Review

# Air pollution and health

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**The health effects of air pollution have been subject to intense study in recent years. Exposure to pollutants such as airborne particulate matter and ozone has been associated with increases in mortality and hospital admissions due to respiratory and cardiovascular disease. These effects have been found in short-term studies, which relate day-to-day variations in air pollution and health, and long-term studies, which have followed cohorts of exposed individuals over time. Effects have been seen at very low levels of exposure, and it is unclear whether a threshold concentration exists for particulate matter and ozone below which no effects on health are likely. In this review, we discuss the evidence for adverse effects on health of selected air pollutants.**

December, 2002, marks the 50th anniversary of the great smog event in London, UK. Stagnant weather conditions caused a sharp increase in the concentration of air pollutants, and over several days, more than three times as many people died than expected, leading to an estimated excess death toll of over 4000. Concentrations of sulphur dioxide and smoke reached several thousands of μg per $m^3$.[1] The London 1952 smog was not without precedent—similar events occurred in the Meuse valley, Belgium, in 1930, and elsewhere.[2,3]

Conditions have changed; effective legislation has eliminated most of the air pollution of 50 years ago. Yet the 1952 London smog event keeps attracting the attention of contemporary air pollution scientists. One question that remains important is the extent to which air pollution affects life expectancy. The 1954 report[1] suggests that death occurred mostly in individuals who were on the brink of death already, but if this were the case, the death rate should have dropped sharply after the episode. On the contrary, the death rate remained high for several months, and a recent re-analysis of the data indicates that the number of additional deaths due to the episode was about 12 000.[4] Another question is that of causality; although concentrations of sulphur dioxide and black smoke were greatly increased during the episode, sulphuric acid was thought to be the critical component. On this basis, bottles of ammonia were distributed among bronchitis patients so that they could neutralise acids during episodes of air pollution.[5]

In this review, we have focused on recent studies that have answered key questions that have arisen in the past 5 years. There is no shortage of recent reviews in this field,[6–22] and we have tried to add to, rather than duplicate, these reviews. For further reading, we have also added a list of relevant websites. These give access to comprehensive reviews produced by organisations such as the World Health Organisation, the European Union, the US Environmental Protection Agency, and the UK Department for Environment, Food and Rural Affairs (panel).

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## A new era of air pollution research

20 years ago, the era of successful abatement of traditional air pollutants culminated in a voluminous review of the health effects of ambient particulates.[23] At concentrations seen in the late 1970s in the developed world, adverse health effects were then regarded as unlikely. In the two decades since then, however, air pollution has re-emerged as a major environmental health issue. One reason is that, although air pollution from combustion of traditional fossil fuel is now present in much lower concentrations than 50 years ago, other components have gained prominence. Photochemical air pollution, characterised by high ozone concentrations during warm and sunny weather, was found to occur not only in places like Los Angeles and Mexico City, but also in large areas of Europe. Oxides of nitrogen produced by the ever rising number of motorised vehicles have increased until recently. Airborne particles have changed size distribution and composition, altering their toxicity.

### *From episodes to time-series studies*

In the 1980s, a few air pollution episodes related to long-range transport from the east occurred in western Europe. In 1985, increases in mortality and hospital admissions in Germany and temporary lung function changes in the Netherlands were seen during one such episode.[24,25] Because concentrations of sulphur dioxide and particulate matter were in the hundreds rather than thousands of μg/$m^3$ even under such episodic conditions, health effects of short episodes became hard to detect. Attention shifted to weather-driven, day-to-day variations in air pollution over long periods of time as determinants of day-to-day variations in mortality, hospital admissions, and other public-health indicators. Such time-series studies were

### Search strategy and selection criteria

The key words "air pollution and health" produce over 500 references a year from Medline alone. The present review is therefore, of necessity, our selection of just some of the major studies. The selection is based on a systematic Medline search until early 2002, on more than 20 years of continuous research in the field, and on participation in many advisory boards nationally and internationally.

**Useful websites containing information on air pollution and health**

*WHO*
WHO air quality guidelines for Europe, 2000
http://www.euro.who.int/document/e71922.pdf
WHO air quality guidelines for Europe, 2000 (background documents)
http://www.euro.who.int/air
Transport, environment, and health, 2000
http://www.euro.who.int/document/e72015.pdf

*US Environmental Protection Agency (EPA)*
National ambient air quality standards (NAAQS), 2001
http://www.epa.gov/airs/criteria.html
EPA's national ambient air quality standards: the standard review/re-evaluation process (1997)
http://www.epa.gov/ttn/oarpg/naaqsfin/naaqs.html
Health and environmental effects of ground-level ozone (1997)
http://www.epa.gov/ttn/oarpg/naaqsfin/o3health.html
Health and environmental effects of particulate matter (1997)
http://www.epa.gov/ttn/oarpg/naaqsfin/pmhealth.html
Transportation and fuels (2002)
http://www.epa.gov/air/transport/index.html
Air quality guide for ozone (1999)
http://www.epa.gov/airnow/consumer.html
A guide to air quality and your health (2000)
http://www.epa.gov/airnow/aqi_cl.pdf
Air quality criteria for particulate matter (third external review draft), July 2002
http://cfpub.epa.gov/ncea/cfm/partmatt.cfm?ActType=default

*European Union (EU)*
European commission air quality website (2001)
http://europa.eu.int/comm/environment/air/
Air quality framework directive (2002)
http://europa.eu.int/comm/environment/air/ambient.htm
Clean air for Europe programme (2001)
http://europa.eu.int/comm/environment/air/cafe.htm
EU Particulate Matter position paper (1997)
http://europa.eu.int/comm/environment/air/pp_pm.pdf
EU ozone position paper (1999)
http://europa.eu.int/comm/environment/docum/pos_paper.pdf

*UK Department for Environment, Food and Rural Affairs*
Air quality—what it means for your health (2001)
http://www.defra.gov.uk/environment/airquality/airpoll/index.htm
Expert panel on air quality standards. Airborne particles: what is the appropriate measurement on which to base a standard? A discusson document (2001; 110 pp)
http://www.defra.gov.uk/environment/airquality/aqs/air_measure/index2.htm

*Other sources of information*
A thematic network on air pollution and health: funded by EU, gives access to a network of research projects and information on air pollution and health.
http://airnet.iras.uu.nl
The *Health and Clean Air Newsletter* is an attempt to make scientific information available to non-specialist readers, including reporters, without sacrificing accuracy.
http://healthandcleanair.org

sporadic until about 1990,[26,27] but have increased exponentially since then. These studies have several advantages: weather-driven variations in air pollution concentrations generate large contrasts in exposure over time; populations serve as their own controls; and studies can often use routinely collected data. As a result, the number of deaths or hospital admissions studied can easily be in the hundreds of thousands, leading to great statistical power to detect small increases in adverse health effects of air pollution. Limitations of this approach include lack of individual characteristics; an assumption that exposure is representative for large populations by measurements made at central monitoring sites; and an assumption that confounding by long-term time trends, seasonal variations, weather, and influenza epidemics are controlled for by sophisticated statistical methods.

*Life shortening due to air pollution*

Interest in health effects of air pollution became more intense after two US cohort studies suggested that exposure to fine particulate matter in the air was associated with life shortening.[28,29] Both studies were based on observations from the late 1970s to late 1980s, when air pollution concentrations were much lower than they had been in the past. A third cohort study (AHSMOG) found significant effects of particulate matter with a diameter of less than 10 μm (PM10) on non-malignant respiratory deaths in men and women, and on lung-cancer mortality in male, non-smoking Seventh-Day Adventists.[30] The effect on shortening life expectancy has been estimated at 1–2 years for realistic exposure contrasts,[31] which is substantial compared with the effects of other lifestyle or environmental risk factors related to mortality.

New observations from the largest study to date show that the findings persist after inclusion of several more years of observation, with more consistent effects on lung cancer, in addition to non-malignant cardiopulmonary deaths, than in the original paper.[32] Case-control studies also continue to provide evidence of a link between air pollution (especially from traffic) and lung cancer.[33] Recent work has suggested that effects on life expectancy are not uniformly distributed but depend on factors such as education and antioxidant vitamin status,[30,32,34] which implies that life expectancy could be reduced more in disadvantaged population groups. On the basis of the cohort study findings, stringent standards for fine particulate matter have been proposed in the USA. Because large investments would be needed to improve air quality, the findings of the US cohort studies have received intense scrutiny (see section on disputing the evidence).

Until recently, no European cohort studies have provided data on life shortening. A Dutch study suggests that exposure to traffic-related air pollution is associated with cardiorespiratory deaths in much the same way as in the USA.[35]

## Pollutants of current interest: ozone, particulates, nitrogen dioxide

Now that the concentration of sulphur dioxide has decreased strikingly, attention has shifted to ozone, nitrogen dioxide, and particulates. Before discussing these pollutants in more detail, some qualification is needed to put our discussion in a wider global perspective. For millions of people living in rural areas in developing countries, indoor pollution from the use of biomass fuels occurs at concentrations that are orders of magnitude higher than currently seen in the developed world.[36–38] Deaths due to acute respiratory infections in children resulting from these exposures are estimated to be over

2 million per year. In the largest cities of the developing world, extreme exposures occur with both the traditional and the modern variety of pollutants.[39,40] Ideally, lessons learned in the developed world could help developing countries follow a more sustainable, less polluting path to industrialisation and modernisation. However, the available data suggest that the combined pressures of global competition and population increase leave little, if any, room to manoeuvre in this respect.

*Sources of ozone, particulate matter, and nitrogen dioxide*

Ozone is a strong oxidising agent formed in the troposphere through a complex series of reactions involving the action of sunlight on nitrogen dioxide and hydrocarbons.[41] Concentrations in city centres tend to be lower than those in suburbs, mainly as a result of the scavenging of ozone by nitric oxide originating from traffic.

The major source of anthropogenic emissions of nitrogen oxides into the atmosphere is the combustion of fossil fuels from stationary sources (heating, power generation) and in motor vehicles.[41] In ambient conditions, nitric oxide is rapidly transformed into nitrogen dioxide by atmospheric oxidants such as ozone.

Particulate air pollution is a mixture of solid, liquid, or solid and liquid particles suspended in the air. The size of suspended particles varies, from a few nm to tens of μm. The largest particles (coarse fraction) are mechanically produced by attrition of larger particles. Small particles (<1 μm) are largely formed from gases, the smallest (<0·1 μm, ultrafine) of which are formed by nucleation resulting from condensation or chemical reactions that form new particles. In practical terms, a distinction is made between PM10 ("thoracic" particles smaller than 10 μm in diameter that can penetrate into the lower respiratory system), PM2·5 ("respirable" particles smaller than 2·5 μm that can penetrate into the gas-exchange region of the lung), and ultrafine particles smaller than 100 nm which contribute little to particle mass but which are most abundant in terms of numbers and offer a very large surface area, with increasing degrees of lung penetration.

## Main findings from epidemiological studies

*Short-term studies*

There have been abundant studies on the short-term effects of air pollution on health, with emphasis on mortality and hospital admissions. Panel studies have been done in volunteers, which have provided data on health endpoints such as respiratory and cardiovascular symptoms, and objective measures of lung or cardiac function on a daily or weekly basis. Large, collaborative efforts are under way in Europe and the USA which will be summarised.

In Europe, the APHEA (Air Pollution and Health: a European Approach) studies have provided many new insights. Initial studies were based on older data (APHEA-1),[42] and in the late 1990s a new series of studies (APHEA-2) was done which was able to make use of data on the PM10 fraction. The APHEA-2 mortality study covered a population of more than 43 million people living in 29 European cities, which were all studied for more than 5 years in the early-mid 1990s.[43] From data involving 21 cities, the combined effect estimate showed that all-cause daily mortality increased by 0·6% (95% CI 0·4–0·8) for each 10 μg/m$^3$ increase in PM10, with some heterogeneity to be discussed later. The APHEA-2 hospital admission study covered a population of 38 million living in eight European cities, which were studied for 3–9 years in the early to mid 1990s.[44] Hospital admissions for asthma and chronic obstructive pulmonary disease (COPD) among people older than 65 years were increased by 1·0% (0·4–1·5) per 10 μg/m$^3$ PM10,[44] and admissions for cardiovascular disease (CVD) were increased by about 0·5% (0·2–0·8) per 10 μg/m$^3$ PM10 and by about 1·1% (0·4–1·8) per 10 μg/m$^3$ black smoke, suggesting an important role for diesel exhaust.[45] In APHEA-1, daily mortality increased in six cities[46] by 2·9% for each 50 μg/m$^3$ increase in the 1-h maximum ozone concentration. Associations between nitrogen dioxide and mortality were also found, but these were sensitive to adjustment for black smoke, suggesting that the nitrogen dioxide represented a mixture of traffic-related air pollution. The corresponding data from APHEA-2 are awaited.

In the USA, the National Mortality, Morbidity and Air Pollution Studies (NMMAPS) focused on the 20 largest metropolitan areas in the USA, home to 50 million inhabitants, during 1987–94. All-cause mortality increased by 0·5% (0·1–0·9) for each 10 μg/m$^3$ of PM10, a value close to the European results.[47,48] However, a recent communication suggests that an unrecognised software problem led to significant overestimation of this effect estimate, albeit without affecting its statistical significance or sensitivity to co-pollutant adjustment; details can be found at http://www.healtheffects.org/Pubs/NMMAPSletter.pdf (accessed July 11, 2002). Effects on hospital admissions were studied in ten cities with a combined population of 1 843 000 individuals older than 65 years.[49] Effects of PM10 on COPD admissions were 1·5% (1·0–1·9) and on CVD admissions 1·1% (0·9–1·3) per 10 μg/m$^3$ of PM10. There was also a weak effect of ozone on mortality in the summer but not winter. After adjustment for ozone and PM10, none of the other gaseous pollutants (including nitrogen dioxide) were associated with mortality.

Smaller-scale studies have been done on panels of individuals with daily or weekly observations of their exposure and health status.[50,51] These studies provide greater insight into the role of individuals' characteristics, but are dependent on participants' collaboration and provide relatively small data sets. These shortcomings make the results less reliable, especially with respect to uncontrolled confounding by incompletely modelled long-term time trends and medication use. One large-scale collaborative study, the PEACE (Pollution Effects on Asthmatic Children in Europe) study, has been completed in 28 regions of Europe. It failed to show effects of particulate matter and nitrogen dioxide on lung function and acute symptoms.[52,53] Because this was a winter-time study, no effects of ozone were assessed. Similar, smaller-scale studies have documented acute effects on lung function as well as acute symptoms in children and adults. One interpretation of these findings is that the inherent limitations of panel studies make them less suitable to detect subtle effects of air pollution than the large-scale mortality and hospital admission studies.

In both short-term and long-term studies, air pollution has an effect on cardiac deaths and hospital admissions in addition to respiratory effects. In Augsburg, Germany, during the 1985 air pollution episode, intriguing epidemiological observations were made serendipitously during a large cardiovascular study, the MONICA project. In retrospect, plasma viscosity, as well as heart rate and concentrations of C-reactive protein, were increased during the episode,[54–56] all of which can contribute to an increased risk of cardiovascular events. Studies in Boston, MA, USA, showed that nitrogen dioxide and PM2·5 were associated with life-threatening arrhythmia leading to

therapeutic interventions by an implanted cardioverter defibrillator,[57] and that PM2·5 concentrations were higher in the hours and days before onset of myocardial infarction in a large group of patients.[58] Cardiovascular events are now being studied in panel studies to ascertain more precisely the role of various pollutants and mechanisms.[10]

*Long-term studies*

In addition to cohort studies on mortality, air pollution effects on morbidity endpoints have been studied. Most of these have been cross-sectional, and assume that current air pollution exposure is sufficiently representative of long-term, previous exposure to make a plausible link with current health status. A series of Swiss studies on the association between air pollution and health among children and adults stand out for their careful design and conduct. Although Switzerland is a small country, exposure contrasts are relatively large because of the mountainous terrain. In eight different communities, lung function in adults was negatively associated with PM10, nitrogen dioxide, and sulphur dioxide,[59] in association with symptoms of bronchitis but not asthma.[60] In children from ten Swiss communities, the same pollutants were found to be associated with symptoms of bronchitis but not asthma or allergy.[61] The associations were seen at a range of PM10 concentrations of 10–33 $\mu g/m^3$ only, which is well below the concentrations in many European countries. The high correlation between pollutants prevented separation of their individual effects.

In children living in 24 US and Canadian communities, significant associations were reported between exposure to fine particles and their acidity and lung function, symptoms of bronchitis, but again not asthma.[62–64] Exposure to particles has now also been related prospectively to reduced lung function growth in children,[65] and even children relocating from high to low pollution areas (or vice versa) were shown to experience changes in lung function growth that mirrored changes in exposure to particulate matter.[66]

Relation of variations in asthma prevalence to air pollution has been difficult;[67,68] however, prospective studies in California have recently suggested that some incident asthma cases[69,70] could be related to ozone but not other pollutants.

## Mechanisms

Chamber studies provide a method by which to pursue the acute mechanisms of individual air pollutants, but do not reproduce either the mixtures or temporal variation that occur in natural exposures. Although individual air pollutants can exert their own specific individual toxic effects on the respiratory and cardiovascular systems, ozone, oxides of nitrogen, and suspended particulates all share a common property of being potent oxidants, either through direct effects on lipids and proteins or indirectly through the activation intracellular oxidant pathways.[71]

Animal and human in-vitro and in-vivo exposure studies have demonstrated the powerful oxidant capacity of inhaled ozone with activation of stress signalling pathways in epithelial cells[72] and resident alveolar inflammatory cells.[73] This mechanism involves activation of the transcription factor nuclear factor (NF) κB and its translocation to the nucleus. There it binds to DNA consensus sequences in the promoters of proinflammatory genes that code for cytokines (eg, granulocyte-macrophage colony-stimulating factor, tumour necrosis factor α [TNFα], and interleukin 1β), chemokines that attract neutrophils (eg, interleukin 8, neutrophil activating protein 78, and Gro α), and adhesion molecules (eg, intercellular adhesion molecule 1).[74] These molecules increase neutrophil recruitment into the airways and alveoli and activate them for mediator secretion and the capacity to cause tissue damage.[75,76]

The large interindividual differences in responsiveness to inhaled ozone have an important genetic basis, as recently shown in mice[77,78] and human beings.[79] Candidate genes have included those for TNFα, manganese superoxide dismutase, glutathione peroxidase, NAD(P) quinone oxidoreductase, and glutathione S transferases. This finding emphasises the importance of locally available antioxidants such as uric acid, albumen, reduced glutathione, vitamin C, and vitamin E present in the lung lining fluid and epithelial barrier[71,80] in protecting the lung against ozone, and the protective effect exerted by diets supplemented with antioxidants.[81] An inflammatory response induced in the lung on exposure to ozone, together with increasing neuropeptide release from sensory neurons, contributes to the acute broncho-constrictor response and hyper-responsiveness seen in asthma on exposure to this pollutant,[82,83] as well as to the tolerance induced by repeated short-term ozone exposure.[83,84] The significance of this induced tolerance on the recognised adverse effect of this pollutant on exacerbations of asthma during the summer months is not known. Studies have shown wide interindividual variability in responses to air pollutants. Although genetic factors undoubtedly account for part of this inconsistency, other more subtle factors could be operating, such as the distribution of ventilation in the different lung compartments, and in the case of particles, differences in regional deposition within the lungs.

By contrast with ozone, little is known about the effects of nitrogen dioxide on normal and diseased lung. In-vitro studies in animals and human beings confirm the capacity of nitrogen dioxide to activate oxidant pathways, albeit less potently than ozone.[72,85] The ensuing inflammatory response also differs by enhancing the recruitment of T lymphocytes and macrophages.[86] However, one feature of nitrogen dioxide that might contribute to exacerbations of respiratory disease is its capacity to impair the function of alveolar macrophages and epithelial cells, thereby increasing the risk of lung infection.[87,88] Although nitrogen dioxide can also enhance airway responses to inhaled allergens in asthmatic individuals,[89] short-term exposure remains relatively benign. Little is known about the long-term effects of nitrogen dioxide in human beings, but in rodents, prolonged exposure to either ozone or nitrogen dioxide results in destruction of peripheral airways.

The increase in respiratory and cardiovascular morbidity and mortality that has been epidemiologically linked to inhaled particulates has, until recently, defied a mechanistic explanation. In-vitro and in-vivo studies in animals and human beings have revealed potent proinflammatory effects involving lung epithelial cells[90] and alveolar macrophages.[91] Both directly and through uptake into epithelial cells[92] and macrophages,[93,94] oxidant pathways are activated[95,96] with the downstream consequences of stimulating cytokine and mediator release,[97] resulting in extensive neutrophil migration, but also T lymphocyte recruitment and activation.[98,99] On reaching the bone marrow, cytokines and chemokines released from the lung stimulate egression of neutrophils and their precursors into the circulation.[100] In the short term there is acute tissue damage with activation of the epidermal-growth-factor receptor (EGFR) pathway, and evidence for organ-repair responses.[101] This reaction is partly due to surface processing of EGFR ligands such as heparin-binding EGF-like growth factor (HB-EGF) and

oxidant-induced transactivation of the EGFR.[102] If this cycle of damage and repair continues, epithelial mucus metaplasia results, as does ongoing cytokine and chemokine secretion that contributes to airway inflammation.

Although knowledge of the respiratory actions of particulates has grown, an understanding of how particulates increase the risk of cardiovascular events has proven much more difficult to achieve. Again, through activation of stress signalling pathways from the epithelium to the lung microvessels, factors that influence blood clotting are generated. Increased concentrations of fibrinogen and platelets, and sequestration of red blood cells in the lung mass[103] have also been detected in relation to particulate pollution, but, along with increasing the risk of cardiac arrhythmia,[10] their significance in the cardiovascular events linked to particle pollution remains to be established.[11]

Diesel particulates and ozone have been shown to increase the synthesis of the allergic antibody IgE in animals[104] and human beings,[105] which would increase sensitisation to common allergens.[106] By interacting together and with other environmental factors, particulates and gaseous air pollutants can have long-term effects on allergic individuals. Although pollutants are unlikely to be able to interact to enhance proallergic and inflammatory responses, no studies have investigated mixtures. Similarly, long-term exposure to pollutant mixtures can have tissue-damaging effects which could be irreversible.[13] The recent recognition that ultrafine particles (mass median diameter <0·1 μm) are more toxic when inhaled than PM10 suggests that their ability to be absorbed into tissues and the circulation, and their greatly increased surface area, might be important factors in determining cardiopulmonary toxicity.[107]

## Air quality guidelines and standards

Several guidelines and standards exist for ozone, nitrogen dioxide, and particulate matter in ambient air. The table lists the most recent air quality guidelines and standards recommended by WHO, the US Environmental Protection Agency, and the European Union (EU). The EU standards are targets to be reached in 2005 or 2010. The most remarkable difference lies in the annual value for nitrogen dioxide. The WHO and EU value is only 40% of the US value.

WHO has not proposed guidelines for particulate matter, arguing that it was unable to define a threshold below which no adverse effects are expected. Instead, dose-response information was provided to help policy makers decide when setting a standard. The effect estimates given in the table were based on information as it was available until 1996. As described earlier, the newest large-scale studies[43,48] tend to show somewhat smaller effects per unit particulate matter. For particulate matter, the proposed US standards for PM2·5 are not very different from the EU 2010 annual average and the 2005 24-h average for PM10, considering that PM2·5 usually comprises about 60–70% of the PM10 concentration, and considering the number of exceedances allowed in the 24-h EU standard.

All guidelines and standards mentioned in the table are subject to periodic revision when new scientific information becomes available. WHO has just recently started a process to re-evaluate the guidelines for these three pollutants.

| | Maximum concentration allowed when averaged over time* | | | |
|---|---|---|---|---|
| | 1 h | 8 h | 24 h | 1 year |
| **Ozone (μg/m³)** | | | | |
| WHO | .. | 120 | .. | .. |
| EPA | 235 | 157 (proposed) | .. | .. |
| EU | .. | 120 (2010) | .. | .. |
| **Nitrogen dioxide (μg/m³)** | | | | |
| WHO | 200 | .. | .. | 40 |
| EPA | .. | .. | .. | 100 |
| EU | 200 (2010) | .. | .. | 40 (2010) |
| **PM10 (μg/m³)** | | | | |
| WHO (mortality relative risk per 10 μg/m³)† | .. | .. | 1·007 | 1·10 |
| EPA | .. | .. | 150 | 50 |
| EU | .. | .. | 50‡ (2005), 50§ (2010) | 40 (2005), 20 (2010) |
| **PM2·5 (μg/m³)** | | | | |
| WHO (mortality relative risk per 10 μg/m³)† | .. | .. | 1·015 | 1·14 |
| EPA | .. | .. | 65 (proposed) | 15 (proposed) |

For details see http://www.euro.who.int/document/e71922.pdf, http://www.epa.gov/airs/criteria.html, and http://www.irceline.be. *Short averaging times are used when the guideline was developed to prevent acute effects, long averaging times to prevent long-term effects. †No guideline value for particulate matter was given because no threshold concentration was identified below which no effects on health were expected. Relative risk estimates were provided to help policy makers set standards based on quantitative dose-response information. ‡To be exceeded on no more than 35 days per year. §To be exceeded on no more than 7 days per year.

**WHO, US Environmental Protection Agency (EPA), and European Union (EU) air quality guidelines and standards for ozone, nitrogen dioxide, and particulate matter**

## Current issues

### *Thresholds*

A key question is whether threshold concentrations exist below which air pollution has no effect on population health. If such a threshold could be identified, no additional public-health benefits would be expected from bringing air pollution concentrations far below this level. Theoretical and empirical work has been done to shed light on this issue.[108,109] In an analysis of NMMAPS data, no evidence was found for a threshold for PM10 and daily all-cause and cardiorespiratory mortality.[109] By contrast, a threshold of about 50 μg/m³ was estimated for non-cardiorespiratory causes of death, illustrating the specificity of the approach. Earlier analyses restricted the analysis to concentrations below a certain value.[37,110] These analyses suggest that a threshold for acute effects of ozone on lung function changes must lie well below 100 μg/m³ as an hourly maximum.

### *Displacement of daily mortality and hospital admissions*

Although time-series studies have shown a link between day-to-day variations in air pollution concentrations and daily deaths and hospital admissions, by how many days, weeks, or months such events are brought forward is unclear. If deaths occur just a few days earlier than they would have occurred anyway, the public-health significance of these associations would be much less than if life expectancy is being reduced by months or years.[111] Recent analyses show that, in the time-series studies, there is no evidence that deaths or hospital admissions are being brought forward by just a few days.[112–115] On the contrary, effect estimates increase with increasing duration of exposure to air pollution, suggesting that cumulative exposures have stronger effects on mortality than can be extracted from associations between day-to-day variations in air pollution and deaths. Previous data have shown that many of the deaths associated with air pollution were occurring outside hospital, which also supports the suggestion that these patients were often not terminally ill.[116]

*Relation between ambient and personal exposure to particulate matter, nitrogen dioxide, and ozone in short-term and long-term studies*

In developed countries, people spend more than 80% of their time indoors, and most of that time in their own home. Indoor pollutant concentrations can differ from outdoor concentrations because of ventilation patterns and indoor sources. Therefore whether measurement of air pollution outdoors is a valid method of assessing exposure of the population has been questioned. The day-to-day variation in personal exposure to particulate matter correlates with the day-to-day variation in ambient concentrations of particulate matter; correlations are especially high in the case of fine particles (PM2·5).[117] One study that addressed this issue simultaneously for particulate matter and gaseous components found that there was no association between the day-to-day variation in personal exposure to nitrogen dioxide, sulphur dioxide, and ozone and ambient measurements of these three components.[118] Ambient PM2·5, nitrogen dioxide, sulphur dioxide, and ozone were closely associated with personal PM2·5, which strongly suggests that gaseous and PM2·5 concentrations outdoors act as a surrogate for personal exposure to PM2·5.[118]

Few studies have addressed the question of whether spatial variations in long-term average outdoor concentrations are reflected in similar variations in long-term personal exposures. For PM2·5 and nitrogen dioxide, regional and local-scale spatial variations in outdoor concentrations have been shown to be reflected in similar variations in personal exposures.[119,120] The US AHSMOG study and the recent Dutch cohort study have used estimates of small-scale spatial variations in air pollution exposure to their advantage,[30,121] suggesting that further improvements can be expected when such within-community differences in exposure are taken into account.

*Causality*

Knowledge of which pollution components are responsible for any health effects observed in epidemiological studies is of obvious importance. For ozone, the situation is relatively simple. A large experimental database exists to document that ozone has significant biological effects at ambient concentrations. In addition, the correlation between ozone and other pollutant concentrations in outdoor air is often low, so the effects of ozone and other pollutants can be separated relatively easily.

For nitrogen dioxide, the situation is more complex. Evidence for biological effects at ambient concentrations is much weaker than for ozone. In outdoor air, nitrogen dioxide is often highly correlated with other combustion products, notably fine particulate matter, and to personal PM2·5, but not personal nitrogen dioxide.[118] Our assessment is that, in most circumstances, nitrogen dioxide serves as a surrogate for all traffic-related combustion products.

Most complex is the question of which particulate matter components or attributes are most important in determining health effects. Many candidates have been proposed. One is ultrafine particles—ie, particles of less than 100 nm which can be found in very high numbers (>100 000 $cm^3$) near busy roads.[122] The thinking is that such particles can easily find their way from the lungs into the bloodstream and then lead to systemic inflammatory changes which may affect blood coagulability. Similarly, some suggestive evidence from epidemiological studies points to ultrafine particles being related to respiratory health endpoints.[123] However, the number of ultrafine particles in the air is often poorly correlated with PM2·5, so ultrafine particles are unlikely to explain much of the association between particulate matter mass and health endpoints.[124]

Specific components related to traffic exhaust, especially diesel combustion products, could be important.[125] The APHEA and NMMAPS analyses have suggested that particulate matter effects are larger in areas with high nitrogen dioxide (ie, traffic density)[43] or in areas with high emissions of particulate matter from highway vehicles and diesel locomotives.[126] An intriguing observation from a time-series study is that individuals who live on the main roads of Amsterdam have much higher relative risks of death than people who live away from the main roads, when analysed with data from the same background air pollution monitoring station.[127] This finding clearly suggests that traffic-related particulate matter is involved in explaining increases in mortality on high pollution days.

Factor analysis suggested that particles from mobile and coal combustion sources, but not coarse particles originating from the earth's crust, are responsible for effects on mortality.[128] Studies from the Utah Valley, USA, have linked transition metal content of particulate matter with particulate matter toxicity in human bronchial instillation studies.[129]

Much attention has been devoted to separating the effects of fine particulate matter (PM2·5) and coarse mass. Initial observations that fine particulate matter was associated with mortality whereas coarse mass was not[130] have been corroborated in several recent studies,[131,132] but others have found independent effects of coarse mass on hospital admissions for asthma,[133] and one study was unable to separate effects of fine particulate matter from those of coarse mass.[134]

Support for causality also comes from studies on effects of reducing air pollution on health outcomes. One of the best examples is a labour dispute that shut down a large steel mill in the Utah Valley for 14 months in 1987. Ambient particulate matter concentrations as well as respiratory hospital admissions were clearly decreased during the strike, only to increase to prestrike levels after the dispute ended.[135] Mortality was decreased as well.[136] In combination with the recent toxicological studies of particulate matter collected before, during, and after the strike, the Utah Valley example provides strong evidence of a causal relation between exposure to ambient particulate matter and mortality and morbidity. Other examples include reductions in acute-care visits and hospital admissions for asthma in Atlanta, GA, USA, in conjunction with reduced air pollution due to traffic measures taken during the 2000 Olympic games,[137] and reductions in bronchitis in association with reduced air pollution over several years in the former German Democratic Republic.[138]

## Disputing the evidence

In view of the potentially large costs and benefits associated with abatement of air pollution, questions surrounding the relation between air pollution and health have been an area of fierce debate in the past decade. The early time-series studies have been criticised for their analytical approach and inadequate control for confounding by weather variables etc, whereas the US cohort studies have been criticised for inadequate confounder and co-pollutant control. Reanalyses of such studies were done to investigate whether findings depended more on analytical approach than on robust

relations. The USA-based Health Effects Institute, itself a partnership between (automobile) industry and government, has taken a leadership role in this debate by commissioning two reanalysis projects—one to reanalyse the Philadelphia time-series study,[139] which had generated much of the debate on short-term effects, and another to reanalyse the two main US cohort studies. These reanalyses were done by independent researchers who were granted access to all original data and largely confirmed the findings of the original studies.[140,141] In addition, the reanalysis revealed new insights into the role of weather variables in time-series studies,[142,143] and new methods for enabling analysis of spatial association between air pollution, mortality, and potential confounding variables.[144] The reanalyses themselves have served as role models on how to provide policy makers with the best possible scientific evidence.[145]

## Concluding remarks

An excess risk of death of "0·5% per 10 μg/m³ PM10" requires some translation before the effect on public health becomes clear. For the Netherlands (16 million inhabitants, about 140 000 deaths per year, and an average PM10 concentration of >30 μg/m³), the number of deaths attributable to day-to-day variations in PM10 would translate into at least 2100 deaths brought forward by air pollution per year—almost twice the number of deaths due to traffic accidents. Estimates derived from the cohort studies are much higher still because these incorporate long-term as well as short-term effects. For Austria, France, and Switzerland combined (population about 74·5 million), 40 000 deaths per year are estimated to be attributable to air pollution, about half to air pollution from traffic specifically.[146] Similarly high numbers have been estimated for respiratory and cardiovascular hospital admissions, bronchitis episodes, and restricted activity days. Because of such numbers, health effects from air pollution have been estimated to be higher than effects from a long list of other environmental factors.[147] These estimates are based on three major assumptions: causality of the epidemiological associations, linearity of the exposure-response relations, and that a threshold is absent or has a very low value. All of these assumptions are being tested rigorously; further proof could arise from research specifically targeted at assessment of changes in air pollution concentrations, such as those being done in a series of studies in the former German Democratic Republic.[138]

Given the high cost of further measures to reduce air pollution, and the many new findings which suggest that health effects can be seen at ever lower concentrations, the health effects of air pollution will need to receive much scientific and regulatory interest for years to come.

*Conflict of interest statement*
None declared.

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# Uses of error

## Uncertainty

*David A Grimes*

Everything pointed to the same diagnosis: an ectopic pregnancy. Nonetheless, I was nervous making the diagnosis by myself. I was a very junior house officer in obstetrics and gynaecology, alone on call at a municipal hospital. My patient had an abnormal last menses about 8 weeks ago, no recent use of contraception, and vague pelvic pain. Her pulse and blood pressure were normal without orthostatic changes. She looked uncomfortable but not in acute distress. Her abdomen was tender, and the pelvic examination caused her discomfort, more on one side than the other. I could feel no adnexal mass, but my clinical experience was very limited. Her haemoglobin was around 110 g/L; not unusual for our indigent patients.

From my readings and observations as a medical student, I knew just what to do to confirm my diagnosis: a culdocentesis. At this time, sensitive pregnancy tests were not available, diagnostic ultrasound was in its infancy, and laparoscopy had just reached the USA and was not available by night at my hospital. After obtaining informed consent, I introduced a speculum and inserted a 20-gauge needle through her vaginal vault into her rectouterine pouch. To my delight, when I withdrew the plunger, the syringe promptly filled with dark blood. To my considerable dismay, however, the blood promptly clotted in the syringe. This was not supposed to happen: the hallmark of an ectopic pregnancy was non-clotting blood on culdocentesis. I had never read, seen, or heard of blood clotting in this setting.

Alone with this diagnostic dilemma, I excused myself from the patient and her family and slipped off discreetly to the hospital library. My memory had been correct: every gynaecology textbook on the shelf concurred that non-clotting blood on culdocentesis indicated an ectopic pregnancy. None, however, mentioned my current quandary: intraperitoneal blood that clotted. Given this uncertainty, I did not feel comfortable mobilising an operating theatre (which required calling in staff from home) to perform a laparotomy. Nor did I feel comfortable sending my patient home. I admitted her to the hospital, where I watched and fretted over her all night.

By morning, her pain was unchanged. Her repeat haemoglobin, however, had plummeted, and my error was apparent. We rushed her to the operating theatre. At laparotomy, she had litres of blood in her abdomen and required transfusion of several units of blood as a consequence of my timidity. I had erred in trusting the textbooks instead of my inexperienced clinical hunch. I later learned from published articles that a few such patients have blood that will not clot. Some authors call this "non-conclusive" evidence of an ectopic pregnancy.

I learned an important lesson that night about the limitations of textbooks and authorities. As Antman and colleagues showed several decades later, textbooks and their authors are dangerously obsolete. But Mark Twain may have put it best a century ago: "Be careful about reading health books. You may die of a misprint." The same holds true for omissions.

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