

COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

IS THERE A THRESHOLD FOR THE EFFECT OF OZONE ON HEALTH?

1. IS THERE AN EFFECT ON MORTALITY AND RESPIRATORY OR CIRCULATORY HOSPITAL ADMISSIONS?

**Introduction**

1. Members may recall that one of the reasons for looking at ozone again was to determine whether the increase in ozone concentrations in urban areas is of public health concern. This increase is occurring at low concentrations so, if there is a threshold for the effects of ozone, and the increase is below the threshold, it may not have health implications. So a crucial issue is whether there is any evidence of a threshold. However, it first needs to be determined whether the literature to date supports an effect of ozone on a particular health outcome at all.

2. An initial overview of the results available on all cause mortality, respiratory mortality, cardiovascular mortality and respiratory hospital admissions was given at the last meeting (COMEAP/2002/1). This suggested that the associations for all-cause and cause-specific mortality and respiratory hospital admissions all showed mainly positive associations but that the lower confidence limits could be negative. However, it was noted that this was for single pollutant models with mixed lag times and averaging times.

3. This paper looks at the evidence in more detail. It uses the St. George's database as the basis for an overview of the studies. The database is based on literature searches of the medical literature, currently up to January 2002, and considers only studies containing regression estimates. As noted above, studies on a particular health outcome can vary in the choice of ozone averaging time used, in season, in age group examined etc. Assessing all these studies together can give a qualitative indication of whether ozone is having an effect on the health outcome but for a quantitative meta-analysis, the studies analysed should be as similar as possible. A positive association of a health outcome with 1-hour average ozone and one with 8 hour average ozone would not be expected to have the same size coefficient even in the same dataset. There was therefore a need to select particular averaging times, seasons and age groups in order to group studies for meta-analysis.

4. (a) An 8-hour averaging time was selected since the ozone air quality standard is on an 8-hour average basis and it is known from chamber studies that both concentration and duration of exposure are important. [On any one day, a maximum 1 hour average would be missing some of the information about the other hours in the day when ozone was raised.] It should be noted that this selection results in the omission of most of the studies in the American literature which use 1-hour or 24-hour averages.

(b) In most cases, an all age group category was used although in certain cases for respiratory admissions, other age groups were examined.

- (c) Coefficients for all year rather than winter or summer were included.
- (d) Single pollutant models were used. Although examination of multipollutant models is useful for checking whether there is confounding by other pollutants, there were too few studies in which this was done for a grouped analysis to be possible.
- (e) Even after selecting for the above, there could still be several coefficients from a single dataset as a result of the use of different lags. A ‘selected lag’ was used i.e. the lag highlighted by the authors in the study or the most significant lag (in either direction) (a full definition is given in the St. Georges’ report to DH on the database, previously circulated to the Committee).

### All-cause mortality

5. The COMEAP Quantification Report (Department of Health Committee on the Medical Effects of Air Pollutants, 1998) concluded that there was an effect of ozone on all-cause mortality. Has the recent literature confirmed this view?
6. There are around 250 coefficients for ozone and all-cause mortality on the database. However, just 21 of these relate to 8-hour average ozone concentrations, all year, all ages, single pollutant models and one lag per study. These are shown in Table 1 and Figure 1.<sup>1</sup> Most coefficients are positive and around half are significant associations. The size of the coefficient ranges from a 2.42% decrease to a 1.58% increase per 10  $\mu\text{g}/\text{m}^3$  increase in 8-hour average ozone concentration. The random effects summary estimate is for a 0.3% increase with a 95% confidence interval of 0.2 to 0.4%. This is lower than the suggested exposure-response coefficient of 3% per 50  $\mu\text{g}/\text{m}^3$  increase in ozone (0.6% for a 10  $\mu\text{g}/\text{m}^3$  increase) in the COMEAP Quantification report.
7. Six of the studies in the table examined seasonal effects. Anderson *et al.* (2001), Hoek *et al.* (2000), Simpson *et al.* (1997) and Saurina *et al.* (1999) found that the effect of ozone on all-cause mortality was greater in the summer. Bremner *et al.* (1999) found no seasonal differences in the all ages group. Wong *et al.* (2001) found a greater effect in the cool season but, in fact, the ozone level was slightly higher in the cool season (35 vs 32  $\mu\text{g}/\text{m}^3$ ). An increased effect in the summer could be supporting evidence for a threshold although it could also be due to different correlations with other pollutants in the summer compared with the winter. It could also be due to people spending more time outdoors.
8. Studies that examined associations between ozone and mortality in different age groups found either similar (Saurina *et al.* (1999), Simpson *et al.* (1997)) or increased (Tenias Burillo *et al.* (1999), Bremner *et al.* (1999), Borja-Aburto *et al.* (1997), Galan Labaca *et al.* (1999)) relative risks in the elderly.
9. Only a minority of studies examined multi-pollutant models. Simpson *et al.* (1997) found no significant interactions of the ozone effect with those of  $\text{SO}_2$ ,  $\text{NO}_2$  or particles measured by nephelometry. Anderson *et al.* (1996) also found that control for  $\text{SO}_2$ ,  $\text{NO}_2$  and black smoke made little difference to the ozone effect. Hoek *et al.*

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<sup>1</sup> Please note that this figure can be found in the accompanying paper entitled “june2002comeappaperplots”

(2000) found the association of ozone with all cause mortality was still significant after control for black smoke, PM<sub>10</sub> and sulphate and Wong *et al.* (2001) found no

**Table 1 All-Cause Mortality**

1. All Cause, all age, all season, single pollutant models, 8 hour averages. **21 estimates.**

% change in mortality for an increase of 10  $\mu\text{g}/\text{m}^3$  in ozone

ID reference	Author	Year of Publication	City	ICD	Lag	Mean / Median O <sub>3</sub> level ( $\mu\text{g}/\text{m}^3$ )	% change	95% Confidence Interval
69	Anderson,H.R.	2001	West Midlands	<800	lag 0-1	48.0	0.50	(-0.02, 1.02)
175	Hoek,G.	2000	Netherlands	<800	lag 1	47.0	0.22	(0.13, 0.31)
176	Klemm R J	2000	Georgia	<800	lag 0	81.2	-0.20	(-1.27, 0.88)
182	Bremner SA	1999	London	<800	lag 2	32.0	-0.14	(-0.45, 0.18)
192	Galan L	1999	Madrid	<800	lag 4	79.1	0.33	(-0.13, 0.79)
197	Saurina C	1999	Barcelona	<800	lag 1	67.5	0.35	(0.03, 0.68)
219	Michelozzi P	1998	Rome	<800	lag 1	21.0	0.38	(-0.03, 0.79)
233	Simpson RW	1997	Brisbane	<800	lag 0	33.4	1.18	(0.39, 1.98)
245	Borja-Aburto VH	1997	Mexico City		lag 0	188.0	0.21	(0.10, 0.32)
258	Zmirou D	1996	Lyon	<800	lag 0	9.9	0.59	(-1.02, 2.23)
268	Anderson HR	1996	London	<900	lag 0	28.0	0.46	(0.21, 0.71)
889	Fairley D	1999	Santa Clara County, California	<800	lag 0	58.0	0.45	
1070	Hong, YC	1999	Inchon	<800	lag 1	30.8	-2.42	(-4.50, -0.29)
1094	CadumE.	1999	Turin	<800	lag 0	73.7	0.32	(-0.12, 0.76)
1140	Tenias Burillo, J.M	1999	Valencia	<800	lag 2	45.5	1.18	(-0.15, 2.53)
1327	Wong,C.M.	2001	Hong Kong	<800	lag 5	33.5	0.18	(-0.18, 0.54)
1332	Zeghnoun,A.	2001	Paris	<800	lag 1	26.0	0.28	(0.06, 0.50)
1332	Zeghnoun,A.	2001	Strasbourg	<800	lag 1-2	37.0	0.75	(0.07, 1.43)
1332	Zeghnoun,A.	2001	Lyon	<800	lag 0-1	52.0	0.65	(-0.05, 1.35)
1332	Zeghnoun,A.	2001	Toulouse	<800	lag 2-3	68.0	1.58	(0.59, 2.57)
1360	Roemer,W.H.	2001	Amsterdam		lag 2	41.0	-0.17	(-0.52, 0.18)

difference after adjustment for NO<sub>2</sub>. In contrast, Borja-Aburto *et al.* (1997) found that, in Mexico City, the association between ozone and daily mortality became non-significant after adjustment for total suspended particles (TSP).

10. A few studies have examined the dose-response relationship between 8-hour average ozone concentrations and mortality risk. Wong *et al.* (2001) (Fig. 2)<sup>2</sup> found a slight increase above about 40 µg/m<sup>3</sup> and Hong *et al.* (1999) (Fig 3)<sup>3</sup> found a steeper increase above about 23ppb (46 µg/m<sup>3</sup>) in smoothed plots against mortality risk on a log scale. Anderson *et al.* (1996), in a bubble plot (Fig 4)<sup>4</sup> found an increase above about 40-50 ppb (80 to 100 µg/m<sup>3</sup>). Galan Labaca *et al.* (1999) found an increased effect on mortality at lower doses which then decreased at intermediate concentrations and increased again at higher concentrations.

11. There are similar numbers of studies looking at other averaging times (1-hour and 24-hour). These are not all discussed in detail here but the multi-city studies should give an indication of whether the findings differ from those found for 8-hour averaging concentrations. Touloumi *et al.* (1997) performed a meta-analysis of results from 4 European cities (London, Athens, Barcelona and Paris) as part of the APHEA I project. An increase of 2.9% (95% confidence interval 1% to 4.9%) in all-cause mortality was associated with a 50 µg/m<sup>3</sup> increase in 1-hour maximum ozone concentration. (This was the basis of the exposure-response coefficient suggested in the COMEAP Quantification Report mentioned above). This effect was slightly higher in the warm season and remained significant after inclusion of black smoke in the model.

12. For 24-hour average ozone concentration, Burnett *et al.* (1998) found a significant positive association with all-cause mortality in a meta-analysis of 11 Canadian cities but the ozone risk was greater in cities with higher fine particle concentrations suggesting the possibility of confounding by particles. Samet *et al.* (2000) did not find an association between 24 hour average ozone and all cause mortality in a meta-analysis of 20 US cities. There was a positive association with 24-hour average ozone in the summer but this was not significant. It is worth noting that ozone levels at night can be particularly low on high ozone days (R. Derwent, personal communication), so the 24-hour average concentrations might not necessarily be high on those days.

### **Respiratory mortality**

13. There are just over 100 coefficients for associations between ozone and respiratory mortality on the database. The 24 coefficients for single pollutant models with 8-hour average ozone concentrations, all ages and all year, one lag per study are shown in Table 2. The coefficients for ICD codes 460-519 are generally larger than

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<sup>2</sup> Figure 2 is Figure 4 from Wong *et al.* (2001). *Environ Health Perspect* 109; 335-340

<sup>3</sup> Figure 3 is Figure 4b from Hong *et al.* (1999). *Environ Health Perspect* 107; 873-878

<sup>4</sup> Figure 4 is Figure 1c from Anderson *et al.* (1996). *Br Med J* 312; 665-669

for all cause mortality, although just over half of the lower confidence intervals are negative perhaps due to the reduced statistical power with fewer numbers of deaths. The coefficients vary from a 2.8% decrease to a 6% increase in respiratory mortality for a  $10 \mu\text{g}/\text{m}^3$  increase in 8-hour average ozone concentration (Figure 5).<sup>5</sup> The

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<sup>5</sup> Please note that Figure 5 can be found in the accompanying paper “june2002comeappaperplots”

**Table 2** Mortality from Diseases of the Respiratory System, all ages, all season, single pollutant models, 8 hour measures of ozone. **24 estimates**  
 % change in mortality for an increase of 10 µg/m<sup>3</sup> in ozone

Wong TW (2002) 1995-1998 & Wong CM (2001) 1995-1997 use overlapping Hong Kong data.

ID reference	Author	Year of Publication	City	Disease (as described by author)	ICD	Lag	Mean / Median O <sub>3</sub> level (ug/m <sup>3</sup> )	% change	95% Confidence Interval
69	Anderson,H.R.	2001	West Midlands	all respiratory	460-519	lag 0-1	48.0	0.38	(-0.97, 1.75)
153	Wong,T.W.	2002	Hong Kong	all respiratory	461-519	lag 2	29.3	1.00	(0.40, 1.60)
182	Bremner SA	1999	London	all respiratory	460-519	lag 2	32.0	-0.71	(-1.55, 0.13)
192	Galan L	1999	Madrid	all respiratory	460-519	lag 5	79.1	-0.89	(-2.35, 0.59)
197	Saurina C	1999	Barcelona	all respiratory	460-519	lag 4	67.5	0.51	(-0.55, 1.57)
222	Zmirou D	1998	Barcelona, London, Lyon, Paris	all respiratory	460-519	single		0.98	(0.40, 1.57)
233	Simpson RW	1997	Brisbane	all respiratory	460-519	lag 0	33.4	1.92	(-0.94, 4.86)
253	Dab W	1996	Paris	all respiratory	460-519	lag 0	20.0	0.72	(-0.68, 2.13)
258	Zmirou D	1996	Lyon	all respiratory	460-519	lag 2	9.9	0.20	(-1.65, 2.09)
268	Anderson HR	1996	London	all respiratory	460-519	lag 0	28.0	1.13	(0.42, 1.85)
889	Fairley D	1999	Santa Clara County	all respiratory		lag 0	40.0	-0.62	
1070	Hong, YC	1999	Inchon	all respiratory		lag 1	30.8	0.05	(-8.67, 9.60)
1140	Tenias Burillo, J.M	1999	Valencia	all respiratory		lag 5	45.5	-2.84	(-7.01, 1.52)
1327	Wong,C.M.	2001	Hong Kong	all respiratory	460-519	lag 4	33.5	0.53	(-0.18, 1.25)
1332	Zeghnoun,A.	2001	Paris	all respiratory	460-519	lag 2	26.0	1.20	(0.19, 2.23)
1332	Zeghnoun,A.	2001	Strasbourg	all respiratory	460-519	lag 5	37.0	1.66	(-0.66, 4.05)
1332	Zeghnoun,A.	2001	Lyon	all respiratory	460-519	lag 0-1	52.0	2.70	(0.30, 5.16)
1332	Zeghnoun,A.	2001	Toulouse	all respiratory	460-519	lag 2	68.0	6.08	(2.97, 9.27)
245	Borja-Aburto VH	1997	Mexico City	all respiratory	460-466, 480-487, 490-496, 500-508, 768, 786	lag 0	188.0	0.17	(-0.16, 0.49)
1094	Cadum,E.	1999	Turin	all respiratory	480-519	lag 0	73.7	0.51	(-1.48, 2.55)
153	Wong, T.W.	2002	Hong Kong	Copd	490-496	lag 0-4	29.3	3.40	(1.7, 5.13)
175	Hoek,G.	2000	Netherlands	Copd	490-496	lag 1	47.0	-0.04	(-0.47, 0.39)
153	Wong, T.W.	2002	Hong Kong	pneumonia+influenza	480-487	lag 2	29.3	0.70	(-0.1, 1.51)
175	Hoek,G.	2000	Netherlands	Pneumonia	480-486	lag 0-6	47.0	2.11	(1.37, 2.85)

random effects summary estimate is for a 0.7% increase with a 95% confidence interval of 0.3 to 1.2%. It should be noted that there is some overlap in some of the data – Zmirou *et al.* (1998) is a meta-analysis of data from London, Barcelona, Paris and Lyon. Individual estimates have also been derived using data from these cities for the same years (Dab *et al.* (1996), Zmirou *et al.* (1996)) or for overlapping years (Anderson *et al.* (1996), Saurina *et al.* (1999)). There are also two papers from Hong Kong (Wong *et al.* (2002), Wong *et al.* (2001) with some data from overlapping years. However, the summary estimate remains positive and significant even if the meta-analysis paper and one or other of the Hong Kong papers are omitted. (Summary estimate without Zmirou *et al.* (1998) and Wong *et al.* (2002) 0.7% (95% confidence interval 0.1 to 1.3%); summary estimate without Zmirou *et al.* (1998) and Wong *et al.* (2001) 0.8% (95% confidence interval 0.2% to 1.4%)).

14. Three studies (Borja-Aburto *et al.* (1997), Cadum *et al.* (1999), Fairley, (1999)) omitted certain ICD codes within diseases of the respiratory system but no statistically significant positive associations were found. Wong *et al.* (2002) found a significant positive association for chronic obstructive pulmonary disease (COPD) (ICD 490-496) but not for pneumonia and influenza (ICD 480-487) but Hoek *et al.* (2000) found the reverse. It is not possible to come to any conclusion on what subdivisions of respiratory mortality are important from the small number of studies available.

15. Some studies examined whether there were any seasonal differences. Anderson *et al.* (2001) and Bremner *et al.* (1999) found no difference between seasons. Saurina *et al.* (1999), Anderson *et al.* (1996) and Wong *et al.* (2001) found smaller effects in the warm season, although in the case of Wong *et al.* (2001), the levels of ozone were actually slightly higher in the cool season. However, some authors commented that it might be difficult to detect seasonal differences due to the small number of respiratory deaths in the summer.

16. Only two studies looked at effects in different age groups. Both Bremner *et al.* (1999) and Simpson *et al.* (1997) found that the associations were still not significant when divided into different age groups although the associations were increased in the 65-74 and over 65 age groups respectively.

17. Four studies looked at multipollutant models. Zmirou *et al.* (1998) found the association with ozone was stable to control for particles but weakened by the addition of sulphur dioxide to the model. Wong *et al.* (2001) found that the non-significant association between ozone and respiratory mortality was unchanged by control for nitrogen dioxide. Borja-Aburto *et al.* (1997) however found that the significant association between ozone and respiratory mortality in Mexico City became non-significant after control for TSP. However, Anderson *et al.* (1996) found in London that the ozone association increased and remained significant after inclusion of black smoke in the model.

18. As shown in Figure 2, Wong *et al.* (2001) found that, in the warm season, respiratory deaths increased slightly at intermediate ozone concentrations but then decreased steeply above about 70  $\mu\text{g}/\text{m}^3$ . However, in the cool season, respiratory deaths increased significantly above about 40  $\mu\text{g}/\text{m}^3$ . No other studies examined dose-response relationships.

## Respiratory hospital admissions

19. There are 375 coefficients on the database relating ozone concentrations to respiratory admissions. However, these cover a range of age groups and averaging times and many coefficients for each study. The 29 estimates for associations between various types of respiratory admissions and 8-hour ozone concentrations, single pollutant models for all year and all ages are shown in Table 3. There are 6 estimates for all respiratory admissions ICD code 460-519 also shown in Figure 6.<sup>6</sup> Most associations are positive although several are not statistically significant. The coefficients range from a decrease of 0.42% to an increase of 1.14% per 10  $\mu\text{g}/\text{m}^3$  increase in 8-hour average ozone concentration. The random effects summary estimate is 0.3% with a 95% confidence interval from 0 to 0.7%. This compares with a 3.5% increase per 50  $\mu\text{g}/\text{m}^3$  increase in ozone concentrations (0.7% per 10  $\mu\text{g}/\text{m}^3$ ) suggested in the COMEAP Quantification Report.

20. Wong *et al.* (1999), with a more restricted group of ICD codes found a larger effect but there are no other studies with the same group of ICD codes.

21. There are 7 estimates for chronic obstructive pulmonary disease (COPD). Two of these are for those over 65 rather than all ages but this is unlikely to be an important difference since most COPD admissions occur in the elderly anyway. The associations tend to be larger than for all respiratory admissions although the confidence intervals are wider and many associations are not significant. The estimates range from 0.03% to 3.2%. The random effects summary estimate is for a 1% increase in COPD admissions with a 95% confidence interval of 0.2% to 1.9% for a 10  $\mu\text{g}/\text{m}^3$  increase in 8 hour average ozone concentration.

22. There are 8 estimates for asthma admissions in the 0-14 years age group. Several of the estimates are greater than for all respiratory admissions but there are also some negative associations. The estimates range from a 1.24 % decrease to a 7.68 % increase in asthma admissions per 10  $\mu\text{g}/\text{m}^3$  increase in 8-hour average ozone concentration. The random effects summary estimate is 0.3% with a 95% confidence interval from -1.3% to + 2.0%. There are 5 estimates for the 15-64 years age group with a narrower range than for children from a 0.3% decrease to a 4.12% increase. The random effects summary estimate (1.4%) is greater than for asthma in children but still not statistically significant (95% confidence interval -0.1% to + 3%).

23. Fusco *et al.* (2001) found a positive but non-significant association with acute respiratory infections and Wong *et al.* (1999) found a positive and significant association with pneumonia. However, no other studies using 8-hour averages have examined these outcomes.

24. Of the studies examining all respiratory admissions and all ages, 4 examined seasonal effects. Ponce de Leon *et al.* (1996) and Anderson *et al.* (2001) found greater effects in the warm season although in the latter study the effect was still not significant. Atkinson *et al.* (1999) found no seasonal differences. Petroschevsky *et al.* (2001) stated that 'significant negative interactions between ozone and season

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<sup>6</sup> Please note that Figure 6 can be found in the accompanying paper "june2002comeap paperplots"

existed in Autumn' (This presumably means that ozone associations are lower in autumn than the rest of the year). Several studies also examined seasonal effects in

**Table 3 Respiratory Admissions**

Diseases of the Respiratory System. **28 estimates.** All year, 8 hour measures of ozone, single pollutant models  
 All ages except for COPD (all ages or 65+) & asthma (0-14 & 15-64)  
 % change in mortality for an increase of 10 µg/m<sup>3</sup> in ozone

ID reference	Author	Year of Publication	City	Disease (as described by author)	ICD	Age group	Lag	Mean / Median O <sub>3</sub> level (ug/m <sup>3</sup> )	% change	95% Confidence Interval
49	Petroeschovsky, A.	2001	Brisbane	all respiratory	460-519	all	lag 2	38.0	1.14	(0.15, 2.15)
69	Anderson, H.R.	2001	West Midlands	all respiratory	460-519	all	lag 0-1	48.0	-0.42	(-0.95, 0.10)
253	Dab W	1996	Paris	all respiratory	460-519	all	lag 0	20.0	0.24	(-0.25, 0.73)
417	Ponce De Leon A	1996	London	all respiratory	460-519	all	lag 1	28.0	0.56	(0.22, 0.90)
1053	Atkinson, R, W	1999	London	all respiratory	460-519	all	lag 1	32.0	0.23	(-0.20, 0.67)
1265	Fusco, D.	2001	Rome	all respiratory	460-519	all	lag 1	27.0	0.87	(-0.17, 1.93)
364	Wong TW	1999	Hong Kong	all respiratory	460-466, 471-478, 480-487, 490-496	all	lag 0-3	24.2	2.20	(1.50, 2.90)
1265	Fusco, D.	2001	Rome	acute resp infections	460-466, 480-486	all	lag 1	27.0	1.33	(-0.21, 2.89)
69	Anderson, H.R.	2001	West Midlands	copd	490-492, 494-496	65+	lag 0-1	48.0	0.03	(-1.26, 1.35)
253	Dab W	1996	Paris	copd	490-492, 494-496	all	lag 0-1	20.0	1.15	(-0.09, 2.40)
364	Wong TW	1999	Hong Kong	copd	490-496	all	lag 0-5	24.2	3.20	(2.10, 4.31)
480	Schouten JP	1996	Rotterdam	copd	490-492, 494, 496	all	lag 2	61.0	0.38	(-0.82, 1.60)
480	Schouten JP	1996	Amsterdam	copd	490-492, 494, 496	all	lag 0	69.0	0.38	(-0.79, 1.57)
1053	Atkinson, R, W	1999	London	copd	490-496	65+	lag 0	32.0	0.73	(-0.23, 1.70)
1265	Fusco, D.	2001	Rome	copd	490-492, 494-496	all	lag 1	27.0	1.49	(-0.38, 3.39)

(Admissions) Diseases of the Respiratory System (continued). All year, 8 hour measures of ozone, single pollutant models

All ages except for COPD (all ages or 65+) & asthma (0-14 & 15-64)

% change in mortality for an increase of 10 µg/m<sup>3</sup> in ozone

ID reference	Author	Year of Publication	City	Disease (as described by author)	ICD	Age group	Lag	Mean / Median O <sub>3</sub> level (ug/m <sup>3</sup> )	% change	95% Confidence Interval
49	Petroeschovsky,A.	2001	Brisbane	asthma	493	0-14	lag 1	38.0	3.15	(0.75, 5.61)
69	Anderson,H.R.	2001	West Midlands	asthma	493	0-14	lag 0-1	48.0	-2.39	(-4.08, -0.66)
263	Ponka A	1996	Helsinki	asthma	493	0-14	lag 0	22.0	7.68	(0.35, 15.55)
380	Anderson HR	1998	London	asthma	493	0-14	lag 0	28.0	0.08	(-0.78, 0.96)
398	Sunyer J	1997	Paris	asthma	493	0-14	lag 1		-0.88	
398	Sunyer J	1997	London	asthma	493	0-14	lag 2		0.22	
1053	Atkinson, R,W	1999	London	asthma	493	0-14	lag 2	32.0	-1.24	(-2.30, -0.18)
1265	Fusco,D.	2001	Rome	asthma	493	0-14	lag 2	27.0	2.31	(-2.12, 6.94)
69	Anderson,H.R.	2001	West Midlands	asthma	493	15-64	lag 0-1	48.0	-0.30	(-2.06, 1.49)
49	Petroeschovsky,A.	2001	Brisbane	asthma	493	15-64	lag 2	38.0	4.12	(1.83, 6.45)
380	Anderson HR	1998	London	asthma	493	15-64	lag 1	28.0	1.95	(0.88, 3.02)
398	Sunyer J	1997	Paris	asthma	493	15-64	lag 1		-0.28	
1053	Atkinson, R,W	1999	London	asthma	493	15-64	lag 1	32.0	0.41	(-0.96, 1.80)
364	Wong TW	1999	Hong Kong	pneumonia	480-487	all	lag 0-3	24.2	2.20	(0.9, 3.52)

different age groups. These have been omitted here for clarity but can be described at a later stage if required.

25. Wong *et al.* (1999), for a more limited set of respiratory ICD codes, found a significant positive interaction with the cold season in Hong Kong.

26. For COPD, Anderson *et al.* (2001) and Atkinson *et al.* (1999) found no seasonal differences. Schouten *et al.* (1996) found a greater effect in the summer in Amsterdam but a greater effect in the winter in Rotterdam. For asthma, in the 0-14 and 15-64 age groups, Anderson *et al.* (2001), Atkinson *et al.* (1999) and Sunyer *et al.* (1997) found no seasonal differences. Petroeschevsky *et al.* (2001) found no significant interaction with season in the 15-64 age group but a negative interaction in the 0-14 age group in the winter. Anderson *et al.* (1998) found a greater effect in the warm season in both age groups.

27. All of the studies of all respiratory admissions except that of Dab *et al.* (1996) examined whether the effects differed in different age groups. (The studies of COPD and asthma admissions are not discussed here since these results have already been divided by age group in the table.) In all studies addressing the elderly (Petroeschevsky *et al.* (2001), Anderson *et al.* (2001), Atkinson *et al.* (1999), Ponce de Leon *et al.* (1996), Wong *et al.* (1999)) the estimates for those over 65 were greater than for all ages. The estimates for children in these same studies were always less than those for all ages although another study by Fusco *et al.* (2001) found a greater effect in the 0-14 age group. The results for adults were not consistently above or below those for all ages. The greater strength of an effect in the elderly may provide indirect support for the view that ozone has more of an effect on COPD than asthma.

28. The effect of ozone was unaffected by control for other pollutants for all respiratory admissions (Petroeschevsky *et al.* (2001), Ponce de Leon *et al.* (1996)), COPD admissions (Schouten *et al.* 1996) or asthma admissions (Anderson *et al.* 1998). The one exception was the study by Wong *et al.* (1999) which found that the effect of ozone on respiratory hospital admissions (excluding certain ICD codes) was higher when PM<sub>10</sub> was high as well. This phenomenon did not occur with high levels of nitrogen dioxide.

29. Three papers examined the dose-response relationship with 8-hour average ozone and respiratory or asthma admissions. Ponce de Leon *et al.* (1996) found an increase in effects above about 50 ppb (see bubble plot in Fig7).<sup>7</sup> This was not clearly seen in the study by Atkinson *et al.* (1999) although there was a very slight indication that the effect was just above zero rather than around zero above about 35 ppb (Fig. 8).<sup>8</sup> In contrast, Petroeschevsky *et al.* (2001) found a curvilinear dose-response for asthma admissions in which the relative risks (compared with the bottom quintile of 1 part per hundred million (10ppb) and below) were greater in the lower quintiles than the higher quintiles (Fig. 9).<sup>9</sup>

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<sup>7</sup> Figure 7 is Figure 2 from Ponce de Leon *et al.* (1996). J Epidemiol Community Health 50(suppl 1): s63-70

<sup>8</sup> Figures 8(a) and 8(b) are from Atkinson *et al.* (1999). Arch Environ Health 54; 398-411

<sup>9</sup> Figure 9 is from Petroeschevsky *et al.* (2001). Arch Environ Health 56; 37-52

30. There are a large number of studies on respiratory admissions and 1-hour or 24-hour average ozone. These have not been summarised here but can be described in a future paper, if required.

### **Mortality from all diseases of the circulatory system**

31. There are around 100 coefficients relating ozone to cardiovascular mortality on the database. This reduces to 27 when selecting for 8 hour average ozone, all year, all ages, single pollutant models and one lag per study and to 24 when excluding studies with no specified ICD codes. These coefficients are shown in Table 4. These coefficients are still based on varied ICD code groupings. The largest group of coefficients is for ICD 390-459, all diseases of the circulatory system. These varied from a 0.81% decrease to a 1.22 % increase in mortality per 10  $\mu\text{g}/\text{m}^3$  increase in 8 hour average ozone (Fig. 10).<sup>10</sup> Most coefficients showed a small positive association but with a negative lower confidence interval. There were three significant positive associations in London, Barcelona and Toulouse. The random effects summary estimate was a marginally significant 0.3% increase in all circulatory mortality with a 95% confidence interval from 0% to 0.6%.

32. All diseases of the circulatory system is a very wide grouping and it could be argued that there could be an effect on a more specific outcome that is not picked up in the results for the wider grouping due to dilution by unaffected outcomes. Some studies have kept a large grouping but excluded certain outcomes such as

diseases of veins and lymphatics (ICD 451-459),  
diseases of arteries, arterioles and capillaries (ICD 440-448),  
cerebrovascular disease (ICD 430-438),  
acute rheumatic fever (ICD 390-392),  
chronic rheumatic disease (ICD 393-398)  
essential hypertension/hypertensive renal disease/secondary hypertension (ICD 401/403/405),  
other diseases of the pulmonary circulation (ICD 417)  
acute pericarditis/acute and subacute endocarditis/ acute myocarditis/other diseases of pericardium/other diseases of endocardium/cardiomyopathy/conduction disorders/cardiac dysrhythmias/heart failure (ICD420-428).

33. Unfortunately, different studies exclude different combinations of the above so comparability is difficult. The results are still mixed. Although all coefficients are positive and there are a higher proportion of coefficients with a positive lower confidence interval than with all diseases of the circulatory system, the number of studies is probably too small for this to be taken as a firm conclusion for an effect. However, it would also be difficult to exclude the possibility of an effect. Meta-analysis of this group of studies is perhaps unwise given the disparate ICD groupings.

34. There are also some studies that looked at more specific outcomes. Hoek *et al.* (2001) found greater associations with heart failure (ICD 428) and arrhythmias (ICD 427) than with all cardiovascular mortality (ICD 390-448) although only the effect on heart failure was significant. No significant association was found with ischaemic

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<sup>10</sup> Please note that Figure 10 can be found in the accompanying paper “june2002comeappaperplots”

heart disease (ICD 410-414) and, although significant, the associations with cerebrovascular disease (ICD 430-436) and outcomes related to embolism/thrombosis

**Table 4 Mortality from Diseases of the Circulatory System, all ages, all season, 8 hour measures of ozone. 26 estimates.**

% change in mortality for an increase of 10 µg/m<sup>3</sup> in ozone

ID reference	Author	Year of Publication	City	Disease (as described by author)	ICD	Lag	Mean / Median O <sub>3</sub> level (ug/m <sup>3</sup> )	% change	95% Confidence Interval
69	Anderson,H.R.	2001	West Midlands	cardiovascular	390-459	lag 0-1	48.0	0.16	(-0.60, 0.92)
153	Wong,T.W.	2002	Hong Kong	cardiovascular	390-459	lag 0	29.3	-0.30	(-0.90, 0.30)
182	Bremner SA	1999	London	cardiovascular	390-459	lag 2	32.0	0.67	(0.10, 1.25)
192	Galan L	1999	Madrid	cardiovascular	390-459	lag 1	79.1	-0.81	(-1.59, -0.02)
197	Saurina C	1999	Barcelona	cardiovascular	390-459	lag 1	67.5	0.71	(0.20, 1.23)
268	Anderson HR	1996	London	cardiovascular	390-459	lag 0	28.0	0.28	(-0.09, 0.64)
889	Fairley D	1999	Santa Clara County	cardiovascular		lag 0	40.0	0.30	
1070	Hong, YC	1999	Inchon	cardiovascular		lag 1	30.8	-0.90	(-6.28, 4.80)
1094	Cadum,E.	1999	Turin	cardiovascular	390-459	lag 0	73.7	0.67	(-0.02, 1.37)
1140	Tenias Burillo, J.M	1999	Valencia	cardiovascular		lag 5	45.5	1.27	(-0.71, 3.29)
1327	Wong,C.M.	2001	Hong Kong	cardiovascular	390-459	lag 3	33.5	0.18	(-0.36, 0.72)
1332	Zeghnoun ,A.	2001	Toulouse	cardiovascular	390-459	lag 3	68.0	1.22	(0.02, 2.43)
1332	Zeghnoun ,A.	2001	Lyon	cardiovascular	390-459	lag 2	52.0	0.50	(-0.95, 1.96)
1332	Zeghnoun ,A.	2001	Strasbourg	cardiovascular	390-459	lag 1	37.0	0.57	(-0.39, 1.54)
175	Hoek,G.	2000	Netherlands	cardiovascular	390-448	lag 1	47.0	0.31	(0.17, 0.46)
222	Zmirou D	1998	Barcelona, London, Lyon, Paris	cardiovascular	390-429	single		0.40	(0.00, 0.80)
233	Simpson RW	1997	Brisbane	cardiovascular	393-398.9, 402-402.9, 404-404.9, 410-416.9, 420-420.9, 429-429.9	lag 0	33.4	0.99	(-0.39, 2.38)
258	Zmirou D	1996	Lyon	cardiovascular	390-429	lag 1	9.9	0.00	(-2.30, 2.36)
1275	Hoek,G.	2001	Netherlands	cardiovascular	390-448	lag 1		0.36	(0.21, 0.51)
245	Borja-Aburto VH	1997	Mexico City	cardiac	401-405, 410-417, 430-438, 785	lag 0	188.0	0.37	(0.15, 0.59)
153	Wong,T.W.	2002	Hong Kong	ihd	410-414	lag 3	29.3	0.90	(0.00, 1.81)
1275	Hoek,G.	2001	Netherlands	ihd	410-414	lag 1		0.17	(-0.04, 0.38)
1275	Hoek,G.	2001	Netherlands	arrhythmia	427	lag 1		0.48	(-0.16, 1.11)
1275	Hoek,G.	2001	Netherlands	heart failure	428	lag 1		0.51	(0.06, 0.96)
153	Wong,T.W.	2002	Hong Kong	cerebrovascular	430-438	lag 0	29.3	-0.10	(-0.20, 0.00)
1275	Hoek,G.	2001	Netherlands	cerebrovascular	430-436	lag 1		0.46	(0.15, 0.77)
1275	Hoek,G.	2001	Netherlands	embolism + thrombosis	415, 433, 434, 444, 452, 453	lag 1		0.88	(0.21, 1.55)

(ICD 415.1, 433, 434, 444, 452 and 453) were smaller than for cardiovascular mortality as a whole. In contrast, Wong *et al.* (2002), found a significant association for ischaemic heart disease but not for cerebrovascular disease. There are insufficient studies of the more specific outcomes to distinguish clearly whether one outcome is affected more than another.

35. Of the studies in the table that looked at seasonal differences (Anderson *et al.* (1996), Bremner *et al.* (1999), Saurina *et al.* (1999), Simpson *et al.* (1997), Wong *et al.* (2001)) all but the study in Hong Kong (Wong *et al.* 2001) found higher coefficients in the summer. This could perhaps strengthen the case for there being an effect of ozone on cardiovascular mortality. It could also provide indirect evidence for a threshold since ozone levels are higher in the summer. However, there are also other possible explanations such as a different correlation pattern with other pollutants in the summer.

36. Only 2 of the studies looked at different age groups. Bremner *et al.* (1999) found a larger association in the 65-74 age group than for all ages but Simpson *et al.* (1997) found no significant association with deaths in people over or under 65 years.

37. Most studies did not examine multipollutant models. In the studies that did ((Anderson *et al.* (1996), Borja-Aburto *et al.* (1997), Wong *et al.* (2001), Hoek *et al.* (2000)) adjustment for other pollutants did not affect the statistical significance or direction of the coefficients.

38. Wong *et al.* (2001) produced smoothed plots of ozone concentration against cardiovascular mortality on a log scale (Fig. 2). This showed a steep rise in the risk above about 60  $\mu\text{g}/\text{m}^3$  ozone. The shape of the dose-response for cardiovascular mortality was not examined in the other studies although some looked at the dose-response for all-cause mortality as described earlier. There is thus a possibility that, although, in general, associations of ozone concentrations with cardiovascular mortality are not significant, there could be a small effect at higher concentrations.

39. There are studies examining associations with 1 hour and 24 hour average ozone concentrations in addition to those looking at 8 hour average concentrations described above. However, it is not possible to come to any firmer conclusions from these studies as there are only small numbers of studies related to any particular ICD code or group of codes.

### **Hospital admissions for all circulatory diseases**

40. There are around 130 coefficients relating to ozone and cardiovascular admissions on the database. This reduces to 17 coefficients when selecting for studies which examined 8-hour average ozone, all year, all ages, single pollutant models and one lag per study and when excluding studies with no specified ICD codes. The selected studies are shown in Table 5.

41. The evidence for an association between 8 hour average ozone concentrations and admissions for all circulatory diseases (ICD 390-459) is not convincing (Figure 11).<sup>11</sup>

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<sup>11</sup> Please note that Figure 11 can be found in the accompanying paper “june2002comeappaperplots”

The coefficients range from a 0.95% decrease to a 0.45% increase per  $10 \mu\text{g}/\text{m}^3$  change in 8 hour average ozone concentration. Most associations are not statistically

**Table 5 Admissions for Diseases of the Circulatory System, all ages, all season, 8 hour measures of ozone. 17 estimates.**

% change in mortality for an increase of 10  $\mu\text{g}/\text{m}^3$  in ozone

ID reference	Author	Year of Publication	City	Disease	ICD	Lag	Mean / Median O <sub>3</sub> level	% change	95% Confidence Interval
49	Petroeshevsky, A.	2001	Brisbane	cardiovascular	390-459	lag 3	38.0	-0.65	(-1.46, 0.16)
64	Poloniecki JD	1997	London	cardiovascular	390-459	lag 1	26.0	-0.55	(-1.15, 0.05)
69	Anderson, H.R.	2001	West Midlands	cardiovascular	390-459	lag 0-1	48.0	0.02	(-0.48, 0.51)
1053	Atkinson, R.W	1999	London	cardiovascular	390-459	lag 2	32.0	0.45	(0.04, 0.87)
1184	Ballester, F.	2001	Valencia	cardiovascular	390-459	lag 2	45.9	-0.95	(-2.90, 1.04)
364	Wong TW	1999	Hong Kong	cardiovascular	410-417, 420-438, 440-444	lag 0-5	24.2	1.30	(0.50, 2.11)
64	Poloniecki JD	1997	London	other CV	390-459 minus 410, 413-414, 427-428, 430-438	lag 1	26.0	-0.20	(-0.78, 0.39)
69	Anderson, H.R.	2001	West Midlands	cardiac	390-429	lag 0-1	48.0	0.28	(-0.26, 0.82)
64	Poloniecki JD	1997	London	ami	410	lag 1	26.0	-0.35	(-0.95, 0.25)
364	Wong TW	1999	Hong Kong	ihd	410-414	lag 5	24.2	0.50	(-0.30, 1.31)
64	Poloniecki JD	1997	London	angina pectoris	413	lag 1	26.0	-0.30	(-1.09, 0.49)
64	Poloniecki JD	1997	London	other IHD	414	lag 1	26.0	-0.55	(-1.50, 0.41)
64	Poloniecki JD	1997	London	heart failure	428	lag 1	26.0	-0.12	(-0.80, 0.57)
64	Poloniecki JD	1997	London	arrhythmia	427	lag 1	26.0	0.30	(-0.60, 1.22)
364	Wong TW	1999	Hong Kong	chf	428	lag 0-5	24.2	3.80	(1.80, 5.84)
1184	Ballester, F.	2001	Valencia	heart disease	410-414, 427, 428	lag 5	45.9	-2.14	(-4.65, 0.44)
64	Poloniecki JD	1997	London	cerebrovascular	430-438	lag 1	26.0	-0.30	(-0.90, 0.30)
364	Wong TW	1999	Hong Kong	cerebrovascular	430-438	lag 0	24.2	-0.80	(-1.70, 0.11)
1184	Ballester, F.	2001	Valencia	cerebrovascular	430-438	lag 2	45.9	-2.40	(-5.36, 0.65)



significant and most are small negative associations. The random effects summary estimate is a small negative association - a 0.2% decrease with a 95% confidence interval of -0.7% to +0.3%. This lack of a positive effect is consistent with the lack of strong evidence for an association with mortality from all circulatory diseases.

42. Wong *et al.* (1999) found a significant positive association with a less general group of ICD codes excluding acute rheumatic fever, rheumatic heart disease, hypertensive disease, some but not all diseases of arteries and arterioles and diseases of veins and lymphatics. Poloniecki *et al.* (1997) examined a grouping which included many of those excluded above did not find any significant association with ozone concentration. Anderson *et al.* (2001) with a different set of exclusions (stroke, diseases of arteries and arterioles and diseases of veins and lymphatics) also found no significant association. Ballester *et al.* (2001) with a smaller grouping (ischaemic heart disease, arrhythmia and heart failure) again found no significant association. This group of studies is probably too small to come to any conclusions over whether exclusion of certain ICD codes, which might be considered less relevant to an effect of air pollution, helps to increase the strength of the association.

43. No significant associations were found for the following specific cardiovascular outcomes: myocardial infarction, ischaemic heart disease, angina, other ischaemic heart disease, arrhythmia and cerebrovascular disease and in many cases the associations were not even positive. Wong *et al.* (1999) found a stronger positive association between 8-hour ozone concentrations and heart failure. However, Poloniecki *et al.* (1997) found a non significant negative association with heart failure and the effect in the Wong paper may be confounded by particles (see later). Overall, this group of studies is not suggestive of an effect on any specific cardiovascular outcomes but, as with mortality from these outcomes, the number of studies available on each endpoint is probably too small for any firm conclusions to be made.

44. Most studies (Anderson *et al.* (2001), Atkinson *et al.* (1999), Ballester *et al.* (2001), Poloniecki *et al.* (1997) (acute myocardial infarction only) did not find any significant seasonal differences. Atkinson *et al.* (1999) found a slight indication of a greater effect in the highest tertile of temperatures but the association was still not statistically significant. Wong *et al.* (1999) found a stronger effect for all of the cardiovascular outcomes examined in the cool season (under 20°C) (ozone levels are actually a little higher in Hong Kong in the cool season due to clearer skies). Overall, examination of seasonal differences does not alter the interpretation of the studies described in the paragraphs above.

45. There were no consistent findings in the studies that looked at associations in different age groups. Petroeschovsky *et al.* (2001) found no effect in the 5-64 age group and a significant negative association in the over 65 age group. Atkinson *et al.* (1999) also found no significant association in the under 65 age group but found a significant positive association in the over 65 age group. Wong *et al.* (1999) found no difference between these two age group categories.

46. Only two studies looked at multipollutant models for the ozone associations. Poloniecki *et al.* (1997) looked at associations with acute myocardial infarction only (since this had shown significant associations with some other pollutants). In the case of ozone, the association remained non-significant whether or not other pollutants

were added to the model. Wong *et al.* (1999) found that the effect of ozone on cardiovascular admissions (see table for ICD codes) was increased when PM<sub>10</sub> was high (over 45 µg/m<sup>3</sup>) compared with when it was low. There was no difference between high and low nitrogen dioxide. This suggests that the significant positive association found in this study may have been confounded by particles. Ozone and particles were very highly correlated (Pearson’s correlation coefficient 0.88 to 0.99).

47. It is possible that an overall non-significant association might mask an effect at higher levels of ozone. The only study in the table to examine this was the study by (Atkinson *et al.* 1999) (although this did find an overall significant positive association between ozone and cardiovascular admissions). This included bubble plots showing an apparent threshold at around 35 to 40 ppb (see Fig. 8). However, the size of the effect decreased again at about 70 ppb. It should be noted that the number of observations on days above 35-40ppb was much smaller than those below 35 ppb.

48. The above overview has concentrated on studies using 8-hour average ozone concentrations. Although the results could not be quantitatively combined, it is of interest to see whether there is any clear evidence of an effect of ozone using different averaging concentrations. It should be noted that the American and Canadian literature tend to use 1-hour or 24-hour average concentrations of ozone in their studies. In some cases, this would give a larger group of studies on specific outcomes (e.g. 4 more studies on heart failure, some considering several cities in one paper). However, the vast majority of associations found were not significant, some were significantly negative and only a few were significantly positive. These studies are not described in detail here but this can be done at a later stage if the Committee considers it would be helpful.

### Summary and conclusions

49. The summary estimates from the above overview are shown in the table below and the plots compared on the same page in Figures 12 and 13.<sup>12</sup>

Outcome	Summary estimate (% increase per 10 µg/m <sup>3</sup> 8-hour average ozone concentration)	95% confidence interval
All-cause mortality	0.3%	0.2 – 0.4
Respiratory mortality	0.7%	0.3 - 1.2
All circulatory mortality	0.3%	0 – 0.6
Respiratory admissions	0.3%	0 – 0.7
COPD admissions	1.0%	0.2 – 1.9
Asthma admissions 0-14 y	0.3%	-1.3 – 2.0
Asthma admissions 15-64y	1.4%	-0.1 – 3.0
All circulatory admissions	-0.2%	-0.7 – 0.3

50. **Does the Committee agree with the following interim conclusions?** (Further work on publication bias, dose-response relationships, effect modification and other averaging times could potentially modulate these conclusions).

<sup>12</sup> Please note that Figures 12 and 13 can be found in the accompanying paper “june2002comeappaperplots”

- (i) Ozone is associated with all-cause mortality
- (ii) Ozone has a stronger association with respiratory mortality. There are insufficient studies to determine whether one type of respiratory mortality is more important than another.
- (iii) The evidence for an association between ozone and all circulatory mortality is equivocal. This does not rule out the possibility of an association with mortality from more specific cardiovascular outcomes but there are insufficient studies to determine this at present.
- (iv) The association between ozone and all respiratory admissions is only marginally significant. However, it is supported by stronger evidence for an association between ozone and COPD admissions.
- (v) There is no evidence for an association between ozone and asthma admissions in children. The evidence regarding asthma admissions in adults is more difficult to interpret as the studies are inconsistent – the association is greater than for other outcomes but not statistically significant.
- (vi) There are too few studies on ozone and pneumonia and acute respiratory infections for any conclusions to be drawn.
- (vii) There is no evidence for an association between ozone and all circulatory admissions. The number of studies on admissions for more specific cardiovascular outcomes is too small for any conclusions to be drawn.

#### Grouping of ICD codes

51. Some quite specific groupings of ICD codes have been included in the above overview. This is useful for thinking about possible causal mechanisms. However, if the summary estimates generated were to be used for quantification, the Committee might wish to use wider ICD groupings to deal with the possibility of diagnostic cross-coding. It is not proposed to discuss dose-response functions to choose for quantification at this meeting as further work may generate further insights that could affect the Committee's conclusions. **However, any general comments from the Committee about appropriate ICD code groupings would be helpful at this stage.**

#### Adjustment for other pollutants

52. The above summaries are based on results from single pollutant models and an obvious question is whether the results are confounded by the effects of other pollutants. Only a minority of studies addressed this point. Most of them did not find that adjustment for other pollutants affected the results although there were exceptions (e.g. adjustment for TSP in Mexico City and PM<sub>10</sub> in Hong Kong reduced the size of the associations). **Does the Committee consider that the above summary estimates can be regarded as due to ozone rather than other pollutants or is the number of studies addressing this point insufficient to draw this conclusion?**

### Different age groups

53. It is possible that even where there is only a weak association of ozone with a particular outcome for all ages that there is nonetheless a stronger association with particular age groups. For all-cause mortality effects in the elderly were similar or greater than for all ages and for respiratory admissions all studies found a greater effect in the elderly. There were too few studies examining different age groups for cause-specific mortality and no consistent pattern in which age group was more affected for cardiovascular admissions. In other words, the equivocal evidence on all circulatory mortality and admissions is not strengthened by any evidence of stronger effects in particular age groups for these outcomes. **Does the Committee have any comments on the age group results?**

### Seasonal effects

54. Of the studies looking at seasonal effects most found an increased effect in the summer for all-cause mortality. This was not apparent for respiratory mortality (perhaps due to the rarity of respiratory deaths in the summer) and was only found in some of the studies on respiratory admissions. An increased effect in summer was found in most of the studies examining this for cardiovascular mortality, perhaps giving more support to the possibility of an effect on cardiovascular mortality. There were no apparent seasonal differences for ozone and cardiovascular admissions. The description of the seasonal effects in this paper is based on a qualitative comparison with the all year results. The absolute size of the coefficients in summer and winter has not been described nor have the actual summer and winter levels of ozone. The latter may be useful in considering whether the size of the effect depends on the mean concentration of ozone. **What is the Committee's view on the degree to which seasonal associations can give support to an equivocal all year association? Can indirect indications of thresholds be inferred from the seasonal results? What further work on seasonal effects would be helpful?**

### Dose-response relationships

55. A minority of studies examined dose-response relationships within the raw data, often only one study per outcome. Across all the outcomes, only one study (of asthma admissions) found no indication of a threshold (and this is hard to reconcile with the overall inconsistency of the evidence on asthma admissions). All the other studies found insignificant effects at low levels with a 'switch' to effects above concentrations varying from about 20 to 50ppb. (In some cases, effects then decreased again or were barely raised and did not increase further). The proportion of observations that were above the putative threshold was often very low. Interpretation is also complicated by the fact that the potential for confounding by other pollutants may change as the ozone concentrations increase as higher concentrations of ozone are generally found in the summer in a 'photochemical mix'. Nonetheless, it would be hard to justify a firm 'no evidence for a threshold' conclusion on the basis of this data. **What is the Committee's view of this information on dose-response relationships? Are there sufficient studies to come to any overall conclusion? Would the Committee like to consider the data on dose-response functions for other averaging concentrations?**

### Other averaging times and lags

56. As mentioned earlier, a large amount of literature, particularly the American literature is omitted when examining only 8-hour averaging concentrations. **Would the Committee like a further paper describing the evidence on maximum 1 hour concentrations and 24 hour average concentrations? What do the Committee think about ‘scaling’ other averaging times to an expected 8-hour average concentration)?** (Further papers from the APHEA2 study, which use 8-hour average concentrations, can be added as they become available.)

57. The overview in this paper did not differentiate between different lag times. Some of the variation between different studies may have been affected by a different approach to lag times. For example, Poloniecki *et al* (1997) used a lag of 1 selected *a priori*. It may be less likely that a significant effect is found in this situation than with studies which quote any lag that is significant. **Is the Committee content to consider only one lag per study (the ‘selected’ lag defined in the introduction)? Are there any suggestions for how to deal with this issue?**

### Further work

58. The Committee agreed at an earlier meeting that it might be helpful to examine whether the coefficients were dependent on the mean ozone concentration in the study city. This has not yet been done but can be considered for the next meeting. It may also be worth considering whether there is any evidence of publication bias. There may also be other factors contributing to the variation in results (in particular, some early studies only used one city centre monitor, and, due to ozone scavenging by nitric oxide, this may not be representative of population exposure). **Does the Committee have any views on what further work on the time-series data would be helpful?**

59. There is data on panel studies on the St George’s database but this has not yet been analysed. It is planned to do this. A brief overview of the evidence on the long-term effects of exposure to ozone is presented in an accompanying paper. There is also other literature on ozone that will not be on the database. **What are the Committee’s views on what other types of evidence (mechanistic studies? chamber studies?) would be helpful in interpreting the epidemiological evidence and in judging whether there is a threshold for the effects of ozone?**

60. The Committee’s views on this paper will feed into the preparation of a report on ozone by the end of the year. The Committee may wish to start to consider what form this report might take.

Secretariat  
May 2002

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