

THE EFFECTS ON HEALTH OF LONG-TERM EXPOSURE TO OZONE

This Chapter from the forthcoming report:

**The Committee On The Medical Effects Of Air Pollutants
(COMEAP)
'Ozone in the UK: Health Implications'**

has been provided in advance as background to:

**COMEAP Report On Long-Term Exposure To Air Pollution:
Effect On Mortality– Draft For Technical Comment 2007**

Comments on this chapter are not required at this stage but will be welcome when the full report on ozone is published for comment at a later date.

8 Health Effects of Long-term Exposure to Ozone

Introduction

8.1 Chapters 4 to 7 have discussed the evidence for associations between daily fluctuations in ozone and short-term fluctuations in health effects. Positive associations were found for many of the endpoints. The question therefore arises whether repeated or continuous exposure would lead to further health effects. This question is considered in this chapter¹. For the purposes of defining the studies covered in this chapter, we have excluded short-term studies (those involving exposure over a day or two followed up for a few days afterwards) and included studies covering periods longer than this, from a few months over a summer to decades. The literature search strategy used is described in Annex 8. This chapter considers the evidence for positive associations with long-term exposure to ozone. Chapter 9 considers whether or not any positive associations identified are likely to be causal.

8.2 There are fewer long-term than short-term studies in total and there is more variability in study design. This, in part, reflects the fact that studies of long-term exposure are more difficult to do and more difficult to interpret. It is harder to control for confounding, statistical power is often more limited and it is difficult to distinguish the effect of repeated peak exposures from continuous exposure.

Mortality²

8.3 This section will concentrate on prospective cohort studies, described in more detail below, but there have also been some cross-sectional studies of associations between ozone and mortality. Lipfert and Morris (2002) investigated whether deaths from all causes (other than AIDS and trauma) were related to air pollution levels (including ozone) at various dates in US counties. The study had the advantage that it covered the entire population, was at a relatively fine spatial scale, covered different time periods and considered mortality rates stratified by age. However, individual risk factors were not available. The associations were adjusted for a large range of risk factors at a county level including population change, race, unemployment, median income, cigarette sales per capita or % smokers, education, obesity, alcohol use, exercise, % with air conditioning and various climatic factors. The ozone measure used was the 95th percentile of daily maximum ozone levels averaged across the county. The association with peak ozone was positive and statistically significant in the 64-74 and 75-84 year old age

¹ Some preliminary papers on the effects of long-term exposure to ozone were placed on the COMEAP website in 2002

www.advisorybodies.doh.gov.uk/comeap/pdfs/longtermozonejune2002.pdf . Our thinking has developed over time and the conclusions in this chapter may not match the earlier interim conclusions. This chapter supercedes the earlier papers.

² One study published after the cut off for the literature search (Jerrett *et al* 2005) found no effect of long-term exposure to ozone on mortality across different areas within Los Angeles.

groups. For some time periods, mortality was more strongly related to ozone in the same rather than previous time periods. However, the authors also considered there was evidence for an effect of cumulative or repeated exposure to peak ozone as effects increased with age and with calendar time. Other pollutants were examined but multi-pollutant models were not applied. Ozone had small positive correlations with other pollutants, the highest being a correlation of 0.5 with sulphate.

Six Cities Study

8.4 Dockery *et al* (1993) studied 8111 adults in six US cities in a prospective cohort study with 14 to 16 years of follow-up. Air pollution was measured at the city level. The results were adjusted for individual level risk factors including smoking, education and body mass index. Mortality rate ratios were calculated using Cox proportional hazard modelling with the least polluted city as a reference. Results presented graphically for ozone (mean from 1977 to 1985) showed no apparent positive association with all cause mortality. The authors did note, however, that the small difference in ozone levels (a range of only 8.3 ppb) limited the power of the study to detect associations between mortality and ozone levels.

8.5 In a re-analysis of the Six Cities Study data by the Health Effects Institute (Health Effects Institute, 2000), the following relative risks were tabulated.

Table 8.1 Long-term exposure to ozone and mortality (Six Cities Study)

Relative risk per 8.3 ppb ozone by cause of death (95% CI)		
All causes	Cardio-pulmonary	Lung Cancer
0.87 (0.76-1.00)	0.78 (0.64-0.95)	0.94 (0.56-1.59)

Thus, long term exposure to ozone does not appear to be positively associated with all cause, cardio-pulmonary or lung cancer mortality in this study. No multi-pollutant models were considered as the number of data points (six) was too small but it was noted that ozone was negatively correlated with all the other pollutants examined.

American Cancer Society study

8.6 The HEI reanalysis (Health Effects Institute, 2000) also re-examined the results of the American Cancer Society (ACS) Study. This study followed 552,138 adults in 151 US cities for 7 years from 1982 to 1989, adjusting for a variety of individual risk factors. The original paper (Pope *et al* 1995) had not analysed results for ozone as no association had been found in the Six Cities study. However, the reanalysis did address this using the annual average of 1 hour maximum ozone³ in 1980. There were a large number of different analyses performed, most of which found no evidence of a positive

³ The sum of the maximum 1 hour daily ozone concentrations each day in a year divided by 365 days.

association between long term exposure to ozone and mortality. The results using 117 cities which measured both sulphate and ozone are given below.

Table 8.2 Long-term exposure to ozone and mortality (ACS study, HEI reanalysis)

Model ⁴	Relative risk for ozone ⁵ and mortality (95% CI)		
	All causes	Cardio-pulmonary	Lung Cancer
Single pollutant	0.93 (0.87-0.99)	0.98 (0.90-1.08)	0.74 (0.59-0.92)
Two-pollutant, with sulphate	0.92 (0.86-0.98)	0.96 (0.88-1.05)	0.72 (0.58-0.90)

Again, as with the Six Cities Study, there is no evidence of a positive association between long term exposure to ozone and mortality. Inclusion of sulphate in the model does not seem to affect the results very much. Ozone was not closely correlated with sulphate or the other pollutants examined⁶. The overall range of ozone concentrations was greater than for the Six Cities study (around 30 ppb) but over 70% of the data were in a narrower range between 20 and 30 ppb. Similar results for the relative risks were found when using the 45 cities that measured both ozone and PM_{2.5} (although lung cancer was not examined).

8.7 The reanalysis report also presented results by season. The seasonal mean ozone across all cities (the number of cities was not specified) was 30.44 ppb for April to September and 15.07 ppb for October to March.

Table 8.3 Long-term exposure to ozone and mortality by season (ACS study, HEI reanalysis)

Season	Relative risk for ozone ⁷ and mortality (95% CI)		
	All causes	Cardio-pulmonary	Lung Cancer
Apr – Sep	1.02 (0.96 – 1.07)	1.08 (1.01 – 1.16)	0.81 (0.69 – 0.94)
Oct – Mar	0.81 (0.76 – 0.87)	0.82 (0.74 – 0.91)	0.78 (0.61 – 0.99)

⁴ Based on the 'Extended Model' stratified by 1 year age groups, gender and race and a wide variety of other risk factors such as smoking and education. See HEI (2000) for full list.

⁵ For a range of 10.41 to 41.14 ppb (the least polluted to most polluted city). See Appendix G of the HEI reanalysis report available on request from HEI for full list of concentrations by city or Willis *et al* 2003 for a summary.

⁶ Pearson correlations given in Appendix G of the HEI reanalysis report available on request from HEI. Also reproduced in Willis *et al* 2003.

⁷ Concentration range for ozone by season and correlations between pollutants by season not given.

This shows that cities with higher levels of ozone between April and September are associated with greater cardio-pulmonary mortality. Multi-pollutant models were not performed.

8.8 The re-analysis performed several sensitivity analyses with different types of statistical modelling designed to take into account city level variation, a lack of independence between city level variation and pollutant concentration and the possibility of spatial correlation between cities (i.e. correlations between results for cities closer together as opposed to cities further apart due to unknown regional confounders). Most of the results for ozone did not show clear positive associations with mortality with the exception of the model using regional adjustment. This found a relative risk for all cause mortality of 1.12 (95% CI 1.00-1.26) and for cardiopulmonary mortality of 1.20 (95% CI 1.02-1.41) in the group of cities measuring both fine particles and ozone⁸. This was not so clear for the larger group of cities measuring both sulphate and ozone. After regional adjustment the relative risk for all cause mortality in this larger group was 1.02 (95% CI 0.92-1.12) and for cardiopulmonary mortality was 1.08 (95% CI 0.96-1.32)⁹. However, the reanalysis report notes that the regional adjustment model (which used only very large regions) may overcontrol or undercontrol the actual spatial dependence and smaller area spatial dependence may be neglected. The more comprehensive 'spatial filtering' results which could only be performed on the sulphate cohort did not show positive associations for ozone. The relative risks were 0.96 (95% CI 0.87-1.05) for all cause mortality and 0.99 (95% CI 0.88-1.12) for cardio-pulmonary mortality for a 31 ppb range in ozone concentrations (see footnote 5). In addition, the appropriate form of models to adjust for spatial correlation is debated (HEI Review Committee, in Health Effects Institute 2000).

American Cancer Society study – further follow-up Pope et al (2002)

8.9 Pope *et al* (2002) published further analysis of the ACS cohort after more than 16 years of follow-up, with three times as many deaths. Ozone results were presented graphically in the paper but the full numerical results have been obtained separately (Pope, personal communication). These are shown in Table 8.4 below¹⁰.

⁸ The ozone range for the cities measuring both fine particles and ozone was from 10.41 to 35.17 ppb (range 25 ppb) derived from Appendix G of the HEI reanalysis report available on request from HEI.

⁹ Ozone range 31 ppb, see footnote 5

¹⁰ Relative risks for 'all other causes' are not shown, these were below or at 1 and were not statistically significant.

Table 8.4 Long-term exposure to ozone and mortality (ACS study, Pope *et al*, 2002)

Metric	Relative risk for ozone* and mortality (95% CI)		
	All causes	Cardiopulmonary	Lung Cancer
Ozone (1980)	0.98 (0.92-1.00)	0.99 (0.92-1.07)	0.96 (0.86-1.06)
Ozone (1982-1998)	1.01 (0.93-1.10)	1.05 (0.93-1.19)	0.92 (0.78-1.09)
Ozone (1982-1999) 3 rd Quarter	1.04 (0.98-1.11)	1.08 (0.99-1.18)	0.96 (0.85-1.09)

*Adjusted mortality relative risk ratio evaluated at subject-weighted mean concentration. The mean ozone concentrations in Table 1 of Pope *et al* (2002) are subject-weighted (Pope, personal communication) ie, the subject-weighted mean concentrations are 47.9 ppb for ozone (1980), 45.5 ppb for ozone (1982-1998) and 59.7 ppb for ozone (1982-1999) 3rd quarter (July, August, September). The full year or 3rd quarter values were means of daily 1 hour maximums.

The results do not indicate an effect of ozone when the average of the daily 1 hour maximum ozone for 1980 was used as a metric. However, averaging over a larger number of years probably gives a more reliable measure of long-term exposure. For the average of the daily 1 hour maximum for the whole year for 1982-1988, the relative risks for all cause and cardio-pulmonary mortality were positive but not statistically significant. The relative risks for lung cancer were negative but not statistically significant. For the average of the daily 1 hour maximum for July to September for 1982-1988, the relative risk was larger for all cause mortality. The relative risk for cardiopulmonary mortality was also larger and was very nearly statistically significant. The use of subject-weighted mean concentrations is intended to take account of the risks in the 'real-life' situation i.e. it takes into account both the inherent risks of the pollutant and the actual pollutant concentrations experienced in the relevant US cities. Thus, the higher relative risks for the 3rd quarter probably reflect the higher ozone concentrations that occur in the summer. It should be noted that a larger number of cities (134 vs 119 for all year) were included in the summer analysis, there was more variability in the ozone concentrations (Standard Deviation 12.8 vs 7.3) and the rank order of the cities may not have been the same. No information was given on correlations with other pollutants but it is known from other studies that this can differ in the summer. No adjustment was made for spatial auto-correlation.

8.10 This study is by far the largest of the prospective cohort studies. It does not suggest an effect of ozone on lung cancer and the effect of all year ozone on all cause and cardiopulmonary mortality is unconvincing. However, there is some suggestion of an effect of summer ozone levels on cardio-pulmonary mortality.

Adventist Health Study of SMOG (AHSMOG)

8.11 Abbey *et al* (1999) studied 6,338 non-smoking Seventh-Day Adventists in California from 1977 to 1992. Air pollution concentrations were obtained as monthly averages from 1966 to 1992, interpolated to subjects' work or home locations, cumulated and then averaged over time. Correlations with other pollutants were mostly small and positive except for PM₁₀ (0.77 for ozone with mean PM₁₀). After adjustment for several other risk factors such as smoking, education, occupation and body-mass index, ozone was not found to be significantly associated with all cause, cardiopulmonary, any mention of non-malignant respiratory or lung cancer mortality. The association with lung cancer mortality in men only was positive but not quite statistically significant (Table 8.5). No multi-pollutant models were performed.

Table 8.5 Long-term exposure to ozone and mortality in Seventh Day Adventists in California

	Relative risk per 12.03 ppb ¹¹ long-term average ozone (95% CI)			
	All cause	Cardio-pulmonary	Any mention of non-malignant respiratory	Lung cancer
Male	1.09 (0.95 – 1.25)	1.08 (0.91 – 1.29)	1.12 (0.85 – 1.47)	2.10 (0.99 – 4.44)
Female	0.95 (0.85 – 1.06)	0.97 (0.84 – 1.12)	1.05 (0.82 – 1.35)	0.77 (0.37 – 1.61)
Pooled*	1.00 (0.92 – 1.09)	1.01 (0.91 – 1.13)	1.08 (0.90 – 1.30)	1.26 (0.74 – 2.12)

* Not presented in original paper but derived separately from male and female results

8.12 An alternative ozone measure used was hours above 100 ppb. This gave the results shown in Table 8.6. The relative risks were usually greater than for the mean ozone measure in men. In women, the relative risk was only greater for lung cancer, although it was not statistically significant. The pooled association for lung cancer mortality was positive and statistically significant. In two-pollutant models of PM₁₀ above 100 µg/m³ and ozone above 100 ppb, both coefficients for lung cancer mortality in males remained positive but were reduced in magnitude, with the ozone coefficient remaining strongest. Lung cancer mortality in males remained significantly associated with ozone at all cut-offs from 60 to 150 ppb.

¹¹ Inter-quartile range

Table 8.6 Long-term exposure to ozone (hours above 100 ppb) and mortality in Seventh Day Adventists in California

	Relative risk per 551.1 hours ¹¹ per year ozone above 100 ppb (95% CI)			
	All cause	Cardio-pulmonary	Any mention of non-malignant respiratory	Lung cancer
Male	1.14 (0.98 – 1.32)	1.06 (0.88 – 1.29)	1.20 (0.88 – 1.64)	4.19 (1.81 – 9.69)
Female	0.90 (0.80 – 1.02)	0.88 (0.75 – 1.02)	1.01 (0.77 – 1.33)	1.39 (0.52 – 3.67)
Pooled*	0.98 (0.90 – 1.08)	0.95 (0.84 – 1.07)	1.09 (0.89 – 1.33)	2.63 (1.39 – 4.98)

* Not presented in original paper but derived separately from male and female results

8.13 The association of lung cancer mortality with ozone in males was strongly positive for both past smokers and never smokers. As Seventh Day Adventists are not supposed to smoke, there is a possibility that smokers may not report the fact that they smoke. The authors performed sensitivity analyses assuming a ten-fold greater risk for current smokers and 50% underreporting in the top quartile of air pollution exposure. If this had occurred, it was calculated that the true relative risks would be overestimated by no more than 15%.

8.14 Adjustment of the coefficient between ozone and lung cancer mortality for time spent outdoors gave results consistent with the coefficients without adjustment for time spent outdoors.

US Veterans study

8.15 Lipfert *et al* (2000) report the preliminary results of a prospective study in about 50,000 male US veterans diagnosed with hypertension followed for up to 21 years from 1976 to 1996. Air quality data was averaged by year for the county of residence at the start of the study. For ozone, the 95th percentile levels for each county were used, as a long term estimate of peak levels. (Mean ozone was not found to be associated with mortality in an initial screen). Four separate exposure periods were used: 1960 -1974, 1975-1981, 1982-1988 and 1989-1996. The ozone ranges for these periods were 56-431 ppb, 48-472 ppb, 31-170 ppb and 40-138 ppb respectively. The number of counties was not given for all exposure periods but there were 573 counties with ozone data in 1982. Individual risk factors included in the model were age (deciles), systolic blood pressure, diastolic blood pressure, body mass index, race and current or ever smoking. Ecological variables (years of education, income < 75% of the official poverty level, percent black and annual average heating degree days) were also added. All cause mortality in three follow-up periods 1976-1981, 1982-1988 and 1989-1996 was then related to ozone levels in the four exposure periods mentioned above. No

adjustment was made for spatial autocorrelation, although the authors note that the use of county level data captures the city-suburb spatial gradients to some extent. Nonetheless, it should be borne in mind that significance levels may have been overstated in the proportional hazards regression models.

8.16 The results are shown in Table 8.7.

Table 8.7 Long term exposure to ozone (average of 95th percentile levels by county) and all cause mortality in male US veterans with hypertension

Exposure period	Fractional mortality per mg/m ³ ozone		
	Mortality 1976-1981	Mortality 1982-1988	Mortality 1989-1996
1960-1974	-0.670	-0.250	-0.292
1975-1981	0.898	0.881	-0.087
1982-1988	(2.540)	2.710	1.106
1989-1996	(4.030)	(3.840)	0.962

Figures in brackets are those where deaths precede exposure. Figures in bold are those where exposure and deaths are concurrent. Figures from Table 7 of Lipfert *et al* (2000).

The results are complicated to interpret. Positive associations are found for 'concurrent' exposures but are, in general, less marked or even negative for prior exposure periods (delayed response). Positive associations are also found where mortality precedes exposure (indirect response), although this could be a result of the close correlations for exposures between one exposure period and another (0.94 for the 4th vs 3rd exposure period; 0.88 for the 3rd vs 2nd exposure period). Correlations were less strong for the early exposure period (0.49 for the 2nd vs 1st exposure period). It should be noted that 'concurrent' exposure could still represent an association with exposures up to about 7 years previously.

8.17 Risks were also expressed relative to the mean concentration of pollutant minus the estimated background weighted by the number of subjects in each county. The estimated background was regarded as the mean less 3 standard deviations. Results expressed in this way and averaged across all the concurrent, delayed and indirect responses are shown in Table 8.8.

Table 8.8 Long term exposure to ozone (average of 95th percentiles by county) and all cause mortality in male US veterans with hypertension – averaged responses

	Fractional risk at mean value of pollutant less background			
	Concurrent responses	Delayed responses	Indirect responses	Single mortality period
Peak ozone	0.094	-0.002	0.140	0.036

Figures in bold indicate results which are statistically significant at P < 0.05.

Note that in this table figures in bold indicate statistically significant results. Again, the results support an association with ‘concurrent’ exposures, do not support an association with prior exposures (delayed responses) and show indirect association with exposure after death. The single mortality period column gives the results where mortality over the entire period 1976-1996 is related to each exposure period and then the responses averaged for all exposure periods. This includes some deaths which preceded exposure in later periods but the authors presented this as it was considered analogous to the approach taken in some other cohort studies. This shows a positive association with peak ozone, the only pollutant for which this was found.

8.18 Correlations with other pollutants were presented for each exposure period. Correlations were positive or negative but generally low. The highest correlation was with NO₂ (0.56, 0.63 and 0.62 in 1975-1981, 1982-1988 and 1989-1996). Ozone and NO₂ were examined in two pollutant models as shown in Table 8.9.

Table 8.9 Long term exposure to ozone (average of 95th percentiles by county) and all cause mortality in male US veterans with hypertension – two-pollutant models

	Fractional risks at mean value of pollutant less background					
	Concurrent responses		Delayed responses		Indirect responses	
	Separate	Joint	Separate	Joint	Separate	Joint
Peak ozone	0.094	0.122	-0.002	0.034	0.140	0.178
NO₂	<u>0.045</u>	<u>-0.036</u>	<u>0.064</u>	<u>0.030</u>	<u>0.049</u>	<u>-0.052</u>
Sum	0.139	0.086	0.062	0.064	0.189	0.126

It can be seen that the association with ‘concurrent’ exposure increased with inclusion of NO₂ in the model. There was a possibility that the smaller delayed response was shared between ozone and NO₂. The indirect response (where deaths preceded ozone exposure) was no longer statistically significant after adjustment for NO₂ exposure. Associations with peak ozone were also robust in two pollutant models with TSP, sulphate and PM₁₀ (not shown).

8.19 The World Health Organisation (WHO, 2003) had some concerns about this study. These included the fact that the statistical models included up to 230 terms and that the effect of smoking on mortality in the cohort was smaller than expected. The authors (Lipfert *et al* 2000) note that many of these terms were interaction terms due to non-linearities in the relation between potential confounders and mortality. The authors argue that the low value for the effect of smoking on mortality was due to the inclusion of additional terms in the model compared with other studies. The authors themselves (Lipfert *et al* 2000) note that spatial autocorrelation was not taken into account. Finally, the study was performed in a specific subgroup (male

US veterans with hypertension) who were generally of lower socioeconomic status than the general population. (Other cohort studies also applied to subgroups e.g. the ACS study cohort was predominantly middle class).

Summary

Mortality

All-cause mortality

8.20 Table 8.10 presents the results for all cause mortality where the metric used was some form of long term average of ozone concentrations. This shows an even mixture of positive and negative associations which are rarely statistically significant. The question is whether to give some associations greater weight than others, for example, if multi-pollutant models were performed or if adjustment was made for spatial autocorrelation. The latter point is discussed further below. Table 8.11 presents the results where the metric used was some form of long term average repeated higher ozone exposure such as hours over 100 ppb or summer averages. These showed a greater preponderance of positive associations, although most were not statistically significant. It should be noted that there may be other reasons for an apparent association with ozone peaks – ozone peaks occur more frequently in the summer when windows may be open more¹² (personal exposure will be more closely linked with outdoor ozone concentrations) and temperatures are higher (there could be effect modification by temperature).

Cardio-pulmonary mortality

8.21 The results for cardio-pulmonary mortality are summarised in Tables 8.12 and 8.13. The results in Table 8.12 for ‘mean’ exposures are very similar to those for all cause mortality i.e. a mixture of positive and negative associations which are mostly not statistically significant. Again, as for all cause mortality, the ‘peak’ exposure associations in Table 8.13 are predominantly positive but mostly not statistically significant.

Non-malignant respiratory mortality

8.22 Only one study examined respiratory mortality and found positive but non-significant associations for both ‘mean’ and ‘peak’ exposure (Tables 8.14 and 8.15). In this study, ozone was closely correlated with particles.

Lung cancer mortality

8.23 The results for lung cancer mortality (Tables 8.16 and 8.17) are inconsistent but point in the direction of no effect. Several associations were negative, including the largest study, the ACS study. The association between hours of ozone above 100 ppb and lung cancer mortality in the AHSMOG study was large (around 4), positive and statistically significant in

¹² This point may be of less importance in areas where use of air-conditioning is widespread.

men but not women. (The pooled results for men and women were also positive and statistically significant). The authors suggest that the difference between men and women in the AHSMOG study could be due to men spending more time outdoors. However, the authors also reported that adjustment for time spent out of doors did not affect the result. It is possible that men were more likely to underreport smoking than women although this would also have to be differential with increasing hours of ozone above 100 ppb to account for the results. Under-reporting of smoking may be more likely in Seventh Day Adventists suggesting a cautious interpretation is needed.

Table 8.10 'Mean' long term ozone exposure metrics and all cause mortality

Study	Direction of association (single pollutant model)	Statistically significant?	Correlations with other pollutants?	Mp model result?	Ozone range	Adjusted for spatial correlation?
6 cities	Negative	No	Negative	No	Narrow (8 ppb)	No
ACS (HEI)	Negative	Just	Mostly small, positive	Yes, unchanged with sulphate	Less narrow (range 31 ppb but 70% between 20 and 30 ppb)	No
ACS (HEI) Regional adjustment model	Positive (fine particle cities)	Yes (fine particle cities)	Small, positive (except with CO)	No	Less narrow (range 25 ppb but 85% between 18 and 30 ppb)	Yes
	Positive (sulphate cities)	No (sulphate cities)	Small, positive (except with SO ₂)	No	Less narrow (range 31 ppb but 70% between 20 and 30 ppb)	Yes
ACS (HEI) Spatial filtering model	Negative (sulphate cities)	No (sulphate cities)	Small, positive (except with SO ₂)	No	Less narrow (range 31 ppb but 70% between 20 and 30 ppb)	Yes
ACS follow-up Pope et al (2002)	Positive	No	Not given	No	SD 12 ppb	No
AHSMOG	Positive (men)	No	0.77 with mean PM ₁₀	Only for positive and significant associations	Range 44 ppb	No
	Negative (women)	No				
	Null (pooled)	No				
Lipfert 2000 US Veterans	Negative	No	Not given	No	Not given	No

Table 8.11 'Peak' long term exposure metrics and all cause mortality

Study	Direction of association	Statistically significant?	Correlations with other pollutants?	Mp model result?	Ozone range	Adjusted for spatial correlation?
Lipfert and Morris 2002 (95th percentile)	Positive (in elderly)	Yes	Small, positive	No	Wide in earlier periods (SD 50 ppb)	Examined regional subsets but not for ozone
ACS (HEI) Apr-Sep	Positive	No	Not given	No	Not given	No
ACS (2002) Jul-Sep	Positive	No	Not given	No	SD 12 ppb	No
AHSMOG (hours over 100 ppb)	Positive (men) Negative (women) Negative (pooled)	No No No	0.84 with PM ₁₀ (hours over 100 µg/m ³)	Only for positive and significant associations	Range 988 hours, IQR 551 hours	No
Lipfert 2000 US Veterans	Positive (concurrent 7 years), positive or negative depending on time period (delayed)	Yes (concurrent 7 years or whole period) No (delayed)	Positive or negative but small, highest 0.6 with NO ₂	Yes (concurrent stable to adjustment for NO ₂ ; delayed association became positive after adjustment for NO ₂) Also robust to adjustment for other pollutants.	Range varies from 98 ppb to 424 ppb depending on time period, SDs 12 to 44 ppb	No

Table 8.12 'Mean' long term ozone exposure metrics and cardiopulmonary mortality

Study	Direction of association (single pollutant model)	Statistically significant?	Correlations with other pollutants?	Mp model result?	Ozone range	Adjusted for spatial correlation?
6 cities	Negative	Yes	Negative	No	Narrow (8 ppb)	No
ACS (HEI)	Negative (just)	No	Mostly small, positive	Yes, unchanged with sulphate	Less narrow (range 31 ppb but 70% between 20 and 30 ppb)	No
ACS (HEI) Regional adjustment model	Positive (fine particle cities)	Yes (fine particle cities)	Small, positive (except with CO)	No	Less narrow (range 25 ppb but 85% between 18 and 30 ppb)	Yes
	Positive (sulphate cities)	No (sulphate cities)	Small, positive (except with SO ₂)	No	Less narrow (range 31 ppb but 70% between 20 and 30 ppb)	Yes
ACS (HEI) Spatial filtering model	Negative (sulphate cities)	No (sulphate cities)	Small, positive (except with SO ₂)	No	Less narrow (range 31 ppb but 70% between 20 and 30 ppb)	Yes
ACS follow-up Pope et al (2002)	Positive	No	Not given	No	SD 12 ppb	No
AHSMOG	Positive (men) Negative (women) Just positive (pooled)	No No No	0.77 with mean PM ₁₀	Only for positive and significant associations	Range 44 ppb	No

Table 8.13 'Peak' long term ozone exposure metrics and cardiopulmonary mortality

Study	Direction of association	Statistically significant?	Correlations with other pollutants?	Mp model result?	Ozone range	Adjusted for spatial correlation?
ACS (HEI) Apr-Sep	Positive	Yes	Not given	No	Not given	No
ACS follow-up Pope <i>et al</i> (2002) Jul-Sep	Positive	Almost	Not given	No	SD 12 ppb	No
AHSMOG (hours over 100 ppb)	Positive (men) Negative (women) Negative (pooled)	No No No	0.84 with PM ₁₀ (hours over 100 µg/m ³)	Only for positive and significant associations	Range 988 hours, IQR 551 hours	No

Table 8.14 'Mean' long term exposure metrics and 'any mention of non-malignant respiratory mortality'

Study	Direction of association (single pollutant model)	Statistically significant?	Correlations with other pollutants?	Mp model result?	Ozone range	Adjusted for spatial correlation?
AHSMOG	Positive (men) Positive (women) Positive (pooled)	No No No	0.77 with mean PM ₁₀	Only for positive and significant associations	Range 44 ppb	No

Table 8.15 'Peak' long term exposure metrics and 'any mention of non-malignant respiratory mortality'

Study	Direction of association	Statistically significant?	Correlations with other pollutants?	Mp model result?	Ozone range	Adjusted for spatial correlation?
AHSMOG (hours over 100 ppb)	Positive (men) Positive (women) Positive (pooled)	No No No	0.84 with PM ₁₀ (hours over 100 µg/m ³)	Only for positive and significant associations	Range 988 hours, IQR 551 hours	No

Table 8.16 'Mean' long term exposure metrics and lung cancer mortality

Study	Direction of association (single pollutant model)	Statistically significant?	Correlations with other pollutants?	Mp model result?	Ozone range	Adjusted for spatial correlation?
6 cities	Negative	No	Negative	No	Narrow (8 ppb)	No
ACS (HEI)	Negative	Yes	Small, positive	Yes, unchanged with sulphate	Less narrow (30 ppb but 70% between 20 and 30 ppb)	No
ACS follow-up Pope <i>et al</i> (2002)	Negative	No	Not given	No	SD 12 ppb	No
AHSMOG	Positive (men) Negative (women) Positive (pooled)	No No No	0.77 with mean PM ₁₀	Only for positive and significant associations	Range 44 ppb	No

Table 8.17 'Peak' long term exposure metrics and lung cancer mortality

Study	Direction of association	Statistically significant?	Correlations with other pollutants?	Mp model result?	Ozone range	Adjusted for spatial correlation?
ACS (HEI) Apr-Sep	Negative	Yes	Not given	No	Not given	No
ACS follow-up Pope <i>et al</i> (2002) Jul-Sep	Negative	No	Not given	No	SD 12 ppb	No
AHSMOG (hours over 100 ppb)	Positive (men) Positive (women) Positive (pooled)	Yes No Yes	0.84 with PM ₁₀ (hours over 100 µg/m ³)	In two-pollutant model with PM ₁₀ reduced in magnitude but remained positive and stronger than for PM ₁₀	Range 988 hours, IQR 551 hours	No

General points

8.24 In addition to examining the evidence for associations directly, consideration needs to be given to whether confounding could be affecting the associations. Ozone is known to be correlated with other pollutants, yet most studies did not report results from multi-pollutant models. This limits our ability to come to firm conclusions. Another issue is that of spatial autocorrelation – the likelihood that geographically close cities have similar mortality rates irrespective of air pollution. Adjustment to account for this was rare. The regional adjustment model in the reanalysis of the ACS study found positive and statistically significant associations for ozone (all year) for all cause mortality and cardiopulmonary mortality in the cities which measured fine particles. Positive associations for ozone were not found in the more comprehensive spatially filtered model in the cities which measured sulphates. Controlling for region is difficult and may be better addressed in studies with more information on exposure and other factors on an individual basis. The commentary from the Health Effects Institute Review Committee suggested caution in interpretation of the results from the models developed to adjust for spatial autocorrelation and suggested further research. Models to adjust for spatial autocorrelation were further developed for the longer follow-up of the ACS study but were not applied to the ozone analysis. The issue of adjustment for spatial autocorrelation is discussed in more detail in our report on 'Long-term Exposure to Air Pollution: Effect on Mortality' www.advisorybodies.doh.gov.uk/comeap/statementsreport/longtermeffectsmort2007.pdf

8.25 There were a mixture of positive and negative associations most of which were not statistically significant. Nonetheless, we cannot come to a firm conclusion that long term exposure to ozone is not associated with an increase in mortality, because

- (i) metrics representing long term exposures to peaks were more likely to show positive, although not statistically significant, associations,
- (ii) a regional adjustment model found a positive statistically significant association although this technique is still developing,
- (iii) multi-pollutant model results are rarely provided.

8.26 There is not as strong evidence for an association between long term exposure to ozone on mortality as there is for particles. This may seem surprising since there is clear evidence of an effect of short term exposure on mortality. Some of the positive results in the cohort studies may represent the 'tail' of the distribution of loss of life expectancy from the short-term effects¹³. In considering the fact that, overall, consistent positive evidence was not found, the following points need to be borne in mind:

¹³ The short-term effects may not simply be due to 'harvesting'. If the loss of life-expectancy is large enough, the effects could be picked up in the cohort studies.

- (i) If ozone has a greater effect on respiratory than cardiovascular mortality¹⁴, then the loss of life-expectancy would probably be smaller than if the effect was mainly on cardiovascular mortality as for particles. This is because respiratory mortality tends to affect people at older ages. A smaller loss of life-expectancy would be harder to pick up in the cohort studies.
- (ii) None of the studies was specifically designed to address whether long-term exposure to ozone was associated with mortality,
- (iii) Some studies had a narrow range of exposure to ozone which limits the power to detect an effect,
- (iv) Ozone was sometimes negatively correlated with other pollutants including those known to be associated with mortality – this may explain the negative associations of ozone with mortality and, possibly, have masked a small effect of ozone (although adjustment for sulphate in the ACS study did not alter the relative risks very much),
- (v) The most appropriate ozone metric to examine is unclear. Measures more likely to pick up repeated exposures to peaks may be more important. Significant and almost significant positive association was found for the summer in the HEI reanalysis and in the further follow-up of the ACS study and relative risks were raised (although not significant in most cases) for the ‘hours over 100 ppb’ measure compared with the mean measure in the AHSMOG study. The US veterans study concentrated on peak ozone as associations were not found with mean ozone.
- (vi) If the effects of short-term exposure to ozone on mortality involve only small losses of life-expectancy, this might not be detectable above the city to city variations in mortality in the cohort studies.

8.27 If long-term exposure to ozone had an effect on lung function growth (see later), then an indirect effect on mortality in the long-term might be expected¹⁵ (Evans and Wolff, 1996). If long-term exposure to ozone has an effect on morbidity, then an effect of long-term exposure to ozone on mortality is more plausible. Effects on morbidity are discussed in the following sections.

¹⁴ The HEI reanalysis did not report separate results for ozone and respiratory and cardiovascular mortality as it did for particles. However, the data on ozone and hospital admissions suggests an effect on respiratory not cardiovascular admissions.

¹⁵ A correlation between declines in lung function over time and increased mortality is well established but the causal pathway is unknown. Therefore, it does not automatically follow that ozone-induced declines in lung function would lead to increased mortality.

Overall conclusions

8.28 Overall, the evidence currently published does not support a clear positive association between long-term exposure to ozone and all cause or cardio-pulmonary mortality. However, in the largest study, the ACS study a positive association was found with cardio-pulmonary mortality in the summer and positive associations with all cause and cardiopulmonary mortality were also found in the regional adjustment model (all year). Because of the limitations of the studies published so far, the above overall conclusion should be seen as a provisional one, pending further research.

Morbidity

Lung Cancer

8.29 As lung cancer incidence and lung cancer mortality are closely linked, the evidence on lung cancer mortality discussed above is also relevant to consideration of lung cancer incidence.

8.30 Ozone is a powerful oxidising agent and reacts readily with most biological macromolecules including DNA. The mutagenicity and carcinogenicity data on ozone were considered by the Department of Health's Committees on Mutagenicity and Carcinogenicity¹⁶ in 1999 (Department of Health 1999a; Department of Health 1999b). It was considered that there was some evidence for *in vivo* mutagenic activity at the target site for carcinogenicity in the mouse and that it was prudent to assume that ozone may have *in vivo* genotoxic potential. Ozone was carcinogenic by inhalation in female B6C3F1 mice producing lung tumours associated with chronic irritation of the lung. It was concluded that it was uncertain whether the carcinogenic action was due to genotoxicity or chronic irritation. The carcinogenicity appeared to be specific to the mouse in the presence of chronic irritation and had not been observed in the rat. It was therefore considered that the animal data were inadequate to draw any conclusions regarding the potential carcinogenicity of ozone in humans.

8.31 Calderón-Garcidueñas *et al* (1999) found increased oxidative DNA damage in the nasal epithelium of children from Mexico City compared with children from a less polluted area. It was unclear which pollutants were responsible. Ozone levels were high – during the time of sampling maximum ozone levels ranged from 157 to 225 ppb. It was noted that both the site specificity and the nature of the DNA lesions determined the carcinogenic potential of the DNA lesions and additional studies were needed.

8.32 A 1998 study (Beeson *et al*)¹⁷ looked at the relationship between the sum of monthly interpolated air pollutant concentrations, including ozone, and the risk of an increased incidence of lung cancer. Over 6000 white Seventh Day Adventist adults were included in the study, which took place from 1977 to 1992. 36 cases of lung cancer were identified. The authors found an increased incidence of lung cancer in males, but not in females, with an interquartile range of 556 hours per year above 100 ppb (200 µg/m³) ozone (RR = 3.56 CI 1.35 – 9.42). In females the relative risk was 0.94 (95% CI 0.41 – 2.16). The pooled relative risk for both males and females (calculated for this report to aid comparison with other studies) was 1.78 (95% CI 0.48 – 6.58) i.e. positive but not significant with wide confidence intervals. The gender difference in this study was thought to be due to fact that males reported spending more time outdoors and engaging in more vigorous

¹⁶ Full names – The Committee on the Mutagenicity of Chemicals in Food, Consumer Products and the Environment and The Committee on the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment, respectively.

¹⁷ This paper provides further follow-up of results reported by Mills *et al* 1991.

exercise than females. The authors also added that the associations occurred at exceedance frequencies for ozone thresholds as low as 80 ppb (160 $\mu\text{g}/\text{m}^3$).

8.33 These estimates were adjusted for self-reported pack-years of smoking (as well as for age, education and alcohol consumption). There is a concern that, since Seventh Day Adventists discourage smoking, there might be more under-reporting of smoking than in other cohorts. However, this would have to have happened more for subjects in high ozone areas than low ozone areas. The authors calculated that even if under-reporting was as high as 50% and only occurred in the high ozone quartile, then a relative risk of 2 in males would have been obtained. This is less than the original relative risk of 3.56 but still positive.

8.34 The increased relative risk remained when men working in occupations with exposure to airborne contaminants were excluded. The regression coefficient for ozone was reduced when other pollutants were added to the model. The positive associations of PM_{10} and sulphur dioxide with lung cancer were generally robust to control for other pollutants.

8.35 Pereira *et al* (2005) studied the correlations between air pollution and lung cancer or laryngeal cancer incidence in up to 12 Sao Paulo city districts. Ozone was measured as the 'mean average of days when ozone levels were beyond air quality standards'. When this ozone measure (available in only 4 districts) was calculated over the 1981-1990 period, the correlation with laryngeal cancer incidence in 1997 was 0.9929 ($p=0.007$) and the correlation with lung cancer incidence in 1997 was 0.7234 ($p=0.277$). These correlations were higher than for any other pollutant. However, no account was taken of possible confounding factors such as smoking or alcohol intake. Only one of the districts where ozone was measured had an average income below the city average and this district did not have the highest ozone level. However, income level was not included in the statistical model either. So this study can only be regarded as hypothesis generating.

Respiratory symptoms

8.36 There are substantially more studies of long term exposure to ozone and prevalence of respiratory symptoms than of incidence of respiratory diseases. Some of these provide only limited information, for example where only two areas are compared (Calderón-Garcidueñas *et al* 2000,2003; Stern *et al* 1989, 1994¹⁸). The remainder are discussed below. Cross-sectional studies are described first (paragraphs 8.37 to 8.50) followed by prospective studies (paragraphs 8.51 to 8.64). Within each of these two categories, studies using interpolated concentrations are discussed first followed by studies using a comparison across different areas. The studies are grouped in this way

¹⁸ Although Stern *et al* 1994 examined 10 Canadian communities, ozone was only measured in two.

because the pattern of confounding factors at the smaller spatial scale may be different from those at the area scale.

Cross-sectional studies

Interpolated concentrations

8.37 Hirsch *et al* (1999) studied 5,421 children in two age groups (5-7 years and 9-11 years) in Dresden, Germany. Exposure was examined within the city rather than across cities. Monitoring was performed from 06.00 to 23.00 hours at the gridpoints of 1km² grid squares about once a fortnight, such that an equal distribution of times and weekdays was ensured. The annual mean at each gridpoint was calculated. Individual exposures were allocated according to the average of the four surrounding gridpoints weighted by distance from individual homes and schools. Ozone concentrations calculated in this way ranged from 15.2 to 32 ppb with an interquartile range from 21.5 to 24.5 ppb. A parental questionnaire based on the ISAAC project collected information on wheeze and morning cough in the last 12 months and doctor-diagnosed asthma or bronchitis. Results were adjusted for sex, age group, birth weight, furry pets and carpets and other putative variables such as parental education, maternal smoking, season, central heating, damp and floor level of dwelling were included if shown to be important.

8.38 Ozone showed negative but non-significant associations with wheeze and doctor-diagnosed asthma and significant negative associations with morning cough and doctor-diagnosed bronchitis e.g. OR 0.80 (95% CI 0.65-0.98) for a 5ppb change in ozone at home address for morning cough. This was the inverse of the results found for traffic-related pollutants. Ozone was negatively correlated with NO₂, CO and benzene e.g. $r = -0.66$ for ozone and NO₂. The authors reported that an attempt to disentangle the effects of ozone in multivariate models with traffic-related pollutants results in reduced point estimates of the odds ratios and widened confidence intervals. However, the general pattern of the associations remained unchanged. It should be noted that the range of mean ozone concentrations was rather narrow in this study. The significant negative associations with morning cough and doctor-diagnosed bronchitis were not seen when using 95th percentile ozone concentrations as the exposure metric. No significant associations were found for atopic sensitisation for either the mean or the 95th percentile measure.

Comparison of areas

8.39 Ramadour *et al* (2000) studied the prevalence of wheeze, asthma, rhinitis and cough in 2445 13-14 year old children who had lived for at least 3 years in 7 towns near Marseilles¹⁹. Children completed written and video questionnaires describing various symptoms. Ozone concentrations (2 month means of 8 hour averages) ranged from 15.1 to 26.1 ppb. No significant

¹⁹ The effective number of units of analysis may be less than 7 since 5 of the towns were very close to each other around the Etang-de-Berre lake.

associations were found with respiratory symptoms in a logistic regression model but the authors considered this inappropriate as air pollution was measured on a town not an individual basis. A simple regression analysis found a significant positive correlation with wheezing in the last 12 months ($R=0.714$ $p<0.05$) and with ever asthma ($R=0.959$, $p<0.001$). The authors stated that similar results were found within strata of potential confounders. Particles were not measured and no correlations were found with sulphur dioxide or nitrogen dioxide for these symptoms.

8.40 Galizia and Kinney (1999) examined associations between respiratory symptoms and long term ozone exposure histories in 520 non-smoking Yale College students. Ozone exposure was considered to be high if students had lived for 4 or more years in an area with a 10 year average summer season daily 1 hour maximum ozone concentration greater than or equal to 80 ppb (the 95th percentile of long term average ozone concentrations across all sites in US counties). Symptoms of cough, phlegm, wheeze apart from colds and a composite respiratory symptom index (RSI) were determined by questionnaire. Cough was reported less commonly than the other symptoms. Odds ratios were adjusted for sex, race, parental education and maternal smoking plus air conditioner, fan and gas stove use. Comparing the exposure group above 80 ppb with the exposure group below 80 ppb gave odds ratios of 1.79 (95%CI 0.83-3.82), 1.97 (95%CI 1.06-3.66) and 2.00 (95%CI 1.15-3.46) for phlegm, wheeze without colds and RSI respectively. Other pollutants were not considered so could not be ruled out as an explanation for the effect.

8.41 The SCARPOL study in Switzerland (Braun-Fahrlander *et al* 1997) looked at the effect of long-term exposure to air pollution and symptoms in 4470 schoolchildren in 10 different communities. Children were from 6 years to 14 years old. The symptoms recorded on questionnaires included chronic cough, nocturnal dry cough, bronchitis, current wheeze, asthma, sneezing, hay fever and conjunctivitis. Adjustment was made for age, sex, low birthweight, parental education, nationality, number of siblings, family history of specified respiratory and allergic diseases, maternal smoking, indoor humidity, indoor fuels, carpets and pets.

8.42 A small positive and statistically significant association was found between number of hours per year above 80 ppb and nocturnal dry cough (OR 1.39 (1.02-1.89)) and bronchitis (OR 1.74 (1.22-2.50)). (Odds ratios for a range from 0 to 195 hours). The results were driven by 2 communities with much higher hours above 80 ppb than the other communities. This measure of ozone was positively correlated with other pollutants (r between 0.28 and 0.49). Positive associations were found with ever asthma and bronchitis and annual mean ozone concentrations but the associations were not statistically significant. Associations with annual mean ozone were negative but not statistically significant for other symptoms. Annual mean ozone concentrations were negatively correlated with other pollutants (r between -0.60 and -0.38). The authors considered their study design too limited and the measure of ozone too crude (no information on time spent outdoors) to

come to confident conclusions about the effect of long term exposure to ozone.

8.43 A report from the SAPALDIA study by Zemp *et al* (1999) examined respiratory symptoms in random population samples of adults (n=9651) in 8 areas of Switzerland compared to levels of ambient air pollution. Ozone was measured as an annual average and as excess ozone²⁰. Symptoms were in three categories: bronchitic (chronic cough, phlegm or both), asthmatic (wheeze, breathlessness, asthma) and non-specific cardiopulmonary (dyspnoea on exertion and chest tightness). Adjustment was made for age, body mass index, gender, parental asthma, parental atopy, low education and foreign citizenship. Other adjustments such as for passive smoking, gas cooking or early infections were made in sensitivity analyses. Associations with ozone were only examined in never smokers (n=4229).

8.44 Negative associations that were not statistically significant were found between annual mean ozone levels and respiratory symptoms. 'Excess ozone' (see footnote 20) was positively associated with chronic phlegm (11.2% increase per $\mu\text{g year}/\text{m}^3$, 95% confidence interval 1.7 to 21.5%), breathlessness (12.9% (5.4-20.9)) and dyspnoea on exertion (11.8% (6.3-17.7)), and negatively associated with current asthma (-15.9%(-27.8 – -2.1). There was a negative correlation between annual mean ozone concentrations and other pollutants but a positive correlation between excess ozone and other pollutants. The authors noted that it was difficult to relate the associations to a single pollutant.

8.45 Wang *et al* (1999) studied the 1 year prevalence of adolescent asthma in 165,173 schoolchildren aged 11 to 16 years in two provinces in Taiwan. Annual mean ozone concentrations for the same year (1996) were measured in 15 communities. Asthma prevalence was determined using the ISAAC video questionnaire which shows sequences of young people displaying signs of asthma. Adjustment was made for age, sex, resident area, parental education, exercise, smoking, alcohol, incense use and environmental tobacco smoke. The adjusted odds ratio was 1.11 (95% CI 1.07-1.15) for exposure above compared with below the median annual mean concentration of 22 ppb. Correlations with other pollutants were not reported but several other pollutants were also associated with prevalence of asthma.

8.46 A larger study by some of the same authors (Guo *et al*, 1999) studied the prevalence of asthma in 331,686 non-smoking children in Taiwan. The annual mean of the 1994 monthly averages for several pollutants were measured at 55 monitoring stations across Taiwan. Ozone levels ranged from 12.4 to 34.1 ppb. A written respiratory health questionnaire was given to parents and the ISAAC video questionnaire was shown to the children. Asthma was defined as physician-diagnosed asthma (reported by parents) or questionnaire-determined asthma (dyspnoea and nocturnal dyspnoea with wheezing from the parental or video questionnaire or physician-diagnosed

²⁰ The yearly sum of all half-hourly values of ozone concentrations minus 60ppb for those half hours above 60ppb divided by the yearly number of half hours.

asthma from the parental questionnaire). Adjustment was made for age, history of atopic eczema and parental education, temperature and humidity. In contrast to the smaller study, negative non-significant associations between ozone and asthma prevalence were found in both boys and girls for both physician-diagnosed and questionnaire-determined asthma. A traffic-related pollutant factor was positively associated with asthma prevalence and this was negatively correlated with ozone, perhaps explaining the negative associations for ozone.

8.47 Peters *et al* (1999a) studied the prevalence of respiratory symptoms in 3676 schoolchildren aged 9-16 years in 12 communities in Southern California. This was an initial cross-sectional study for the Southern California Children's Health Study before subsequent prospective follow-up. Maximum 1 hour ozone averaged over 1986-1990 or 1994 was used as the exposure measure. This measure was positively correlated with acid vapour ($r= 0.69$). Information on respiratory health (ever asthma, current asthma, bronchitis, cough and wheeze) was collected by questionnaire. No statistically significant associations were found for the 1986-1990 measure and only those for wheeze and for bronchitis were positive. The 1994 average of peak ozone was significantly associated with a decrease in asthma ever diagnosed by a doctor in girls only. The odds ratio was 0.58 (95% CI 0.37-0.91) for a 40 ppb interquartile range in peak ozone after adjustment for age, sex, grade in school, community, race, parental asthma, hayfever, insurance, plants, water damage and passive smoke. As with the 4 year mean, the 1994 mean was positively associated with wheeze and bronchitis, although the association was not statistically significant. Associations with other symptoms were negative but not statistically significant.

8.48 McConnell *et al* (1999) studied a subset of 493 children with asthma, 653 children with wheeze and 2211 children with neither asthma nor wheeze from the Southern California Children's Health Study described above. The 1994 average of 1 hour maximum ozone was used as the exposure measure (range 35.5 to 97.5 ppb). This measure was positively correlated with other pollutants, the highest correlation being with acid as described above. The outcomes considered within these subgroups were bronchitis, cough and phlegm. Odds ratios were adjusted for age, sex, race, school grade and health insurance and other personal covariates if they were significant confounders. Ozone was not found to be significantly associated with any of the outcomes in any of the subgroups, although several other pollutants were. Associations were negative in the no asthma group, mainly negative in the wheeze group and mainly positive in the asthma group.

8.49 Dockery *et al* (1989) studied 5,422 10-12 year old white children from 6 cities in the United States in the 1980-1981 school year. The annual mean of 24 hour average ozone was allocated to each city. The range across the cities was from 18 to 38 ppb. Information on bronchitis, cough, chest illness, wheeze and asthma was collected by questionnaire. Adjustment was made for sex, age, parental education, maternal smoking, presence of a gas stove and an indicator for each city. The odds ratio between ozone and prevalence of doctor diagnosed asthma was positive and just statistically significant (OR

1.9 95% CI 1.0 to 3.4 for a 20 ppb difference in ozone). Other symptoms showed non-significant associations (positive for persistent wheeze and negative for bronchitis, chronic cough and chest illness). None of the associations for the control symptoms (hayfever, earache, non-respiratory illness - expected to be unrelated to air pollution) were significant, although the association with hayfever was positive. No pollutants other than ozone were positively associated with asthma although various particle measures were positively associated with bronchitis, chronic cough and chest illness. Ozone was negatively correlated with these other pollutants ($r = -0.73$ to -0.96 , the strongest negative correlation being with nitrogen dioxide). It is possible that this explains the negative associations between ozone and bronchitis, chronic cough and chest illness. No multi-pollutant models were performed (these would in any case be difficult to interpret with only 6 cities).

8.50 Dockery *et al* (1996) studied 13,369 white children 8 to 12 years old from 24 communities in the US and Canada between 1988 and 1991. Annual means of three different ozone metrics were used (1 hour maximum, 8 hour daytime average and 24 hour average). Information on respiratory symptoms - ever asthma, wheezing attacks, persistent wheeze, (also grouped as asthmatic symptoms), chronic cough, chronic phlegm, bronchitis (also grouped as bronchitic symptoms) - was collected by questionnaire. Adjustment was made for sex, child history of allergy, parental history of asthma, parental education and current smoking in home. There were no statistically significant positive associations between ozone and any of the respiratory symptoms. All three averaging times for ozone showed higher but non-significant risks with bronchitis e.g. OR 1.49 (95% CI 0.72 - 3.12) for a 45.6 ppb range in annual mean of max 1 hr average ozone. There was a suggestion of a higher risk of chronic cough associated with the annual mean of 24-hr average ozone OR 1.29 (95% CI 0.87-1.91) for an 18.5 ppb range. Particle strong acidity showed a statistically significant positive association with bronchitis. No two pollutant models were performed but by design the city-specific mean particle strong acidity was only weakly correlated with the three ozone measures (strongest $r = 0.37$ with annual mean 1-hr max ozone).

Prospective studies

8.51 The studies described so far in this section have all been cross-sectional studies which assessed the presence of respiratory symptoms at only one time point. Longitudinal studies, in which repeated collection of data occurs over time, are better for studying the occurrence of new cases (incidence)²¹.

Interpolated concentrations

8.52 Abbey *et al* (1991) and Abbey *et al* (1993) reported a ten year follow up of a cohort of 3914 Seventh Day Adventists. Ozone concentrations (mean or hours above specified concentrations) were interpolated to place of work and residence on a monthly basis and averaged over time. Questionnaires were

²¹ The forthcoming COMEAP report 'Does air pollution cause asthma?' will consider the issue of air pollution and asthma incidence in more detail.

completed in 1977 and 1987. Incidence of chronic bronchitis was defined as a report of cough/sputum at least 3 months a year for 2 years in 1987 but not 1977. Ozone was not found to be associated with new cases of chronic bronchitis (relative risk 1.20 (95% CI 0.97 – 1.52) per 500 hours ozone above 100ppb). Concerns about possible underreporting of smoking, and thus possible undetected confounding, in this cohort have been mentioned previously – if this were happening to a serious extent an association with chronic bronchitis might have been expected.

8.53 This follow up (Abbey *et al* 1993) also examined the change in asthma or bronchitis symptom severity score over time. Interpolated ozone concentrations (mean or hours above a 100 or 120 ppb cut-off) showed positive and statistically significant associations with increased asthma symptom severity scores. Associations with bronchitis symptom scores were not statistically significant (direction not specified).

8.54 McDonnell *et al* (1999) report a longer 15 year follow up²² of this cohort. Ozone concentrations (8 hour average) were interpolated to place of work and residence and averaged over a 20 year period. Questionnaires were completed in 1977, 1987 and 1992. Incident asthma was defined as a report of doctor diagnosed asthma in 1987 or 1992 but not 1977. There were 32 cases in men and 79 cases in women. Adjustment was made for age, education, history of pneumonia or bronchitis under 16, ever smoking, years living/working with smokers, childhood colds and exposure to fumes and dust.

8.55 Long term exposure to ozone was found to be significantly related to reported doctor diagnosed asthma (Relative risk 2.05, 95% CI 1.03 – 4.16 per 27 ppb) in men but not in women (Relative risk 0.86, 95% CI 0.58-1.26). The pooled result (calculated for this report to aid comparison with other studies) was 1.28 (95% CI 0.53 – 3.09) i.e. positive but not statistically significant. A significantly increased risk was also found in men for hours of ozone above 60 ppb, coefficients for women were not significant and were close to zero. Ever smoking was also found to be related to doctor diagnosed asthma in men so previous discussion about possible under-reporting of smoking in this cohort (paragraphs 8.13 and 8.23) is also relevant to this outcome. Other pollutants (mean PM₁₀, sulphate, nitrogen dioxide and sulphur dioxide and PM₁₀ over 100 µg/m³) were not related to asthma incidence and did not substantially reduce the association with ozone in two pollutant models.

8.56 One of the key difficulties in studying incidence of asthma is distinguishing genuinely new disease from undiagnosed disease which subsequently comes to a doctors attention due to a worsening of symptoms. The authors reported no difference in the relationship between ozone and subsequent incidence of asthma between those reporting wheeze (but not asthma) in 1977 and those that did not report wheeze in 1977 and suggested that this did not support the hypothesis that only worsening of symptoms

²² Earlier reports of asthma incidence in this cohort given in Abbey *et al* 1993 and Greer *et al* 1993.

accounted for the findings. However, the low statistical power in these sub analyses was noted.

Comparison of areas

8.57 The Southern California Children's Health Study re-examined the children first assessed in 1996 yearly over time to provide longitudinal information. McConnell *et al* (2002) investigated newly diagnosed asthma in 3535 children from the Southern California Children's Health Study. Follow-up was for up to 5 years and 265 new cases of asthma were reported. Four year mean pollutant concentrations were used to classify the communities into 6 high pollution areas and 6 low pollution areas. No increase in risk (Relative risk 0.8 (95% CI 0.6-1.0)) was found when all children in the high ozone areas were compared with all children in the low ozone areas²³. In children living in high ozone (8 hour average 10am-6pm) areas and playing three or more team sports, the relative risk of newly diagnosed asthma was 3.3 (95% CI 1.9-5.8) compared with children playing no sports. This was not thought to be due to sport alone as no increased risk of playing three or more team sports was found in the low ozone areas or with other pollutants. In contrast to the study in Seventh Day Adventists, an increased risk was found in both sexes with a greater risk in girls. It should be noted that only 20 of the new cases (8% of the total) were in children playing three or more team sports in high ozone areas.

8.58 The authors had postulated that playing team sports would increase the dose of ozone to the lung as a result of the increased breathing rate and increased time spent outdoors where ozone concentrations are higher. The risk increased with increasing number of sports played in the high but not the low ozone areas. Time spent outdoors was also associated with an increased risk of asthma in the high but not the low ozone areas.

8.59 The authors considered that the results were consistent with both an increased risk of new-onset asthma and exacerbation of previously undiagnosed asthma. Increased risks were found in the children playing three or more sports in a high ozone area whether or not the children had a history of wheeze at baseline, with the risk being higher in those without wheeze at baseline.

8.60 We previously published a statement on this study (Department of Health, 2002) in which we noted the lack of an overall effect when comparing high and low ozone areas. We concluded that the study did not provide convincing evidence that exposure to air pollution played a significant part in causing asthma.

8.61 Both the Seventh Day Adventist study and the Southern California children's health study were performed in California, where ozone levels are quite high. In addition, both studies found associations only in certain sub-

²³ A positive association that was not statistically significant was found when 24 hour average ozone was used to classify high and low ozone areas.

groups (men only or children who played three or more team sports), which may have occurred by chance.

8.62 McConnell *et al* (2003) studied whether bronchitic symptoms were related to pollutant concentrations in a subset from the Southern California children's cohort of 475 children with asthma who had provided at least two follow-up questionnaires. The ozone metric used this time was the daytime average (10am to 6pm) averaged over the total 4 years (range 28.3-65.8 ppb) or the annual average for individual years expressed as the deviation from the 4 year mean (range 1.7-13.2 ppb). Bronchitic symptoms were defined as a report of a daily cough for 3 months in a row, congestion or phlegm for 3 months in a row or bronchitis. Adjustments were made for potential confounders including age, sex, race, community, smoking history, secondhand tobacco smoke exposure, family history of asthma or allergy, socioeconomic status and health insurance.

8.63 Ozone was not found to be significantly associated with bronchitic symptoms in asthmatics when using the 4 year mean of the daytime average as an exposure measure (OR 0.80 (95%CI 0.42-1.54) for a 37.5ppb range). Correlation of this ozone metric with other pollutants was low. The yearly deviation from the 4 year mean ozone was positively and significantly associated with bronchitic symptoms in the asthmatic subjects (OR 1.06 (95% CI 1.00-1.12) per 1 ppb deviation in ozone). However, the ozone association was reduced in two pollutant models with several other pollutants.

8.64 Although considering a shorter time scale (a summer season), Kinney and Lippmann (2000) also considered respiratory symptoms at more than one time point. They examined 72 military cadets attending summer training in a high ozone area (summer mean 71.3 ppb) or in one of three moderate ozone areas (mean 61.7 ppb or less). Respiratory symptoms (sore throat, cough, phlegm, chest pain, chest tightness, wheeze, stuffy nose, eye irritation, head cold, chest cold, any symptoms and lower respiratory symptoms) were assessed by questionnaire in April and again in late August/September. The authors hypothesised that adverse respiratory outcomes would be more pronounced in the cadets who attended training in the high ozone area. Increased reporting of sore throat, cough, chest tightness, eye irritation, any symptoms and lower respiratory symptoms was found at the end of the summer in all groups of cadets but there was no clear pattern with ozone exposure (or with 'dust, exhaust or smoke'). Thus, for respiratory symptoms at least, the hypothesis was not confirmed.

Summary

Respiratory symptoms

8.65 The results of these studies are difficult to summarise²⁴ as the results are very mixed. Table 8.18 sets out the results. A + or – sign is used for a positive or negative association and ‘sig’ for associations that are statistically significant ($p < 0.05$) or ‘ns’ for associations that are not statistically significant. A positive association indicates an increase in respiratory symptoms. Twelve of the sixteen studies found positive associations with at least one type of respiratory symptom. Eight of these were statistically significant.

8.66 There was an indication that positive and statistically significant associations were more likely in those studies that included a measure of long term exposure to ozone ‘peaks’²⁵:

Galizia and Kinney (1999). Living 4 or more years in an area with a 10-year summer season average of daily 1 hour maximum ozone greater than or equal to 80 ppb.

Braun-Fahrlander *et al* (1997). Number of hours per year with ozone concentrations above 80 ppb.

Zemp *et al* (1999) ‘Excess ozone’ - The yearly sum of all half-hourly values of ozone concentrations minus 60ppb for those half hours above 60ppb divided by the yearly number of half hours.

Hirsch *et al* (1999) The 95th percentile of the values over the year at the four surrounding grid points.

Kinney and Lippmann (2000) High ozone area (summer mean of daily 1 hour maximum 71.3ppb, 23 hours over 100 ppb) vs moderate ozone areas (summer means 61.7 ppb or below, 1 hour or less over 100 ppb).

Abbey *et al* (1991/1993) Cumulated hours in excess of 100 or 120 ppb from monitoring stations closest to zipcodes from monthly residential and work location histories.

McDonnell *et al* (1999) Hours per year above 60, 80, 100, 120 or 150 ppb 8 hour average

With the exception of Hirsch *et al* (1999) and Kinney and Lippmann (2000), all these studies found positive and statistically significant associations with at

²⁴ The summary uses overall rather than subgroup analyses where there is a choice i.e. all children for McConnell *et al* 2002 and pooled results for men and women for McDonnell *et al* 1999.

²⁵ Again, actual ozone concentrations may not be the only explanation for higher associations apparently occurring with ozone peaks (see para 8.20).

least one respiratory symptom. There were fourteen studies which used mean²⁶ measures which were not based exclusively on higher ozone concentrations. Only five of these (Ramadour *et al* 2000; Wang *et al* 1999, Dockery *et al* (1989), McConnell *et al* 2003 and Abbey *et al* 1993) found positive and statistically significant associations with at least one respiratory symptom.

8.67 There was no clear picture as to whether asthmatic symptoms (asthma, wheeze or breathlessness) were more likely to be increased than bronchitic symptoms (cough, phlegm, bronchitis). This is in any case a difficult distinction to make as asthmatics can experience cough or phlegm symptoms. All the studies examined asthmatic symptoms (including McConnell *et al* (1999) and McConnell *et al* (2003) who studied bronchitic symptoms in asthmatics). Most of the studies found positive associations with a type of asthmatic symptom and many were statistically significant. Studies examining bronchitic type symptoms also found several positive associations, although fewer were statistically significant. For any particular individual symptom covered in more than two studies, there were a mixture of positive and negative associations, although positive and statistically significant associations were found more often than negative and statistically significant associations. This mixed picture is probably insufficient to conclude whether any particular type of symptom is more affected than another.

²⁶ These were usually longer term means (2 months or more) of daily maximum (1 hour or 8 hour) ozone concentrations. They were not confined to high overall mean values and were usually means of all daily values not just high daily values.

Table 8.18 Long term exposure to ozone and respiratory symptoms

Study	Ozone measure	Ever asthma	Current asthma	Wheeze	Cough	Phlegm	Bronchitis	Breathlessness	Dyspnoea on exertion	Chest cold	Chest tightness	Lower respiratory symptoms	Head cold, sorethroat stuffy nose	Rhinitis	Hayfever or sneezing in pollen season	Conjunctivitis or eye irritation	Respiratory symptom index
Hirsch <i>et al</i> (1999) 5421 children, 1 km grid squares across Dresden	Annual mean of 0600 to 2300 hrs once every 2 weeks	-ns		-ns	-sig -ns (95%ile)		-sig ns (95%ile)										
Ramadour <i>et al</i> (2000) 2445 children, 7 areas	2 month mean of 8 hour ave	?+ sig		?+ sig (last 12 months)	(dry) Not sig, direction not specified									Not sig, direction not specified	Not sig, direction not specified		
Galizia & Kinney (1999) 520 students, 2 exposure groups	Summer ave above or below 80 ppb			+ sig (apart from colds)	() ¹	+ ns											+ sig
Braun-Fahrlander <i>et al</i> (1997) 4470 children, 10 areas	Annual mean or hours over 80 ppb	+ns (mean) -ns (> 80 ppb)		-ns (mean) -ns (> 80 ppb)	(Nocturnal dry no cold) - ns (mean) + sig (over 80ppb)		+ ns (mean) + sig (over 80 ppb)										
Zemp <i>et al</i> (1999) 9651 adults, 8 areas	Annual mean or excess ozone ²		-ns (mean) -sig (excess)	-ns (mean) -ns (excess)	(Chronic) -ns mean + ns	- ns (mean) + sig (excess)		- ns (mean) + sig (excess)	- ns (mean) + sig (excess)		OR = 1 (mean) -ns (excess)				- ns (mean) + ns (excess)	- ns (mean) + ns (excess)	
Wang <i>et al</i> (1999) 165,173 children, 15 areas	Annual mean above and below 22 ppb		+sig														

Study	Ozone measure	Ever asthma	Current asthma	Wheeze	Cough	Phlegm	Bronchitis	Breathlessness	Dyspnoea on exertion	Chest cold	Chest tightness	Lower respiratory symptoms	Head cold, sorethroat stuffy nose	Rhinitis	Hayfever or sneezing in pollen season	Conjunctivitis or eye irritation	Respiratory symptom index
Guo <i>et al</i> (1999) 331,686 non-smoking children, 55 areas	Annual mean of monthly ave	-ns boys -ns girls															
Peters <i>et al</i> (1999a) 3676 children, 12 areas	1 or 4 year mean of daily 1 hour max	-ns (4 year) -sig (1 year, girls)	-ns (4 year) ns (1 year)	+ns (4 year) +ns (1 year)	-ns (4 year) -ns (1 year)		+ns (4 year) +ns (1 year)										
McConnell <i>et al</i> (1999) children with asthma (493) or wheeze (653) or neither (2211), 12 areas	1 Year mean of daily 1 hour max				+ns (asthmatic) -ns (wheeze or no asthma)	+ns (asthmatic) -ns (wheeze or no asthma)	OR 1 (asthmatic) +ns (wheeze) -ns (no asthma)										
Dockery <i>et al</i> (1989) 5,422 children, 6 cities	Annual mean of 24 hr ave	+sig		+ns	(chronic) -ns		-ns			(chest illness) -ns					+ns		
Dockery <i>et al</i> (1996) 13,369 children, 24 areas	Annual mean of daily 1 hr max	+ns		-ns	(chronic) +ns	(chronic) +ns	+ns										

Study	Ozone measure	Ever asthma	Current asthma	Wheeze	Cough	Phlegm	Bronchitis	Breathlessness	Dyspnoea on exertion	Chest cold	Chest tightness	Lower respiratory symptoms	Head cold, sorethroat stuffy nose	Rhinitis	Hayfever or sneezing in pollen season	Conjunctivitis or eye irritation	Respiratory symptom index
<u>Prospective studies</u>																	
Abbey <i>et al</i> (1993) 3914 adult Seventh Day Adventists 10 year follow-up	Monthly mean or hrs above 100, 120 ppb based on residence history		(severity score) +sig mean and excess				(incidence, report in 1987 not 1977) + ns (hrs above 100 ppb); (severity score) Not significant (direction not specified) (mean and excess)										
McDonnell <i>et al</i> (1999) 2091 adult Seventh Day Adventists 15 year follow-up	20 year average of 8 hour average interp. to place of work and residence also hrs of ozone > 60 ppb		(doctor diag. asthma in 1987 or 1992 but not 1977) + ns all (mean) + sig men only mean and excess														
McConnell <i>et al</i> (2002) 3535 children 6 high ozone, 6 low ozone areas	4 year mean of 8 hr (10am to 6pm) ozone		(newly diag. asthma) - ns in all children, + sig only in children playing ≥3 team sports														

Study	Ozone measure	Ever asthma	Current asthma	Wheeze	Cough	Phlegm	Bronchitis	Breathlessness	Dyspnoea on exertion	Chest cold	Chest tightness	Lower respiratory symptoms	Head cold, sorethroat stuffy nose	Rhinitis	Hayfever or sneezing in pollen season	Conjunctivitis or eye irritation	Respiratory symptom index				
McConnell et al (2003) 475 children with asthma, 12 areas	4 yr mean of daily 8 hr max, yearly deviation from 4 yr mean						(Bronchitis symptoms) -ns (4 year mean) +sig (deviation) ³														
Kinney and Lippmann (2000) 72 cadets, 2 areas	Summer ave high (1 area) vs moderate			No pattern	No pattern	No pattern				No pattern	No pattern	No pattern	No pattern			No pattern	No pattern				
1 Measured but too few reports to assess vs ozone																					
2 The yearly sum of all half-hourly values of ozone concentrations minus 60ppb for those half hours above 60ppb divided by the yearly number of half hours.																					
3 But not robust in two pollutant models with several other pollutants																					
+ sig or + ns indicates a statistically significant or non significant positive association, -sig or -ns indicates a statistically significant or non-significant negative association. Odds ratios with confidence intervals are given in the text. Results relate to single pollutant models. Note that the studies vary considerably in statistical power - as a general rule studies with greater numbers of areas have greater statistical power.																					

8.68 A sharp yes/no division between associations that were or were not statistically significant is not ideal. Some of the 'non-significant' associations could be close to statistical significance. In addition, a preponderance of positive associations even if not all are statistically significant may lead to a meta-analytical estimate that is positive and statistically significant. Even where meta-analysis is not possible, earlier chapters have been able to present quantitative results graphically after scaling the results to a common metric. The respiratory symptom long term exposure studies use a wide variety of long term exposure metrics, subject groups, statistical approaches and symptom definitions. This makes quantitative comparison very difficult.

8.69 The statistical power of the long term exposure studies is much more limited than for the time-series or panel studies. This also makes interpretation of the results difficult – is the lack of a statistically significant association simply due to lack of statistical power? In addition, it is much harder to disentangle the effects of different pollutants when the number of areas studied is low. The interpretation of the previous suggestion that associations are more likely for 'peak' rather than 'mean' ozone measures is complicated by the fact that the 'peak' measures tended to be positively correlated with other pollutants whereas the 'mean' measures tended to be negatively correlated with other pollutants.

8.70 Overall, the evidence on associations between long term exposure to ozone and respiratory symptoms is mixed, with a majority of positive associations with at least one respiratory symptom but less consistency across studies for individual symptoms.

Cystic fibrosis exacerbations

8.71 Goss *et al* (2004) examined the association between ozone (annual mean of 1 hour averages) and cystic fibrosis exacerbations in 11,484 cystic fibrosis patients aged more than 6 years. Subjects were included if living less than 30 miles from one of 616 monitors across the United States. The interquartile range of median ozone concentrations was 46.1 to 55.7 ppb. Adjustment was made for sex, age, weight, race, airway colonisation with *P. aeruginosa*, *B. cepacia*, pancreatic function and insurance status. Adjustment for smoking was not possible. An odds ratio of 1.10 (95% CI 1.03-1.17) per 10 ppb rise in ozone was found for two or more pulmonary exacerbations in the year 2000. Effects of PM₁₀ and PM_{2.5} were also found.

Lung function

8.72 Given the clear evidence for an effect of short-term exposure to ozone on lung function from chamber and panel studies, there has been considerable interest in the possibility that long-term exposure to ozone might lead to longer term changes in lung function. This is, however, quite challenging to study. Kunzli *et al* 1997 discusses many of these difficulties and gives an overview of earlier 2 or 3 area studies which are difficult to

interpret. More recent 2 area studies (Calderón-Garcidueñas *et al* 2003; Centanni *et al* 2001) have also been excluded from the discussion below. Larger cross-sectional studies are discussed first followed by prospective studies. Again, studies using interpolated finer scale concentration allocations are presented first before the studies allocating concentrations to wider areas.

Cross-sectional studies

Interpolated concentrations

8.73 In the study by Hirsch *et al* (1999) described in paragraph 8.37, measurements of lung function were performed in a subsample of 1,999 9-11 year old children. Bronchial responsiveness was also assessed. Ozone showed a positive association with the numbers of children with $FEV_1 < 85\%$ predicted, although this was not statistically significant (OR 1.20 95% CI 0.70-2.07). A negative non-significant association was found with numbers of children with $FEF_{25-75} < 70\%$ predicted (OR 0.75 95% CI 0.51-1.10). A positive, just significant association was found for bronchial hyperreactivity tested in children with an $FEV_1 > 75\%$ predicted (OR 1.52 95% CI 1.00-2.31).

8.74 Kunzli *et al* (1997)²⁷ allocated exposure on a more individualised basis. 130 students were asked for their lifetime residential history and this was used with interpolated monthly averages of 10am to 6pm 8 hour average ozone or hours above 60ppb ozone from nearby monitoring sites to calculate a lifetime effective exposure. For some analyses adjustment was made for time spent outdoors, moderate or heavy outdoor activity and typical indoor/outdoor ratios of ozone. These lifetime effective exposures were then compared with lung function measurements. Adjustment was made for gender, region, ethnicity, height and a region/sex interaction term. For a 20ppb increase in the 8 hour average ozone lifetime measure there was a decrease in FEF_{75} by 334ml/sec (95% CI 11-657ml/sec) and a decrease in FEF_{25-75} of 420 ml/sec (95% CI +46 to -886 ml/sec). Reductions in FVC and FEV_1 were not statistically significant. This was consistent with ozone having more of an effect on the small rather than the large airways. In fact, it was found that use of time activity data had a limited effect on the coefficient. Addition of PM_{10} or NO_2 to the model also had little effect on the coefficient although the coefficient lost significance if PM_{10} , NO_2 , temperature and humidity were all added to the model.

²⁷ This study was a pilot study. The full paper (Tager *et al* 2005) was published after the cut off date for the literature search strategy. The later paper found that lifetime exposure to ozone was associated with decreased levels of small airways function (FEF_{75} and FEF_{25-75}). There was an interaction with the FEF_{25-75}/FVC ratio, a measure of intrinsic airway size – adolescents with intrinsically smaller airways appeared to be at greater risk. The authors note the failure of several longitudinal studies (Gauderman *et al* 2004; Ihorst *et al* 2004) to find decreases in lung growth related to ozone exposure and could not fully account for the difference compared with the findings in their own study. However, they suggest that their use of the FEF_{25-75}/FVC ratio as a marker of susceptibility could account for some of the differences.

Comparison of areas

8.75 The study by Galizia and Kinney (1999) described in paragraph 8.40 above also examined whether lung function²⁸ was reduced in 520 students who had lived for 4 or more years in a US county with a 10-year average of summer 1 hour maximum ozone levels greater than 80 ppb compared with students with lower exposures. This was found to be the case for FEV₁ (3.07% decrease (95% CI -0.22 to -5.92%)) and FEF₂₅₋₇₅ (8.11% decrease (95% CI -2.32 to -13.9%)). FVC and FEF₇₅ were also decreased by 1.06% and 6.73% respectively although the result was not statistically significant (95% CI 1.84 to -3.96% and 1.37 to -14.83% respectively). Other pollutants were not measured.

8.76 Ackermann-Liebrich *et al* (1999) examined whether long-term exposure to ozone affected lung function in 3115 healthy non-smokers aged 18 to 60 in 8 areas of Switzerland. Ozone was measured as an annual average or summer daytime average of half hourly mean ozone or as 'excess ozone'²⁹. Annual mean ozone was negatively correlated with PM₁₀ (-0.55), SO₂ (-0.39) and NO₂ (-0.78). Excess ozone was positively correlated with PM₁₀ (0.67), SO₂ (0.73) and NO₂ (0.36). Adjustment was made for various confounders including age, sex, height and atopy. A more marked effect was found for excess ozone than annual mean ozone. FVC was significantly lower per 1 µg-year/m³ increase in excess ozone as was FEV₁. However, this result was heavily influenced by a single area. Similar effects were found in all non-smokers (including those with respiratory disease) and in smokers. Effects were also found for other pollutants and it was not possible to distinguish the effects of the different pollutants.

8.77 In a companion paper to that described in paragraph 8.47, Peters *et al* (1999b) studied lung function in 3293 schoolchildren aged 9-16 years in 12 communities in Southern California. Maximum 1 hour ozone averaged over 1986-1990 or 1994 was used as the exposure measure. This measure was positively correlated with acid vapour. Adjustment was made for age, sex, height, race, community, grade in school, spirometer and technician and a variety of other personal covariates including body mass, asthma, active or passive smoking, exercise, pets and gas stove use. PEF and MMEF showed a statistically significant reduction in the areas with higher ozone exposure, FEV₁ showed a non-significant reduction and FVC showed a non-significant increase. These results were mainly composed of an effect in girls rather than boys. PEF, MMEF, FVC and FEV₁ were reduced in girls but the reduction was not statistically significant for the latter two measures. Boys who spent more time outdoors did show reductions in FVC, FEV₁, PEF and

²⁸ Abbreviations for measures of lung function are as follows – FVC forced vital capacity; FEV₁ forced expiratory volume in 1 second; FEV_{0.75} forced expiratory volume in 0.75 seconds; PEF peak expiratory flow; FEF₂₅₋₇₅ forced expiratory flow at 25-75% of FVC; MMEF maximal mid expiratory flow (another term for FEF₂₅₋₇₅); MEF₂₅₋₇₅ maximal expiratory flow at 25-75% of FVC (a further term for FEF₂₅₋₇₅); FEF₇₅ forced expiratory flow at 75% of FVC; MEF₅₀ maximal expiratory flow at 50% of FVC.

²⁹ The yearly sum of all half-hourly values of ozone concentrations minus 60ppb for those half hours above 60ppb divided by the yearly number of half hours.

MMEF although only the former two were statistically significant. Some other pollutants did have effects so the possibility of confounding by other pollutants remains.

8.78 Schwartz (1989) were able to consider a larger number of neighbourhoods by making use of lung function measurements in 1005 children and young adults (6-24 years) participating in the second National Health and Nutrition Examination Survey (NHANES II) in the US. The annual mean of the 11am to 5pm daytime average ozone was used as the exposure measure. The 10th to 90th percentiles of the annual means were 23 to 40 ppb. It was not possible to consider all the pollutants together but effects of other pollutants were also found. Adjustment was made for age, race, sex, height, body mass index, a sex/height interaction, and various sensitivity analyses on other personal covariates. Statistically significant negative regression coefficients were found for FVC, FEV₁ and peak flow. Plotting of the exposure response function suggested that most of this effect was accounted for by effects above an annual mean of about 40 ppb. Excluding subjects with respiratory conditions resulted in smaller but still statistically significant reductions. Exclusion of smokers gave greater reductions in lung function in response to ozone. Ozone was also associated with a significantly increased risk of having an FVC less than 70% of predicted.

8.79 The 6 cities study (Dockery *et al* 1989), described in paragraph 8.49, included a spirometric examination of each child. FEV₁, FEV_{0.75}, FVC, MMEF, the FEV₁/FVC ratio and the MMEF/FVC ratio were all examined. For the lung function relationships, adjustment was made for height, age, maternal smoking, sex, parental education, gas cooking and an interaction between sex and height. The authors reported that there was little evidence for an association between lower pulmonary function level and the annual mean concentration of any other pollutant than TSP.

8.80 In a companion paper (Raizenne *et al* 1996) to that by Dockery *et al* (1996) described in paragraph 8.50, lung function was examined in 10,251 children from the same 24 areas. FEV₁, FEV_{0.75}, FVC, FEF_{25-75%}, PEF, the FEV₁/FVC ratio, the FEV_{0.75} /FVC ratio and the FEF_{25-75%} /FVC ratio were all examined. Adjustments were made for sex, age, height, weight and an interaction between sex and height. All three ozone metrics (annual means of 24 hour average, 8 hour daytime average and 1 hour max) were significantly associated with reductions in FVC and FEV₁ with the daytime average giving the largest effect – a reduction of -3.74% (95% CI -6.45 to -0.94) in FVC and a reduction of -3.55% (95% CI -6.24 to -0.78) in FEV₁ for a 39.4 ppb range in ozone. The reduction in FEF_{25-75%} was not statistically significant (-3.98% 95% CI -8.89% to +1.20 %). No reduction was found for PEF or the FEV₁ or FEV_{0.75} to FVC ratio. There was a reduction in the FEF_{25-75%} to FVC ratio with a change in daytime average ozone although this was not statistically significant.

8.81 The association between daytime ozone and FVC was examined in a two-pollutant model with particle strong acidity. The association with ozone was attenuated although still significant – a reduction of -2.2% (95% CI -4.2 to

-0.2) as opposed to 3.7% without adjustment. The association of particle strong acidity with FVC was unaffected by adjustment for ozone. This suggests that the association between ozone and FVC is partially explained by the correlation between daytime mean ozone and particle strong acidity.

8.82 Daytime average ozone was also associated with the number of children with FVC < 85% predicted with an odds ratio of 2.9 (95% CI 1.4-5.8). This was reduced to 2.0 (95% CI 1.6-2.5) after adjustment for particle strong acidity.

Prospective studies

Interpolated concentrations

8.83 The cohort of Seventh Day Adventists in California, mentioned previously, has also been studied for effects of air pollution exposure on lung function (Abbey *et al* 1998). Monthly residential/work location histories were obtained from 1391 non-smoking Seventh Day Adventists over a 20 year period (questionnaires in 1977, 1987 and 1992). Interpolated 8 hour average ozone concentrations were allocated to the place of residence/work summed and averaged over the 20 year period. Lung function was measured in 1993. Adjustment was made for a variety of personal covariates. The main focus of the paper was on PM₁₀ but it was noted that % predicted FEV₁ decreased by 6.3% (95%CI -10.8% to -1.8%) across a 23ppb range in ozone concentration (8hr ave, 1973-1993) in men with a parental history of asthma, bronchitis, emphysema or hayfever. No other results were given for other lung function measures or other subgroups. Ozone exposure was correlated with mean PM₁₀ exposure (0.85). The effect of PM₁₀ was stable to adjustment for ozone; results were not presented for the effect of ozone adjusted for PM₁₀.

Comparison of areas

8.84 A series of papers on lung function growth in children have been published from the Southern California Children's Health Study. The first of these (Gauderman *et al* 2000), examined 3035 children of mixed ages from 9 to 16 in 12 communities. 4 year averages of 10am to 6pm 8 hour average ozone were used as the exposure measure, with a range from about 30 to about 70 ppb. The communities had been deliberately chosen to limit the correlation between ozone and other pollutants. The correlations for ozone with the respective pollutants were as follows: PM₁₀ 0.28, PM_{2.5} 0.35, PM₁₀-PM_{2.5} 0.15, NO₂ 0.06 and acid 0.5. Lung function tests were performed annually. Regressions were adjusted for height, body mass index, race, asthma, smoking, exercise on day of test, the technician and the spirometer. None of the declines in various lung function measures (annual % growth rate in FVC, FEV₁, MMEF and FEF₇₅) were statistically significant. The growth rates were not found to decline for several of the lung function measures in older children. More consistent and significant negative results were found for other pollutants. The ozone results for FEV₁ in 4th grade children after adjustment for other pollutants were small and not statistically significant. Adjustment for time spent outdoors did not obviously explain the lack of an

effect of ozone exposure. The authors did note, however, that the range in ozone exposure (two fold) was modest compared with other pollutants and that the low indoor/outdoor ratio for ozone might also explain why associations were not observed.

8.85 Gauderman *et al* (2002) report on the results of a second cohort of 1,678 4th grade children (average age 9.9 years) from the same 12 communities using the same ozone measure. Correlations with other pollutants were as follows – PM₁₀ 0.13, PM_{2.5} 0.14, PM₁₀-PM_{2.5} 0.10, NO₂ -0.23, acid 0.3, elemental carbon -0.05, organic carbon 0.11. Regressions were adjusted for the same covariates as before, with the addition of the presence or absence of a cold on the day of the lung function test. Again, negative but non-significant % growth rates were found for FVC, FEV₁ and MMEF. This was also found for MMEF/FVC. However, a negative and statistically significant % growth rate was found for PEF -1.21% (95%CI -2.06 to -0.36%) per 39.8 ppb ozone. This was a larger effect than found for other pollutants. Results for PEF were not reported for the first cohort in the previous paper but were included in this paper for comparison – a small negative but non-significant result was found. So this was not a consistent finding. Adjustment for other pollutants had less effect on the results for FEV₁ growth rate than in the previous paper, the growth rate became more negative and statistically significant after adjustment for nitrogen dioxide. A statistically significant negative % growth rate was found for FVC in a subgroup spending more time outdoors.

8.86 Gauderman *et al* (2004) reported on a longer follow-up of lung development in this cohort. 1759 children aged 10 years at the outset from the same 12 communities performed lung function testing annually for 8 years. The results were related to an 8 year average of 8 hour average (10am to 6pm) ozone (range about 28 to 65 ppb). Correlations between ozone and other pollutants were as follows: PM₁₀ 0.18, PM_{2.5} 0.18, NO₂ -0.11, acid 0.35, elemental carbon -0.03, organic carbon 0.13. Adjustment was made for the same personal covariates as before with the addition of ETS. Although there was a decline in average growth of FVC per 37.5 ppb ozone of 50.6ml (95% CI -171 to 69.7ml) and of FEV₁ of 22.8 ml (95%CI -122.3 to 76.6 ml), neither decline was statistically significant. No reduction in MMEF was found – change in average growth +85.6 ml/sec (95% CI -130 to 301.1 ml/sec) per 37.5 ppb ozone. In addition, a low absolute value of FEV₁ (<80% predicted) was not significantly correlated with ozone in the main group or in subgroups of children with no history of asthma or smoking. Other pollutants such as NO₂, acid and elemental carbon had more marked effects. It was noted that two pollutant models did not provide a better fit than single pollutant models³⁰, presumably indicating that an effect of ozone was not masked by the effect of other pollutants.

8.87 A linked paper (Avol *et al* 2001) studied 110 children from the Southern California Children's Health Study who had relocated to areas with different pollution levels. The children were 10 years old at enrolment and 15 years old

³⁰ Although it should be noted that two pollutant models tend to yield less precise estimates.

at follow up. The children needed to have moved away to their new location at least 1 year before follow-up. Children were visited at their new location and assessed for FVC, FEV₁, MMEF and PEF. Annual average changes in lung function were individually determined by subtracting the subject's baseline value from their follow-up value and dividing by the difference in age at testing. Adjustment was made for sex, race, year of entry into study, height, weight, body mass index and interaction of sex with change in height. Children who originated in high pollution communities tended to move to lower-pollution communities and vice versa.

8.88 The annual mean of 10am to 6pm ozone was associated with a decline in lung function growth rates but the change was not statistically significant. The changes for a 10 ppb increase in ozone on relocation were -1.4 ml (95% CI -10.8 to 8.0) for FVC; 0.1 ml (95% CI -8.7 to 8.9) for FEV₁; -3.4 ml/s (95% CI -23.6 to 16.8)³¹ for MMEF and -8.9 ml/s (95% CI -41.6 to 23.8) for PEF. Statistically significant declines in lung function growth rates were found with increases in PM₁₀ for MMEF and PEF. No two-pollutant models were performed.

8.89 Frischer *et al* (1999) published the first of a series of papers on ozone and lung function growth from Austria. 1150 children aged around 8 years were studied in 9 communities. Lung function tests were performed twice a year for 3 years in spring and in autumn. The exposure measure was the mean of all half hourly means between lung function tests i.e. 'summertime ozone' and 'wintertime ozone'. Summertime ozone was adjusted for the percentage of time children spent away from their town of residence between June and September. Ozone was negatively correlated with PM₁₀ (-0.07), SO₂ (-0.27) and NO₂ (-0.62), although these correlations were only based on a 14 day period. Results were adjusted for baseline lung function, atopy, community, passive smoking, season and change in height. Over the 3 year period, summertime ozone was associated with a decline in FEV₁ growth (β = -0.029 ml/day/ppb; p < 0.001), FVC (β = -0.018 ml/day/ppb; p < 0.001) and MEF₅₀ (β = -0.76 ml/sec/day/ppb; p < 0.001). Similar results were found for wintertime ozone except that the decline in FVC growth was not statistically significant.

8.90 Horak *et al* (2002) studied 975 children in 8 of the 9 areas examined by Frischer *et al* (1999) (as PM₁₀ was not measured in one of the areas). Again, spirometry was performed twice a year from 1994-1997 (an extra year compared with the previous study). The same ozone measure and the same adjustments for confounding factors were used. Results were similar to the previous study – statistically significant declines in FVC and FEV₁ growth following summertime ozone and, in this case, the declines in growth for both FEV₁ and FVC were also statistically significant following wintertime ozone. A different flow measure was used – MEF₂₅₋₇₅. This also showed a decline in growth but it was only statistically significant after wintertime ozone (p <

³¹ The lower 95% confidence interval appears in the paper as +23.6. This is a typographical error. The authors have confirmed that this should read -23.6 (J Gauderman, personal communication).

0.012) not after summertime ozone ($p < 0.217$). Two-pollutant models were performed in this analysis. Adjustment for PM₁₀ made very little difference to the results following summertime ozone. In contrast, the results following wintertime ozone were less marked (although still negative) and of more borderline statistical significance after adjustment for PM₁₀.

8.91 Ihorst *et al* (2004) combined results from the 9 Austrian sites studied by Frischer *et al* (1999) with results for an additional 6 sites in South Western Germany over a 3.5 year period. This gave a total of 2153 children assessed for lung function twice yearly. The median of the half hourly means ranged from 17 to 49 ppb across the sites in summer and from 5 to 34 ppb in winter. Results were adjusted for sex, age, height, passive smoking, season and short term ozone concentration at the time of the test. A significantly lower increase in FVC of -19.2 ml/100 days (95% CI -10.6 to -27.8 ml/100 days) was found over the summertime period for the 25-54 ppb semi-annual mean exposure group compared with the 22-30 ppb exposure group. Declines in growth were also found for the intermediate groups. Similar results were found for FEV₁. The results were in the opposite direction for the wintertime period. The results were not affected by control for NO₂ or SO₂. The authors interpreted the opposing results over the wintertime period as a 'catching up' process as the effects of the higher summertime ozone levels were reversed. No association between lung function growth and mean summertime ozone was found overall for the 3.5 year period.

8.92 The study by Kinney and Lippmann (2000) described in paragraph 8.64 also examined changes in lung function after a summertime period. Young adults (military cadets aged around 20 years) rather than young children were studied and the endpoint studied was change in absolute lung function rather than decline in lung function growth. As had been hypothesised, a greater decline in FEV₁ (-78 ml +/- 41 ml) was found in cadets who had trained in the high ozone area compared with cadets who had trained in the moderate ozone areas (-31 ml +/- 24 ml). This was also true for FVC (-6ml +/- 52 ml compared with +24 ml +/- 30 ml) and FEF₂₅₋₇₅ (-173 ml/sec +/- 104 ml compared with -75 ml +/- 76 ml). The reduction in FEV₁ in the high ozone area was significantly different from the pre-summer values ($p = 0.07$), as was the overall pooled result for the high and moderate ozone areas together (-44 ml +/- 21 ml). This suggested that the ozone might not be the only factor linked to a decline in lung function after the summer training camps. An attempt was made to examine the link between lung function changes and reported hours of exposure to dust, exhaust or smoke but the results were inconclusive. No other pollutants were examined so an effect due to other pollutants could not be excluded. Exclusion of subjects with colds at the time of lung function testing did not change the results. The authors did not consider that the results were due to a short term effect of ozone exposure as the ozone levels on the days of testing were similar and relatively low before and after summer training. Although a wintertime period was not studied to test for reversibility, the authors did examine the results in the subset of cadets examined in the first 2 weeks rather than the second 2 weeks after return from summer training. The reductions were greater in the first 2 weeks suggesting a declining effect over time.

Table 8.19 Long term exposure to ozone and lung function (single pollutant models)

Study	Ozone measure	Lung function measure								
		FEV ₁	FEV _{0.75}	FVC	PEF	MMEF or FEF ₂₅₋₇₅	FEF ₇₅	FEV ₁ /FVC ratio	FEV _{0.75} /FVC ratio	MMEF or FEF ₂₅₋₇₅ /FVC ratio
Kunzli <i>et al</i> (1997) ³² 130 students	Lifetime cumulated exposure from monthly residence and interpolated 8 hour ave	- ns		- ns		- ns	- sig			
Galizia and Kinney (1999) 520 students, 2 exposure groups	> 4 years with 10 year average 1 hour max over 80 ppb	- sig		- ns		- sig	- ns			
Ackermann-Lieblich <i>et al</i> (1999) 3115 adult non-smokers, 8 areas	Annual ave of half hourly means or 'excess ozone' ³³	- sig		- sig						
Peters <i>et al</i> (1999b) 3293 children, 12 areas	Annual (1994) or 4 year ave of 1 hour max	- ns		+ ns	- sig	- sig				
Schwartz <i>et al</i> (1989) 1005 children/ young adults, 60 areas, 24 sampling units	Annual mean of daytime ave	- sig		- sig	- sig					
Dockery <i>et al</i> (1989) 5,422 children, 6 cities	Annual mean of 24 hr ave	'Little evidence for association'	'Little evidence for association'	'Little evidence for association'		'Little evidence for association'		'Little evidence for association'		'Little evidence for association'
Raizenne <i>et al</i> (1996) 10,251 children 24 areas	Annual mean of 8 hour daytime average	- sig	- sig	- sig ³⁴	+ ns	- ns		+ ns	+ ns	+ ns
Abbey <i>et al</i> (1998) 1391 adult Seventh Day Adventists (prospective)	20 year cumulated exposure from monthly residence/work location and interpolated 8 hour ave	- sig (men with parental history resp disease)								
Kinney and Lippmann (2000) ³⁵ 72 cadets, 2 areas (prospective)	Summer ave high (1 area) vs moderate	- ?ns		- ?ns		- ?ns				

See footnote 28 for an explanation of abbreviations for lung function measures.

+ sig or + ns indicates a statistically significant or non significant association with an increase in lung function, - sig or - ns indicates a statistically significant or non-significant association with a reduction in lung function. **(Note that in contrast to earlier tables a negative relationship indicates the presence of an adverse effect)**. Slopes with confidence intervals are given in the text. Results relate to single pollutant models. Note that the studies vary considerably in statistical power – as a general rule studies with greater numbers of areas (or a greater number of subjects where exposures are allocated individually) have greater statistical power.

³² Results maintained in 2 pollutant models with PM₁₀ or NO₂

³³ The yearly sum of all half-hourly values of ozone concentrations minus 60ppb for those half hours above 60ppb divided by the yearly number of half hours. Results shown are for excess ozone.

³⁴ Attenuated but still – sig after control for particle strong acidity

³⁵ Statistical significance not given but standard errors overlap.

Table 8.20 Long-term exposure to ozone and numbers of children with FVC < 85% or 70% predicted, with FEF_{25-75%} < 75% predicted or with bronchial hyper-responsiveness

Study	Ozone measure	Lung function measure				
		FVC < 85% predicted	FVC < 70% predicted	FEV ₁ < 80% predicted	FEF _{25-75%} < 75% predicted	Bronchial hyper-responsiveness
Hirsch <i>et al</i> (1999) 5421 children, 1 km grid squares across Dresden	Annual mean of 0600 to 2300 hrs once every 2 weeks	+ ns			- ns	+ sig
Raizenne <i>et al</i> (1996) 10,251 children 24 areas	Annual mean of 8 hour daytime average	+ sig ³⁶				
Schwartz <i>et al</i> (1989) 1005 children/ young adults, 60 areas, 24 sampling units	Annual mean of daytime ave		+ sig			
Gauderman <i>et al</i> (2004) 1759 children, 12 areas (prospective)	8 year ave of daily 8 hour ave			Not sig correlated ³⁷		

See footnote 28 for an explanation of abbreviations for lung function measures.

+ sig or + ns indicates a statistically significant or non significant association with an increase in the odds ratio for a decline in lung function, - sig or - ns indicates a statistically significant or non-significant association with a decrease in the odds ratio for a decline in lung function. **(Note that in contrast to the previous table but as with many earlier tables, a positive relationship indicates the presence of an adverse effect).** Odds ratios with confidence intervals are given in the text. Results relate to single pollutant models. Note that the studies vary considerably in statistical power – as a general rule studies with greater numbers of areas (or a greater number of subjects where exposures are allocated individually) have greater statistical power.

³⁶ Attenuated but still + sig after control for particle strong acidity

³⁷ R positive but very small (0.04), P value well over 0.05

Table 8.21 Long term exposure to ozone and lung function growth (single pollutant models)

Study	Ozone measure	Lung function measure					
		FEV ₁ growth	FVC growth	PEF growth	MMEF or MEF ₂₅₋₇₅ growth	FEF ₇₅ growth	MEF ₅₀ growth
Gauderman <i>et al</i> (2000) ³⁸ 3035 children, 12 areas (prospective)	4 year ave of daily 8 hour ave	- ns	- ns		- ns	- ns	
Gauderman <i>et al</i> (2002) ³⁹ 1678 children, 12 areas (prospective)	4 year ave of daily 8 hour ave	- ns	- ns ⁴⁰	- sig	- ns		
Gauderman <i>et al</i> (2004) 1759 children, 12 areas (prospective)	8 year ave of daily 8 hour ave	- ns	- ns		+ ns		
Avol <i>et al</i> (2001) 110 children, 12 areas (prospective)	Change in annual mean 10am to 6pm ozone on relocation	+ ns	- ns	- ns	-ns		
Frischer <i>et al</i> (1999) 1150 children, 9 areas (prospective)	Semi-annual ave of half hourly means	- sig (summer or winter)	- sig (summer) – ns (winter)				- sig (summer or winter)
Horak <i>et al</i> (2002) ⁴¹ 975 children, 8 areas (prospective)	Semi-annual ave of half hourly means	- sig (summer or winter)	- sig (summer or winter)		- ns (summer) – sig (winter)		
Ihorst <i>et al</i> (2004) ⁴² 2153 children, 15 areas (prospective)	Semi-annual ave of half hourly means	- sig (summer) + sig (winter)	- sig (summer) + sig (winter)				

Peters *et al* (1999b). Gauderman *et al* (2000), Gauderman *et al* (2002), Gauderman *et al* (2004) and Avol *et al* (2001) are related papers from the Southern California Children's Health Study. Frischer *et al* (1999), Horak *et al* (2002) and Ihorst *et al* (2004) are related papers from a study in Austria and SW Germany.

See footnote 28 for an explanation of abbreviations for lung function measures.

+ sig or + ns indicates a statistically significant or non significant association with an increase in lung function growth, - sig or - ns indicates a statistically significant or non-significant association with a decline in lung function growth.

(Note that in contrast to some earlier tables a negative relationship indicates the presence of an adverse effect). Slopes with confidence intervals are given in the text. Results relate to single pollutant models. Note that the studies vary considerably in statistical power – as a general rule studies with greater numbers of areas (or a greater number of subjects where exposures are allocated individually) have greater statistical power.

³⁸ Results shown are for 4th grade children, results not maintained in 2 pollutant models

³⁹ Results shown are for 4th grade children, results not maintained in 2 pollutant models

⁴⁰ Result became statistically significant when adjusted for time spent outdoors

⁴¹ After adjustment for PM₁₀ summer results maintained, winter results less marked (although still negative) and of more borderline statistical significance.

⁴² Results unaffected by adjustment for NO₂ or SO₂. Paper states no association between growth rates and mean summer O₃ over full 3.5 year period.

Summary

Lung Function

8.93 The results of the studies described above are summarised in Table 8.19. A + or – sign is used for a positive or negative association and ‘sig’ for associations that are statistically significant ($p < 0.05$) or ‘ns’ for associations that are not statistically significant. A negative association indicates that children living and measured in high ozone areas tend to have lower lung function. It can be seen that the vast majority of associations are negative, although there are a mixture of statistically significant and non-significant associations. As the ozone metrics differ, it is not appropriate to meta-analyse the results. However, the overall impression is suggestive of a negative association between long term exposure to ozone and lung function in single pollutant models. The positive odds ratios for numbers of children with FVC < 85% predicted shown in Table 8.20 supports this.

8.94 The results for declines in lung function growth shown in Table 8.21 are also predominantly negative⁴³, but again there is a mixture of statistically significant and non significant associations. The results of the study in Austria and South West Germany (Ihorst *et al* 2004) suggest that declines in lung function growth are linked to ozone in the summer but that the effect is reversed over the winter when ozone levels are lower. Gauderman *et al* (2000) found declines in lung function growth with increased exposure to ozone in younger 4th grade schoolchildren (although these were not statistically significant) but increases rather than declines were found in older 10th grade schoolchildren. These results perhaps suggest that medium term exposure rather than long term exposure to ozone is linked to declines in lung function growth. The implications of declines in lung function growth are less serious if the declines are not maintained long term (reduced lung function may⁴⁴ be a risk factor for increased respiratory disease and increased mortality in adulthood). However, a recent study by Tager *et al* (2005) found that students with intrinsically smaller airways who grew up in high ozone areas had decreased levels of smaller airways function.

8.95 Several of the studies found associations between other pollutants and declines in lung function so there is clearly a possibility of confounding by other pollutants. Some studies did not measure other pollutants (Galizia and Kinney 1999; Kinney and Lippmann 2000). Other studies found associations for other pollutants but did not perform multi-pollutant models so were unable to confirm whether the negative ozone associations are due to ozone itself or due to other pollutants. Of the studies that did include multi-pollutant models, most found the results to be robust to control for other pollutants but this was only true for the summer in Horak *et al* (2002). Gauderman *et al* (2000) found the ozone results were not maintained in 2 pollutant models, although

⁴³ Ideally, lung function growth should be measured by taking children from areas with different ozone levels to an area with no ozone, allowing time for acclimatisation and only then measuring lung function. This is difficult and was not done in any of the studies described here.

⁴⁴ See footnote 15 for further discussion.

Gauderman *et al* (2002) found results that were less sensitive to adjustment for other pollutants in a second cohort of children from the same areas in California. The Southern California Children's Health Study had been specifically designed to minimise correlations between ozone and other pollutants. Although declines in lung function growth were found these were not statistically significant and the results were more marked for other pollutants (such as nitrogen dioxide and elemental carbon).

8.96 Table 8.19 does not show clear differences in results between one measure of lung function and another. Within individual studies, this was sometimes discussed. For example, Kunzli *et al* (1997) considered that the stronger relationships with mid and end expiratory flows than with FEV₁ and FVC were consistent with biological models of chronic effects of ozone on the small airways.

8.97 The difficulty of distinguishing the ozone associations from those of other pollutants, the possible reversibility of the associations with declines in lung function growth and the fact that several associations are not statistically significant mean that the evidence for a link between long term exposure to ozone and a decline in lung function is not as clear cut as might be expected from the strong evidence from short term exposure to ozone in chamber studies and panel studies. Nonetheless, the preponderance of negative associations between long term exposure to ozone and lung function suggests that a link with declining lung function cannot be dismissed.

Overall Conclusions

Associations⁴⁵ with long term exposure to ozone

8.98 We note that studies of long term exposure are more difficult to perform than time series studies of short term exposure. There are therefore a much smaller set of studies available. In addition, control of confounding is more difficult in long-term studies. This brings an additional level of uncertainty to the conclusions we draw below. For this chapter we did not convert the results to a common scale - we recommend future work to do this and to consider whether it would be possible to meta-analyse the results. The conclusions below only relate to epidemiological evidence – animal studies on long-term exposure to ozone will be considered briefly in Chapter 9.

All-cause and cardio-pulmonary mortality

8.99 The evidence currently published does not, overall, support a clear positive association between long term exposure to ozone and all cause or cardiopulmonary mortality.

⁴⁵ Causality is discussed in Chapter 9.

Lung cancer

8.100 The evidence for a positive association between ozone and lung cancer is inconsistent but points in the direction of no effect.

Respiratory symptoms

8.101 The evidence for a positive association between long term exposure to ozone and respiratory symptoms is mixed. The majority of studies found positive associations with at least one respiratory symptom but there was less consistency across studies for individual symptoms. Studies that included measures of long term exposure to ozone 'peaks' reported positive and statistically significant associations more often than long term mean exposure but interpretation of this is complicated by the fact that positive correlations with other pollutants were more likely for the 'peak' measures. Distinguishing between the effects of different pollutants was a general problem with these studies.

Lung function

8.102 Children living and measured in high ozone areas tended to have lower lung function. Associations with declines in lung function growth in children were found in some studies but not others⁴⁶. There was some suggestion that declines in lung function growth in children were reversible over a winter period or with increasing age. Overall, the difficulties in distinguishing the effects from those of other pollutants, the possible reversibility of the associations with declines in lung function growth and the fact that several associations were not statistically significant give a less clear cut picture than might have been expected from the short term exposure studies.

⁴⁶ None of the studies were able to use the ideal approach for measuring the effects of ozone on lung function growth – see footnote 43.

References

- Abbey, D.E., Burchette, R.J., Knutsen, S.F., McDonnell, W.F., Lebowitz, M.D. and Enright, P.L. (1998) Long-term particulate and other air pollutants and lung function in nonsmokers. *Am.J.Respir.Crit.Care Med.* **158**, 289-298.
- Abbey, D.E., Mills, P.K., Petersen, F.F. and Beeson, W.L. (1991) Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. *Environ.Health Perspect.* **94**, 43-50.
- Abbey, D.E., Nishino, N., McDonnell, W.F., Burchette, R.J., Knutsen, S.F., Lawrence Beeson, W. and Yang, J.X. (1999) Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *Am.J.Respir.Crit.Care Med.* **159**, 373-382.
- Abbey, D.E., Petersen, F., Mills, P.K. and Beeson, W.L. (1993) Long-term ambient concentrations of total suspended particulates, ozone, and sulfur dioxide and respiratory symptoms in a nonsmoking population. *Arch.Environ.Health* **48**, 33-46.
- Ackermann-Lieblich, U., Leuenberger, P., Schwartz, J., Schindler, Ch., Monn, Ch., Bolognini, G., Bongard, J.P., Brandli, O., Domenighetti, G., Elasser, S., Grize, L., Karrer, W., Keller, R., Keller-Wossidlo, H., Kunzli, N., Martin, B.W., Medici, T.C., Perruchoud, A.P., Schoni, M.H., Tschopp, J.M., Villiger, B., Wuthrich, B., Zellweger, J.P., Zemp, E. and SAPALDIA Team (1997) Lung function and long term exposure to air pollutants in Switzerland. *Am.J.Respir.Crit.Care Med.* **155**, 122-129.
- Avol, E., Gauderman, W.J., Tan, S., London, S. and Peters, J. (2001) Respiratory effects of relocating to areas of differing air pollution levels. *Am. J. Crit. Care Med.* **164**, 2067-2072.
- Beeson, W.L., Abbey, D.E. and Knutsen, S.F. (1998) Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: results from the AHSMOG study. *Environ.Health Perspect.* **106**, 813-823.
- Braun-Fahrlander, C., Vuille, J.C., Sennhauser, F.H., Neu, U., Kunzle, T., Grize, L., Gassner, M., Minder, C., Schindler, C., Varonier, H.S. and Wuthrich, B. (1997) Respiratory health and long-term exposure to air pollutants in Swiss schoolchildren. SCARPOL Team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen. *Am.J.Respir.Crit.Care Med.* **155**, 1042-1049.
- Calderón-Garcidueñas, L., Wen-Wang, L., Zhang, Y.-J., Rodríguez-Alcaraz, A., Osnaya, N., Villarreal-Calderon, A. and Santella, R.M. (1999) 8-Hydroxy-2'-deoxyguanosine, a major mutagenic oxidative DNA lesion, and DNA strand breaks in nasal respiratory epithelium of children

- exposed to urban pollution. *Environ. Health Perspect.* **107**, 469-474.
- Calderon-Garciduenas, L., Mora-Tiscareno, A., Chung, C.J., Valencia, G., Fordham, L.A., Garcia, R., Osnaya, N., Romero, L., Acuna, H., Villarreal-Calderon, A., Devlin, R.B. and Koren, H.S. (2000) Exposure to air pollution is associated with lung hyperinflation in healthy children and adolescents in Southwest Mexico City: a pilot study. *Inhalation Toxicol.* **12**, 537-561.
- Calderon-Garciduenas, L., Mora-Tiscareno, A., Fordham, L.A., Valencia-Salazar, G., Chung, C.J., Rodriguez-Alcaraz, A., Paredes, R., Variakojis, D., Villarreal-Calderon, A., Flores-Camacho, L., Antunez-Solis, A., Henriquez-Roldan, C. and Hazucha, M.J. (2003) Respiratory damage in children exposed to urban pollution. *Pediatr. Pulmonol.* **36**, 148-161.
- Centanni, S., Di Marco, F., Castagna, F., Santus, P., Guarnieri, R. and Allegra, L. (2001) Atopy prevalence and spirometric performance in asymptomatic schoolchildren exposed to air pollution. *Monaldi Arch. Chest Dis.* **56**, 304-308.
- Department of Health. (1999a) Committee on the Mutagenicity of Chemicals in Food, Consumer Products and the Environment. COM Statement on mutagenicity of ozone. COM/99/S3. Available at the following website address: <http://www.advisorybodies.doh.gov.uk/Com/ozone1.htm>
- Department of Health. (1999b) Committee on the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Animal carcinogenicity data on ozone. COC Statement – July 1999 – COC/99/S4. Available at the following website address: <http://www.advisorybodies.doh.gov.uk/coc/ozone.htm>
- Department of Health. (2002) Committee on the Medical Effects of Air Pollutants. Statement on papers by Dr Andrea Venn and Dr Rob McConnell. Available at the following website address: <http://www.advisorybodies.doh.gov.uk/comeap/pdfs/asthmaozone.pdf>
- Dockery, D.W., Speizer, F. E., Stram, D.O., Ware, J.H., Spengler, J.D. and Ferris, B.G. (1989) Effects of inhalable particles on respiratory health of children. *Am. Rev. Respir. Dis.* **139**, 587-594.
- Dockery, D.W., Pope, C.A., Xu, X., Spengler, J.D., Ware, J.H., Fay, M.E., Ferris, B.G. and Speizer, F.E. (1993) An association between air pollution and mortality in six U.S. cities. *N.Engl.J.Med.* **329**, 1753-1759.
- Dockery, D.W., Cunningham, J., Damakosh, A.I., Neas, L.M., Spengler, J.D., Koutrakis, P., Ware, J.H., Raizenne, M. and Speizer, F.E. (1996) Health effects of acid aerosols on North American children: respiratory symptoms. *Environ. Health Perspect.* **104**, 500-505.

- Evans, J. and Wolff, S. (1996) Modeling of Air Pollution Impacts: One Possible Explanation of the Observed Chronic Mortality. In: Wilson, R. and Spengler, J. (editors). *Particles in Our Air. Concentrations and Health Effects*. Harvard School of Public Health: Boston, MA.
- Frischer, T., Studnicka, M., Gartner, C., Tauber, E., Horak, F., Veiter, A., Spengler, J., Kuhr, J. and Urbanek, R. (1999) Lung function growth and ambient ozone: a three-year population study in school children. *Am.J.Respir.Crit.Care Med.* **160**, 390-396.
- Galizia, A. and Kinney, P.L. (1999) Long-term residence in areas of high ozone: associations with respiratory health in a nationwide sample of nonsmoking young adults. *Environ.Health.Perspect.* **107**, 675-679.
- Gauderman, W.J., Avol, E., Gilliland, F., Vora, H., Thomas, D., Berhane, K., McConnell, R., Kuenzli, N., Lurmann, F., Rappaport, E., Margolis, H., Bates, D. and Peters, J. (2004) The effect of air pollution on lung development from 10 to 18 years of age. *N.Engl.J.Med.* **351**, 1057-1067.
- Gauderman, W.J., Gilliland, G.F., Vora, H., Avol, E., Stram, D., McConnell, R., Thomas, D., Lurmann, F., Margolis, H.G., Rappaport, E.B., Berhane, K. and Peters, J.M. (2002) Association between air pollution and lung function growth in southern California children: results from a second cohort. *Am.J.Respir.Crit.Care Med.* **166**, 76-84.
- Gauderman, W.J., McConnell, R., Gilliland, F., London, S., Thomas, D., Avol, E., Vora, H., Berhane, K., Rappaport, E.B., Lurmann, F., Margolis, H.G. and Peters, J. (2000) Association between air pollution and lung function growth in southern California children. *Am.J.Respir.Crit.Care Med.* **162**, 1383-1390.
- Goss, C.H., Newsom, S.A., Schildcrout, J.S., Sheppard, L. and Kaufman, J.D. (2004) Effect of ambient air pollution on pulmonary exacerbations and lung function in cystic fibrosis. *Am.J.Respir.Crit.Care Med.* **169**, 816-821.
- Greer, J.R., Abbey, D.E. and Burchette, R.J. (1993) Asthma related to occupational and ambient air pollutants in nonsmokers. *J.Occup.Med.* **35**, 909-915.
- Guo, Y.L., Lin, Y-C., Sung, F-C., Huang, S-L., Ko, Y-C., Lai, J-S., Su, H-J., Shaw, C-K., Lin, R-S. and Dockery, D.W. (1999) Climate, traffic-related air pollutants and asthma prevalence in middle-school children in Taiwan. *Environ. Health Perspect.* **107**, 1001-1006.
- Health Effects Institute. (2000) Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. A Special Report of the Institute's Particle Epidemiology Project. Health Effects Institute: Cambridge, MA.

- Hirsch, T., Weiland, S., von Mutius, E., Safeca, A., Gräfe, H., Csaplovics, E., Duhme, H., Keil, U. and Leupold, W. (1999) Inner city air pollution and respiratory health and atopy in children *Eur. Respir. J.* **14**, 669-677.
- Horak, F. Jr, Studnicka, M., Gartner, C., Spengler, J.D., Tauber, E., Urbanek, R., Veiter, A. and Frischer, T. (2002) Particulate matter and lung function growth in children: a 3-yr follow-up study in Austrian schoolchildren. *Eur.Respir.J.* **19**, 838-845.
- Ihorst, G., Frischer, T., Horak, F., Schumacher, M., Kopp, M., Forster, J., Mattes, J. and Kuehr, J. (2004) Long- and medium-term ozone effects on lung growth including a broad spectrum of exposure. *Eur.Respir.J.* **23**, 292-299.
- Jerrett, M., Burnett, R.T., Ma, R., Pope, C.A., Krewski, D., Newbold, K.B., Thurston, G., Shi, Y., Finkelstein, N., Calle, E.E. and Thun, M.J. (2005) Spatial analysis of air pollution and mortality in Los Angeles. *Epidemiology* **16**, 727-736.
- Kinney, P.L. and Lippmann, M. (2000) Respiratory effects of seasonal exposures to ozone and particles. *Arch.Environ.Health* **55**, 210-216.
- Kunzli, N., Lurmann, F., Segal, M., Ngo, L., Balmes, J. and Tager, I.B. (1997) Association between lifetime ambient ozone exposure and pulmonary function in college freshmen--results of a pilot study. *Environ.Res.* **72**, 8-23.
- Lipfert, F.W., Perry, H.M., Miller, J.P., Baty, J.D., Wyzga, R.E. and Carmody, S.E. (2000) The Washington University-EPRI veterans' cohort mortality study: preliminary results. *Inhalation Toxicol.* **12(Suppl 4)**, 41-73.
- Lipfert, F.W. and Morris, S.C. (2002) Temporal and spatial relations between age specific mortality and ambient air quality in the United States: regression results for counties, 1960-97. *Occup.Environ.Med.* **59**, 156-174.
- McConnell, R., Berhane, K., Gilliland, F., London, S.J., Islam, T., Gauderman, W.J., Avol, E., Margolis, H.G. and Peters, J.M. (2002) Asthma in exercising children exposed to ozone: a cohort study. *Lancet* **359**, 386-391.
- McConnell, R., Berhane, K., Gilliland, F., London, S.J., Vora, H., Avol, E., Gauderman, W.J., Margolis, H.G., Lurmann, F., Thomas, D.C. and Peters, J.M. (1999) Air pollution and bronchitic symptoms in Southern California children with asthma. *Environ.Health Perspect.* **107**, 757-760.
- McConnell, R., Berhane, K., Gilliland, F., Molitor, J., Thomas, D., Lurmann, F., Avol, E., Gauderman, W.J. and Peters, J.M. (2003) Prospective Study of Air Pollution and Bronchitic Symptoms in Children with Asthma. *Am.*

J.Respir.Crit.Care Med. **168**, 790-797.

- McDonnell, W.F., Abbey, D.E., Nishino, N. and Lebowitz, M.D. (1999) Long-term ambient ozone concentration and the incidence of asthma in nonsmoking adults: the AHSMOG Study. *Environ.Res.* **80**, 110-121.
- Mills, P.K., Abbey, D., Beeson, W.L. and Petersen, F. (1991) Ambient air pollution and cancer in California Seventh-day Adventists. *Arch. Environ.Health* **46**, 271-280.
- Pereira, F.A., de Assuncao, J.V., Saldiva, P.H., Pereira, L.A., Mirra, A.P. and Braga, A.L. (2005) Influence of air pollution on the incidence of respiratory tract neoplasm. *J.Air Waste Manag.Assoc.* **55**, 83-87.
- Peters, J.M., Avol, E., Navidi, W., London, S.J., Gauderman, W.J., Lurmann, F., Linn, W.S., Margolis, H., Rappaport, E., Gong, H. and Thomas, D.C. (1999a) A study of twelve Southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. *Am.J.Respir.Crit.Care Med.* **159**, 760-767.
- Peters, J.M., Avol, E., Gauderman, W.J., Linn, W.S., Navidi, W., London, S.J., Margolis, H., Rappaport, E., Vora, H., Gong, H. Jr and Thomas, D.C. (1999b) A study of twelve Southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. *Am.J.Respir.Crit.Care Med.* **159**, 768-775.
- Pope, C.A., Thun, M.J., Namboodiri, M.M., Dockery, D.W., Evans, J.S., Speizer, F.E. and Heath, C.W. (1995) Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am.J.Respir.Crit.Care Med.* **151**, 669-674.
- Pope, C.A., Burnett, R.T., Thun, M.J., Calle, E.E., Krewski, D., Ito, K. and Thurston, G.D. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* **287**, 1132-1141.
- Raizenne, M., Neas, L., Damokosh, A., Dockery, D., Spengler, J., Koutrakis, P., Ware, J. and Speizer, F.(1996) Health effects of acid aerosols on North American children: Pulmonary function. *Env. Health Perspect.* **104**, 506-514.
- Ramadour, M., Burel, C., Lanteaume, A., Vervloet, D., Charpin, D., Brisse, F., Dutau, H. and Charpin, D. (2000) Prevalence of asthma and rhinitis in relation to long-term exposure to gaseous air pollutants. *Allergy* **55**, 1163-9.
- Schwartz, J. (1989) Lung function and chronic exposure to air pollution: a cross-sectional analysis of NHANES II. *Environ.Res.* **50**, 309-321.
- Stern, B., Jones, L., Raizenne, M., Burnett, R., Meranger, J.C. and Franklin, C.A. (1989) Respiratory health effects associated with ambient sulfates and ozone in two rural Canadian communities. *Environ.Res.*

49, 20-39.

- Stern, B.R., Raizenne, M.E., Burnett, R.T., Jones, L., Kearney, J. and Franklin, C.A. (1994) Air pollution and childhood respiratory health: exposure to sulfate and ozone in 10 Canadian rural communities. *Environ.Res.* **66**, 125-142.
- Tager, I., Balmes, J., Lurmann, F., Ngo, L., Alcorn, S. and Kunzli, N. (2005) Chronic exposure to ambient ozone and lung function in young adults. *Epidemiology* **16**, 751-759.
- Wang, T.N., Ko, Y.C., Chao, Y.Y., Huang, C.C. and Lin, R.S. (1999) Association between indoor and outdoor air pollution and adolescent asthma from 1995 to 1996 in Taiwan. *Environ.Res.* **81**, 239-247.
- World Health Organization (2003). Health Aspects of Air Pollution with Particulate Matter, Ozone and Nitrogen Dioxide. Report on a Working Group Meeting Bonn, Germany, 13-15 January 2003. Available at the following website address: www.euro.who.int/documents/e79097.pdf
- Willis, A., Krewski, D., Jerrett, M., Goldberg, M.S. and Burnett, R.T. (2003) Selection of ecological covariates in the American Cancer Society Study *J.Toxicol.Environ Health, Part A* **66**, 1563-1589.
- Zemp, E., Elsasser, S., Schindler, Ch., Kunzli, N., Perruchoud, A.P., Domenighetti, G., Medici, T., Ackermann-Liebrich, U., Leuenberger, P., Monn, C., Bolognini, G., Bongard, J.-M., Brandli, O., Karrer, W., Keller, R., Schoni, M.H., Tschopp, J.-M., Villiger, B., Zellweger, J.-P. and SAPALDIA Team (1999) Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA Study). *Am.J.Respir.Crit.Care Med.* **159**, 1257-1266.

Annex 8 Literature Search Strategy for Chapter 8 on Long Term Exposure to Ozone

PubMed was searched in early 2005 using the following terms:

Ozone and

- asthma or
- respiratory symptoms or
- lung function or
- mortality or
- lung cancer

and

- long term or
- chronic or
- cohort.

The articles retrieved were then sifted to remove:

- reviews
- studies in animals
- occupational rather than environmental exposures
- chamber studies
- time series studies
- *in vitro* studies
- other irrelevant papers
- papers not in the English language (very few)

Thus, the articles retrieved were epidemiological studies of long term exposure at environmental levels in humans.

Any subsequent exclusions based on the quality of the studies (e.g. only 2 sites considered) are mentioned in the main text of the chapter.

Studies identified for a report in preparation on air pollution and asthma were added where they had not already been identified in the above PubMed search.