less-developed countries are thought to be related to indoor combustion products [12, 15, 17, 18].

PM/NO$_x$. Geographic differences occur in the prevalence rates of asthma as well, based on more recent studies [5, 13]. For instance, there is an increased level of asthma even when risk factors for asthma in different communities may be similar, when there is more pollution from power plants [290], or when there is more pollution from auto exhaust [41, 235, 263]. The relationship of asthma prevalence (and immunological changes) to auto exhaust was also noted by ZWICK *et al.* [291]. These studies imply some possible link to a PM-NO₂ complex, and some possible role of hydrocarbons (as has been shown in mining). There is an AQG for NO₂ to avoid chronic effects [61].

ETS. Passive smoking (ETS) has been found to be associated with COPD [159, 292]. ETS in the presence of formaldehyde has been shown to relate to increased prevalence rates of childhood asthma and bronchial responsiveness, whilst formaldehyde alone was also associated with increased prevalence rates of childhood chronic

bronchitis [160]. INFANTE-RIVARD [242] reported that monitored NO_2 had a dose-response relationship with asthma in a case-control study; she also showed that questionnaire information on mothers' heavy smoking, bedroom humidifiers, home heating, a history of pneumonia, a family history of asthma, and the absence of breast-feeding might be important. Other questionnaire surveys, with appropriate controls for these other variables, have yielded conflicting relationships with passive smoking [159]. Many other surveys have not had appropriate controls, especially for family history, and have not measured pertinant pollutants that might affect asthma.

Other pollutants. The effect of other chemical pollutant exposures on the incidence of asthma is not sufficiently known. However, it is known that aeroallergens are strongly associated [8, 249]. There are also some low molecular weight chemicals [171, 172, 293] and certain metals, such as chromium and nickel (WHO EHCs) which can, with significant exposures, produce asthma. Chemical pollutants can also act as adjuvants with allergens in the development of asthma [8]. In addition, chronic exposure to high levels of volatile organic compounds (VOCS) and to NO_x are related to chemical pneumonitis [25, 120].

Risk assessment. COPD appears to increase significantly (relative risk (RR) of 1.5–2.5) as annual TSP increases above 100 µg·m^{-3} and SO_2 (concurrently). Chronic bronchitis appears to increase linearly with SO_4: every 2 µg·m^{-3} above 5.8 µg·m^{-3} adds 1.24% to the prevalence rate [289]. In urban areas, significantly more chronic COPD symptoms may occur with SO_4 above 9 µg·m^{-3} in the presence of high SO_2 and TSP, and 15+ without high TSP [10]. In a Californian study [236], asthma was also found to increase significantly with SO_4 by about 2.9 times per 7 µg·m^{-3}. The Cracow study found a 24% prevalence rate of chronic bronchitis in males (11.5% in women) [253, 254]. Many estimates have been made of excess AOD in parts of Europe, due to the excessive PM/SO_x pollution in certain locales; they have been quite large (*e.g.* 2–7 million cases). A 24 h guideline of 180 µg·m^{-3} of NO_2 was also established by the WHO [61] to avoid chronic effects of repeated exposures.

Lung function and particulates

Differences in lung function in children residing in various areas have also been related to the many differences in air pollution in those areas [4–7, 13]. Furthermore, TOYAMA [287] and WATANABE [294] showed improvement in peak expiratory flow rates in children living in more polluted communities when air pollution concentrations decreased. In France, the PAARC study [256] found differences in children but not in adult females related to SO_2. The sulphate and nitrate particulate forms of SO_x and NO_x appear to have greater impact on lung function in normals than the gaseous form because they have greater airway penetration [4, 8, 25, 102]. Several studies of indoor pollution have shown relationships between monitored NO_2 and PM and reduced lung function [8, 11, 84, 85, 175, 199, 250]. Passive smoking over long periods of time in susceptible children leads to significantly slower and reduced lung growth

[295], and in children in the general population to a reduction of 0.1–3% in FEV1 [159].

Significant decrements (3–8%) appear to be related to ambient annual TSP above 180 µg·m^{-3} (PM10 about 110 µg·m^{-3}) (also associated with SO_2), or 100 µg·m^{-3} of SO_4 and SO_2 in children. Significant differences (<3%) occur in children related to ETS (mostly PM2.5) differences of 60–100 µg·m^{-3} or more. Decreases occur more frequently and are larger in those starting with low lung function, bronchial responsiveness, and/or a chronic respiratory disease.

Bronchial responsiveness is related to various contaminants. Increased bronchial responsiveness was found in children in relation to O_3, possibly related to T-lymphocyte changes but not to atopy or immunoglobulin E (IgE), in an area of high ozone levels in Austria [291]. Increased BR has also been found in an urban-industrial area in Latium, Italy, even though baseline lung function and atopy were not different, and after controlling for ETS exposure and other risk factors [296]. It has also been found that the relationship of BR (indexed by diurnal PEF) and PM2.5 occurred primarily in homes independent of ETS, although rates of BR were higher in homes with more PM10 and ETS; the rates of BR in children were independently related to ETS [161]. Prevalence rates of BR are independently associated with increasing exposure to HCHO, and to NO_2 [176]; the latter association has also been found experimentally [109]. Several metals have also been associated with increased bronchial responsiveness (nickel, chromium, vanadium, platinum salts) [10, 12, 25, 171]. As discussed previously, BR is longitudinally associated with reduced lung function (*op cit.*). Both BR and asthma in childhood are associated with as much as a 25% decrement in function at the onset of adulthood ([208]; S. Weiss, personal communication).

Chronic outcomes of acute changes

Do acute morbidity effects lead to chronic effects? Those with chronic obstructive airway disease have a history of significantly more frequent and severe ARIs [210, 279] and a significant history of childhood respiratory problems [205, 210]. It is also known that childhood ARIs are longitudinally associated with a decrement of lung function [208]. A study of acute pulmonary function changes in healthy children in a smelter town [19] indicated significant acute reversible changes. A further study of children in that town, another smelter town and a control town [228, 229], indicated that pulmonary function values were lower overall in the smelter towns (even despite potential selective migration). Thus, there are grounds for a possible relationship between acute and chronic pulmonary function changes. Furthermore, it is sometimes difficult to separate the acute (peak) exposure effects from the chronic exposure effects ([84, 102, 176, 239]; M. Green, public comments at ERS, Firenze, 1993).

Discussion

The separate effects of gases and PM, though difficult, have been investigated, both epidemiologically as

well as in controlled human exposure studies. PM and gases appear to have an interactive effect in clinical and epidemiological studies (*e.g.* formaldehyde particles, radon and particles, gases and particles in passive smoking, ambient ozone and/or NO_2 and PM). It is still difficult to evaluate the impact of short-term exposures, including peak exposures, on chronic conditions (SO_2 as intermittent outdoor peaks, has also been associated with acute and chronic respiratory conditions [5]). The role of "peak" exposures to gases (NO_2, O_3, SO_2) has also been related to bronchial responsiveness (as discussed).

Factors affecting responses. It has been mentioned that temperature is usually even more important than air pollutants; humidity is also an important factor. For instance, heat and relative humidity (RH) may contribute to symptoms and physiological impairment. A hot (31–40°C) and/or humid (85% RH) environment, combined with exercise, has been shown to reduce forced expiratory volume more than similar exposures (25°C, 50% RH) [297, 298]. Modification of the effects by heat or humidity stress may be attributed to increased ventilation associated with elevated body temperature but there may also be an independent effect of elevated body temperature on pulmonary function. Also, increased ventilation at altitude, as in exercise, increases doses of pollutants in the lung (tracheobronchial and alveoli), as adequate levels of ventilation are necessary to maintain sufficient O_2 partial pressures in alveolar and arterial blood. Thus, all considerations of the effects of air pollutants must take these factors into account.

Effect-modifiers and factors affecting confounding. Host factors are significant effect modifiers. Immunological and physiological status appear to be the most important [8, 11, 12, 16, 22, 55, 175, 179, 208, 293, 295]. (As discussed above, prior ARIs and concurrent morbidity are also of importance). These potential links require further study.

Not all potential confounders are important *per se* [6]. Follow-up studies on a cohort started by DOUGLAS *et al*. [186] did not confirm original social class differences to be significant in accounting for health findings later in life. MANFREDA *et al*. [285] did not find "urban" characteristics to be relevant in explaining results. Thus, one should not overemphasize the relative importance of potential confounding or covariant factors when these have not been specifically ruled out as alternative explanations for specific results [6].

Conclusions

The most important aspects of this issue need to be addressed [4–9, 17, 18, 22, 60, 299, 300]: 1) pollution exposure is a cause, albeit with others (and not the most potent) of chronic respiratory disease; 2) it is a major cause of exacerbations of asthma and COPD. (both aspects are responsible for major disability, cost, and reduction in the quality of life); 3) it influences (and is part of) the aetiological and natural history chain of chronic respiratory disease, which includes increased ARIs, increased inflammation and bronchial reactivity, and reduced lung function. The first two would also imply that at least

some pollutants alter immunological function in more than one way, as found in animal studies [301], and possibly in human studies [302, 303]. Thus, further studies of the epidemiology of air pollution and its control are necessary [8, 10, 304–306].

With regard to asthma and chronic obstructive pulmonary disease, we consider the following to be the future epidemiological perspectives: methods of intervention and associated studies; methods of ascertaining pathophysiological and immunological changes, including biomarkers of noncarcinogenic and of acute changes; further studies of irritation and reactive airways dysfunction syndrome (RADS) (with respect to asthma and chronic obstructive pulmonary disease), the study of the role of acute effects in the aetiology and natural history of chronic disease; and methods and studies to ascertain quantitative exposure dose-response relationships for individual air pollutants and complex mixes.

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