COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

OZONE – EFFECTS ON LUNG FUNCTION IN PANEL STUDIES

Introduction

1. In the Committee's consideration of whether or not there is a threshold for ozone, the first step for each outcome has been to consider whether there is enough evidence for an effect at ambient concentrations. This paper addresses lung function from panel studies. (Volunteer studies are not considered here). The paper also considers whether an overview of the panel studies lends any support or otherwise to the plausibility of effects on respiratory hospital admissions at low concentrations.

2. The paper uses the St. George's database for an overview of the studies. This database is based on literature searches of the medical literature up to January 2002 and considers only studies containing regression estimates. As mentioned in the previous paper (COMEAP/2002/9a), it is ideal for a meta-analysis to include studies that are as similar as possible. For the time-series studies on deaths and hospital admissions selection was based on an 8-hour averaging time, all ages, all year, single pollutant models and a 'selected lag' (the lag highlighted by the author or the most significant lag). Very few panel studies meet these criteria. The panel studies were most likely to use 1 hour average ozone, examine adults and children separately and to take place in the summer rather than all year. An additional complexity concerns whether to use morning or afternoon/evening lung function measurement. The tables below give preference to afternoon/evening measurements.

3. Panel studies published up to 1990 were considered in the MAAPE report on ozone (Department of Health. Advisory Group on the Medical Aspects of Air Pollution Episodes, 1991). It was concluded that effects on lung function were detectable at concentrations as low as 70 ppb and that the effects tended to be greater than predicted by chamber studies. There was considerable individual variability in the results. It was found that ozone reduced both Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 second (FEV_1) indicating a restrictive effect and the FEV_1/FVC ratio indicating a degree of obstruction.

4. Panel studies published up to 1996 were considered in the COMEAP Quantification Report (Department of Health. Committee on the Medical Effects of Air Pollutants, 1998). This did not alter the above conclusions. It was concluded that it was not appropriate to quantify the effects on lung function because, although studies in other countries demonstrated effects, the only 2 UK studies available (Scarlett *et al*. 1996; Higgins *et al*. 1995) were contradictory.

Overview of results

5. The panel studies are described in detail in the attached paper. This update confirms earlier findings that ambient levels of ozone are associated with decrements in lung function. The best body of evidence is for 1 hour average ozone concentrations and healthy children. The summary estimates for this group are given below. (All meta-analyses showed significant heterogeneity so random effects estimates are given. There was no evidence of publication bias.) All estimates are negative and all except FVC are statistically significant.

Random effects summary estimates for 1 hour average ozone and lung function in healthy children

Lung function measure	Estimates (95% CI)	No. of studies	P value
PEF (Table 2)	-0.35 (-0.667 to –0.030) L/min/10 $\mu g/m^3$	9	P=0.032
FVC (Table 8)	-0.003 (-0.006 to 0.001) L/10 $\mu g/m^3$	7	P=0.099
FEV_1 (Table 13)	-0.002 (-0.003 to –0.001) L/10 $\mu g/m^3$	10	P < 0.001
FEV_1/FVC (Table 18)	-0.063 (-0.103 to –0.021) %/10 $\mu g/m^3$	5	P=0.003

6. For other averaging times and subject groups, the number of studies are smaller and the evidence not as clear. Nonetheless, there is a preponderance of negative slopes of lung function against ozone even if these are not always statistically significant.

Random effects summary estimates for lung function and 1 hour average ozone in cross-sectional groups of children

Lung function measure	Estimate (95% CI)	No. of studies	P value
FVC (Table 10)	-0.003 (-0.006 to 0.000) L/10 $\mu g/m^3$	4	P=0.934
FEV_1(Table 15)	-0.001 (-0.002 to –0.000) L/10 $\mu g/m^3$	4	P=0.037

7. Not all studies examined the effect of other pollutants. Sometimes levels of other pollutants were either very low or they had no effect on lung

function. Where other pollutants did have effects, the ozone effect was usually still maintained although on occasion there was confounding by particles or acidity. The potential confounding effect of other pollutants remains an uncertainty but the overall impression is that there is a genuine independent effect of ozone on lung function.

8. For clarity, and based on chamber study evidence that ozone can have an effect within hours, this overview has preferentially selected lag 0 effects on afternoon lung function where available. However, there is evidence of a 'carry-over' effect from the previous day and also of a depressive effect on baseline lung function for several days after a severe episode.

9. It is not clear from the panel study results that subjects with respiratory disease are more susceptible to the effects of ozone. Studies in Mexico found children with chronic phlegm to be more susceptible and a study in hikers found a greater effect in those with wheeze. Some studies have suggested greater effects in bronchoreactive asthmatics. However, several studies found no difference between subjects with and without respiratory symptoms Nonetheless, there is a wide range of responses to ozone.

Thresholds

10. It is clear that the effects of ozone are not limited only to severe photochemical episodes. In fact, some studies have found significant negative effects on lung function in places where ozone levels never rise above 70 or 80 ppb 8 hour average (Korrick *et al* 1998; Cuijpers *et al* 1995). Further, some studies have continued to find significant effects after omitting days above 60, 50 or even 40 ppb 1 hour average (Spektor *et al* 1988a; Brunekreef *et al* 1994; Brauer *et al* 1996).

11. A few authors have plotted out their results. Two studies found small declines in lung function from at least the lowest quartile (up to around 40 ppb half hour average) (Braun-Fahrlander *et al* 1994, Figure 2) or decile (concentration not specified but full range was only 6 to 27 ppb 24 hour average, Figure 6) (Higgins *et al* 1995). Kinney *et al* 1989 found the pattern of residuals suggested a fairly consistent linear relationship in the range 7-78 ppb I hour average. Thurston *et al* 1997 (Figure 4) fitted a linear response across the range 20 to 160 ppb 1 hour average but as the fit was not very tight (r = -0.43), a curved relationship was probably also possible.

12. Some studies do suggest thresholds. Higgins *et al* 1990 found no significant effect below 120 ppb but this is contradicted by several other studies. Two studies found no effect below 40 ppb (Brunekreef *et al* 1994) and 30 ppb 1 hour average (Brauer *et al* 1996). An issue here is whether the loss of statistical significance was due to the reduction in the number of days with ozone levels this low or due to a lack of effect. Some studies suggest the dose-response relationship is curved with lung function beginning a decline around 40 ppb (8 hour average) (Korrick *et al* 1998, Figure 8) and around 50 or 60 ppb 1 hour average (Castillejos *et al* 1995, Figure 10). In several

studies (e.g. Spektor *et al* 1988a), the size of the estimate diminishes at lower concentrations (80 and 60 ppb 1 hour average), again suggesting a curved relationship. Although the volunteer studies are not reviewed here, an example paper by Larsen *et al* 1991 is provided (see COMEAP/2002/12B) which suggests a log normal relationship between ozone exposure and FEV_1.

13. Even if effects on lung function are seen down to quite low ozone concentrations, it also needs to be considered whether the size of the effect is meaningful. This needs to address both the size of the effect in general and the possibility of small numbers of individuals with greater effects.

Conclusions

14. The Committee is invited to discuss the following questions:

(i) Does the Committee agree that the updated evidence still supports an effect of ozone independent of other pollutants on each of the lung function measures considered?

(ii) Are the summary estimates given above appropriate (i.e. choosing 1 hour average ozone and healthy children on the basis of an adequate number of studies and not combining these with cross-sectional studies or studies with half hour averaging times for example)?

(iii) In 1998, the Committee did not wish to quantify these effects in the UK on the basis that the only 2 UK studies available contradicted each other. There are no new UK studies. Does this remain the Committee’s view? (There is also an issue of the degree to which the effects are of any clinical significance).

(iv) To what extent do these studies add plausibility to the effects on deaths and hospital admissions in the time-series studies? Are the effects on lung function sufficiently marked to result in admission to hospital amongst susceptible groups? (There is one study in COPD patients (Linn *et al* 1999) which did not find any effects but 24 hour average ozone concentrations may not be the best metric).

15. If the Committee do believe that the lung function findings have relevance to deaths and hospital admissions, then an examination of the threshold issue in lung function studies may assist in determining the plausibility of a threshold in the time-series studies. More lung function studies have examined the possibility of thresholds of effect. The Committee may wish to discuss the following aspects:

(i) What criteria should apply for accepting the existence of a threshold? For example, is a single study with a statistically significant negative effect below a putative threshold sufficient to dismiss this threshold even if the effect is small and only occurs in exercising subjects?

(ii) Does the Committee agree that there is evidence for an effect down to at least 40 ppb (1 hour average)?

(iii) What is the Committee's view of the evidence for effects below 40 ppb? How much weight can be given to studies which find no effects below 30 or 40 ppb when the number of datapoints available may be restricted?

(iv) Does the Committee believe the evidence is more consistent with a curved or linear dose-response relationship? (It is accepted that these may not be statistically distinguishable).

(v) The above suggestions are based on the existence of any statistically significant negative effect even if small. Does the Committee consider a minimum size of effect on lung function could be specified (e.g. a minimum decline of 10% translated into litres per 10 $\mu g/m^3$) such that only effects greater than this would 'count' in determining a threshold?

(vi) Has the Committee any suggestions for other ways to consider whether the evidence suggests a threshold?

16. It is unlikely that there will be a clear cut answer as to whether there is a threshold or not but the Committee's description of the strength of the evidence for effects on lung function in various concentration ranges would be helpful. The Committee's comments on this paper will contribute to an overview paper for the next meeting drawing together the panel study, time series and mechanistic evidence.

Secretariat
October 2002

Annex. 1. Peak expiratory flow (rate) PEF(R)

1.1 8-hour average ozone

1. Only 3 studies examined the effect of 8-hour average ozone on peak expiratory flow and none of the estimates were for all year or all ages. The results are summarised in Table 1. There are only 4 estimates in total (3 for children (2 cross-sectional – children both with and without respiratory symptoms) and 1 for adults) and within each category the estimates differ by season. A summary estimate for these studies is therefore probably not appropriate. In healthy children, there was a significant negative estimate and in 2 cross-sectional studies of children there was one significant negative estimate and one borderline-significant negative estimate. The adult estimate was not statistically significant. So there is a suggestion of a negative effect (none of the estimates are significantly positive) but the results are rather inconsistent.

2. Comparison of associations between 8 hour average ozone and 1 hour average ozone within the same studies does not lead to a clear conclusion as to whether one is more valid than the other. Spektor *et al*. (1991), found a reduction in peak expiratory flow related to a "morning to afternoon" average although the averaging time was not exactly 8 hours. These authors considered that there was both a shorter (previous hour) and a longer term element (earlier in the day or the previous day) to the ozone effect although the effect on peak expiratory flow appeared to have more of a rapidly reversible component than other lung function measures. There are a greater number of studies on one hour average ozone and they are more consistent (see below).

3. Berry *et al*. (1991) found no effect of acid aerosol on PEF. Levels of other pollutants were low in the study by Cuijpers *et al*. (1995). So none of the authors considered confounding by other pollutants was a problem. None of the studies discussed thresholds for lung function changes directly. It is notable that the study by Cuijpers *et al*. (1995) demonstrated a significant negative effect on peak expiratory flow at only moderate levels of ozone (an episode period of 25 to 82 ppb compared with a baseline period of 1 to 28 ppb).

4. Korrick *et al*. (1998) studied the effect of ozone averaged over the time of a hike (mean 8 hours range 2-12 hours) on the <u>change</u> in PEF after the hike compared with before. Ozone levels averaged in this way ranged from 21 to 74 ppb. Ozone levels had a negative effect on the PEF change which was steeper above 40 ppb than below but the effect was not statistically significant. 71 out of 530 hikers had a greater than 10% decline in PEF. Adjustment for $PM_{2.5}$ and acidity increased the negative effect but it was still not statistically significant. Analogous results were found for forced expiratory flow between 25 and 75% of forced vital capacity (FEF_{25-75}). In this case, after adjustment for covariates, ozone was significantly associated with more than 10% declines in FEF_{25-75} (odds ratio 3.67 CI 1.25 –10.78 per 50 ppb increase

Table 1 Peak expiratory flow and 8 hour average ozone concentrations

Author (date)	Age group	Subjects	Season	Ozone mean (8 h)	Ozone range (8h)	Estimate l/min/10 ìg/m^3	Lower CI	Upper CI	Notes
(Berry *et al*. 1991)	Children	Healthy	Summer	Not given	6 days > 100 ppb; max 131 ppb	-0.71 (lag 0, afternoon)	-1.55	-0.14	Suburban New Jersey, severe ozone episode may have changed baseline
{Cuijpers *et al*. 1995}	Children	Cross-sectional	Summer	Not given	25 to 82 ppb	-4.51 (lag 1)	-6.67	-2.36	Netherlands
(Declercq and Macquet, 2000)	Children	Cross-sectional	Spring (Apr to Jun)	43 ppb	Range 22 to 83 ppb, only 6 days above 60 ppb	-0.64 (lag 1,evening)	-1.28	0.01	Northern France
(Berry *et al*. 1991)	Adult	Healthy	Summer	Not given	6 days > 100 ppb; max 131 ppb	0.18 (lag 0, afternoon)	-0.54	0.90	Suburban New Jersey, severe ozone episode at start may have changed baseline

in hike mean ozone). A cross-sectional study by Hiltermann *et al* 1988 examined the morning to evening change in PEF among asthmatic patients exposed to ozone. Mean 8 hour average ozone was 40 ppb with a range from 6 to 93 ppb and exceeded 60 ppb on 16 occasions. A negative but non-significant effect on the change in PEF was found. This finding was not affected when patients were stratified by asthma severity suggesting that some patients had some unrelated inherent sensitivity to ozone. Just *et al.* (2002) found daily PEF variability increased by 2.6% for a 10 $\mu g/m^3$ increase in ozone (lag 0-2) in a group of asthmatic children. This effect was doubled, but was not significant on days when no steroids were used. Black smoke, PM_{13} and nitrogen dioxide had no effect. The mean ozone level was 29 ppb with a range from 5 to 60 ppb.

1.2 1-hour average ozone, healthy children

5. The majority of the studies on peak expiratory flow in healthy children examined associations with 1 hour average ozone. These are summarised in Table 2. This includes a reanalysis (Kinney *et al*. 1996b) of six previous studies (Spektor *et al*. 1988a; Spektor *et al*. 1991; Higgins *et al*. 1990b; Avol *et al*. 1990; Raizenne *et al*. 1989; Burnett *et al* 1990). The effect on peak expiratory flow across these studies was not significant but a significant reduction in peak expiratory flow was found when one study (Avol *et al*. 1990) was excluded. This study was thought to have been confounded by a training.effect (PEF increased with time at the summer camp and ozone levels happened to be higher in the last week). Three further studies (Berry *et al*. 1991; Hoek *et al*. 1993a; Lioy *et al*. 1985) have examined the effect of summer ozone concentrations on peak expiratory flow. All studies found that 1 hour average ozone was associated with a decrement in peak expiratory flow but only one was statistically significant. Hoek *et al* 1993 was concerned about the high collinearity of ozone and temperature effects although the coefficient was adjusted for temperature. This collinearity was higher than found in other studies. An all year study by Krzyzanowski *et al*. (1992) found an effect on noon PEF. The random effects estimate was –0.360 (-0.667 to –0.030) L/min/10 $\mu g/m^3$ P=0.032 – a statistically significant decrease.

6. Only one of the studies (Higgins *et al*. 1990b) used a multipollutant model. This showed a greater negative effect of 1 hour average ozone on PEF which became statistically significant with the inclusion of coarse and fine particles in the model. Coarse and fine particles were found to be associated with increases in peak expiratory flow. The same study also measured sulphur dioxide and nitrogen dioxide. The latter was closely correlated with ozone levels but was regarded as an implausible confounder because levels were so low (mean 11 ppb 1 hour average range 0 to 40 ppb). Sulphur dioxide levels were also very low. Krzyzanowski *et al*. (1992) found PEF was not related to $PM_{10.}$ Other studies found no effect of H^+ (Berry *et al*. 1991; Lioy *et al*. 1985; Spektor *et al*. 1988a; Spektor *et al*. 1991), sulphate or nitrate (Lioy *et al*. 1985) or PM_{15} (Spektor *et al*. 1988a) on PEF. In other words, none of these studies could dismiss the effect of ozone as being due to some other pollutant.

Table 2 Peak expiratory flow and 1 hour average ozone concentrations (healthy children)

Author (date)	Season, time of day	Ozone (1 hr mean)	Ozone (1 hr range)	Estimate l/min/10 ìg/m^3	Lower CI	Higher CI	Notes
(Kinney *et al*. 1996a)	Summer, afternoon	53 ppb	40 – 113 ppb	-0.60	-1.07	-0.13	New Jersey
"	Summer, afternoon	59 ppb	Max 95 ppb	-0.03	-0.23	-0.17	Ontario
"	Summer, afternoon	71ppb	Max 143 ppb	-0.80	-1.57	-0.02	Ontario
"	Summer, afternoon	123 ppb	20 – 245 ppb	-0.33	-0.79	0.13	California
"	Summer, afternoon	94 ppb	Max 161 ppb	0.65	0.24	1.06	California
(Berry *et al*. 1991)	Summer, afternoon	Not given	8 days above 120 ppb; max 204 ppb	-0.30	-0.99	0.38	New Jersey
(Lioy *et al*. 1985)	Summer, Afternoon	Not given	20 to 186 ppb	-0.90	-1.38	-0.41	New Jersey
(Hoek *et al*. 1993a)	Summer, Afternoon	Not given	25- 118 ppb	-0.91	-2.05	0.23	Netherlands, moderately exercising children
(Krzyzanowski *et al*. 1992)	All year, noon	55 ppb	15 to 92 ppb	-0.60	-1.21	0.02	Arizona

(All estimates are for lag 0)

7. Several of the studies examined whether the results differed at lower ozone concentrations. Krzyzanowski *et al*. (1992) found that the effect on PEF in March (when ozone levels first started to go above 50 ppb) were no different than in other seasons. Further studies examining the possibility of thresholds are shown in Table 3. A variety of approaches were considered and a selection of different ozone levels involved. Nonetheless, it can be seen that (a) estimates for lower ozone levels are mostly smaller than for higher ozone levels (b) the estimates are nonetheless still negative and (c) several estimates at lower ozone levels are still statistically significant including one for ozone levels below 60 ppb. This suggests that, if there is a threshold being approached, then it is below 60 ppb. In addition, as the table gives mean slopes, individual children can have more marked negative slopes (Figure 1 from Spektor *et al* 1988a).

Table 3 Studies of peak expiratory flow in healthy children (1 hour average ozone) which examined the possibility of a threshold

Author/date	Cut off or omission specification	Estimate (SE) in ml/sec/ppb	Estimate (SE) in ml/sec/ppb
Lioy *et al*. (1985)	With and without an ozone episode period (135 to 186 ppb) and some days following it	- 1.92 (1.04) (without episode)	-2.99 (0.82)# (with episode)
Higgins *et al*. (1990b)	Hourly ozone above 120 ppb in preceding 6 hours	- 0.68 (2.03) (days below 120 ppb)	-4.10 (1.32)# (days above 120 ppb)
Spektor *et al*. (1991)	Daily 1 hour maximum above 120 ppb	-2.71 (0.73)# (excluding days above 120 ppb)	-2.67 (0.67)# (including days above 120 ppb)
Spektor *et al*. (1988a)	Dataset truncated at 80 ppb ozone I hour average	-3.05 (1.57) (excluding days above 80 ppb) NB borderline significant	-6.78 (0.73)# (including days above 80 ppb)
Spektor *et al*. (1988a)	Dataset truncated at 60 ppb ozone I hour average	-3.91 (1.71)* (excluding days above 60 ppb)	-6.78 (0.73)* (including days above 60 ppb)

* $P<0.05$
# $P<0.01$

8. Spektor *et al*. (1991) found that the <u>change</u> in PEFR from morning to afternoon was also negatively associated with 1 hour average ozone concentrations but Hoek *et al* 1993 found no significant association of the change in PEFR before and after sports with ozone concentration. Spektor *et*

al. (1988a) and Spektor *et al*. (1991) also found a significant negative association with FEF_{25-75} and, for the latter study, with change in FEF_{25-75}.

9. In summary, there is evidence that 1hour average ozone concentrations are associated with decrements in peak expiratory flow. The summary estimate is –0.36 L/min/10 $\mu g/m^3$ and is statistically significant. However, the change is small. This effect does not appear to be confounded by other pollutants when these are examined. There is no clear evidence of a threshold, at least above 60 ppb, but in some cases slopes are reduced at lower concentrations.

1.3 1 hour average ozone concentrations (cross-sectional studies in children)

10. There is only one cross-sectional study using 1 hour average ozone (range 22 to 90 ppb). Declercq and Macquet (2000) found a negative but non-significant association with peak expiratory flow for both morning (lag 0) and evening (lag 1). Studnicka *et al*. (1995) found a negative effect of daily maximum half hour mean ozone on PEF only during an episode period (mean 56 ppb, range 41-70 ppb) and not during two other periods (mean 45 ppb, range 30-52 ppb and mean 47 ppb, range 35-60 ppb). There was a larger difference in acidity between the episode and non-episode period, which the authors considered to be dominating the effect.

11. A study by (Braun-Fährlander *et al*. 1994) found a significant negative association of half hour mean ozone (range 20 to 77 ppb) with change in peak expiratory flow before and after exercise. Greater reductions in PEF were seen for the 2nd, 3rd and 4th quartiles of ozone concentrations compared with the first quartile (Figure 2). As the mid point of the 2nd quartile was around 90 $\mu g/m^3$ (45 ppb), this suggests an effect down to quite low ozone levels. A wide range of responses was found in individual children (Figure 3).

1.4 1 hour average ozone concentrations (asthmatic children)

12. Three studies examined the effect of 1 hour average ozone on peak expiratory flow in asthmatic children. These are shown in Table 4. Negative effects were found although these were not necessarily significant.

Table 4 Peak expiratory flow and 1 hour average ozone concentrations (asthmatic children)

Author (date)	Season, time of day	Mean ozone	Range of ozone	Estimate (l/min/10 $\mu g/m^3$)	Lower CI	Upper CI	Notes
Romieu *et al*. (1996a)	All year, evening	190 ppb	40 to 370 ppb	Omitted (Central estimate not in middle of Confidence Intervals)			Mexico city
Romieu *et al*. (1996b)	All year, evening	196 ppb	40 to 390 ppb	-0.18	-0.36	-0.001	Mexico city
Krzyzanowski *et al*. (1992)	All year, noon	55 ppb	15 to 92 ppb	-1.55	-3.30	0.20	Arizona

13. Romieu *et al*. (1996a) found that the effect became non-significant after adjustment for PM_{10} whereas Romieu *et al*. (1997) found the effect increased slightly after adjustment for PM_{10}.

14. The study by Krzyzanowski *et al*. (1992) found a greater effect in asthmatics than in healthy children but the effect was not significant. It was suggested this might be due to the increased baseline variability in PEF in asthmatics.

15. Thurston *et al*. (1997) examined the difference between the pm and am peak expiratory flow according to ozone concentration in asthmatic children. The afternoon improvement was about 20 to 30 L/min at low ozone concentrations and 10 to 20 L/min at high ozone concentrations. The mean 1 hour maximum ozone was 84 ppb with a minimum of 20 ppb and a maximum of 160 ppb. Regression of individual children's daily change in PEF gave a coefficient of –1.1 L/min per 10 $\mu g/m^3$ (95% CI –1.96 to –0.23) after adjustment for temperature. This was unaffected by adjustment for sulphate and acidity was unrelated to PEF. The result was similar to that found in healthy children although it was pointed out that the asthmatic children were taking part in less strenuous activities. The results were plotted against ozone concentration (Figure 4). A linear dose-response could be fitted (r=-0.43) but a curved response could probably also be fitted to the data.

1.5 1 hour average ozone concentration (adults)

16. None of the effects of 1 hour ozone on PEF in adults were significant although the estimates were all negative. The effects were less than those in children examined in the same studies. This was not due to differences in activity levels ((Berry *et al*. 1991)). The study by Berry did not find any effect of acid aerosol on PEF.

Table 5 1 hour ozone concentrations and peak expiratory flow (adults)

Author (date)	Season, time of day	Mean ozone	Ozone range	Estimate (l/min/10 $\mu g/m^3$	Lower CI	Upper CI	Notes
Berry *et al*. (1991)	Summer pm	Not given	8 days > 120 ppb; max 204 ppb	0.29	-0.28	0.87	NJ YMCA camp workers
Berry *et al*. (1991)	Summer pm	Not given	8 days > 120 ppb; max 204 ppb	0.49	-0.82	1.80	NJ'Rec' camp workers
Krzyzanowski *et al*. (1992)	All year, evening	55 ppb	15 to 92 ppb	-0.19	-0.49	0.12	Arizona

17. Spektor *et al*. (1988b) compared the pre- and post-exercise PEF difference with the mean ozone concentration during the exercise period of a sample of non-smoking adults. The exercise period had a mean of 29 minutes and a range from 15 to 55 minutes. Ozone exposures varied from

under 20 ppb to over 120 ppb but around 70% of exposures were between 20 and 60 ppb. The coefficient per 10 $\mu g/m^3$ was –2.76 L/min (95% CI –3.76, -1.77). The coefficient was reduced in size but remained significant after truncation of the data at 80 ppb. Effects were greatest in the intermediate minute ventilation group (60-100 L). Acid aerosol levels had no effect on the ozone effect. Pre-exercise PEF was unrelated to the previous days ozone exposure.

18. Brunekreef *et al*. (1994) found similar results in a study of similar design in cyclists. Ozone levels were lower (an 8 hour average of 50 ppb was only exceeded once) and the mean ozone concentration during exercise was 43.5 ppb (range 13 to 97.5 ppb). Exercise duration was longer (mean 75 minutes; range 10 to 145 minutes). Levels of sulphur dioxide and nitrogen dioxide were low. The coefficient per 10 $\mu g/m^3$ was –2.36 L/min (95% CI –3.62, -1.10). Truncation at 60 and 50 ppb gave similar coefficients but after truncation at 40 ppb, many lung function coefficients were close to zero and insignificant. Coefficients were reduced later in the ozone season. Of 275 observations only two gave differences in PEF greater than 10%.

1.6 1 hour average ozone concentration and peak expiratory flow (adult asthmatics)

19. Krzyzanowski *et al*. (1992) only found an effect in adult asthmatics when the amount of time spent out of doors was included in the model. There was also an effect of ozone on the 4 preceding days suggesting a tendency for a longer lasting effect in asthmatics.

1.7 24 hour, 15 hour and 12 hour average ozone concentration and peak expiratory flow

20. Studies using ozone concentrations averaged over more than 8 hours are summarised in Table 6. As with 8-hour average concentrations, the studies differ in the subject groups analysed so the estimates cannot be combined. Gold *et al*. (1999) found a negative but non-significant association with afternoon peak flow at lag 0 but found a much larger and significant estimate (-2.9 L/min per 10 $\mu g/m^3$) for a cumulative lag from day 0 to 8. Both ozone and $PM_{2.5}$ had effects on afternoon PEF but, in multipollutant models, ozone dominated and had a shorter lag period.

21. Naeher *et al*. (1999) also found a negative non-significant association with evening PEF. A negative significant association was found with a 3 day average. Ozone was the only air pollution measure that remained significant as an independent variable with evening PEF as the dependent variable. There was a significant trend of 5 day average ozone and morning PEF across quartiles (5 ppb steps from under 30ppb to over 40 ppb 5 day average) (Figure 5).

22. Higgins *et al*. (1995) studied the effect of 24 hour average ozone in the UK. An negative effect on minimum PEF of borderline significance was found but the effect was doubled in a sub group of bronchoreactive asthmatics. The

effect was adjusted for levels of nitrogen dioxide and sulphur dioxide. In the bronchoreactive subgroup, a consistent decrease in PEF ratio (minimum daily PEF/subjects best PEF) was found across all deciles of ozone concentration although the error bars were relatively large (Figure 6).

23. Jalaludin *et al* 2000 found adjustment for particles and nitrogen dioxide had no marked effect on the ozone coefficient. A steep dose-response function was found for bronchoreactive asthmatics but not other asthmatics (Figure 7). An increase in ozone equivalent to the interquartile range (8ppb) gave a 20% increase in prevalence of children with PEF values more than 20% below the median. Neas *et al*. (1999), in a group of urban children, also found effects of PM_{10}, sulphate and $PM_{2.5}$ but not acidity or coarse particles in the same study. The ozone coefficient was not controlled for these potential confounders. A greater effect was found with 5 day average ozone. Neas *et al*. (1996) found no association of 12 hour average ozone with peak expiratory flow. The coefficient was adusted for spore count as well as the more routine control for temperature but there was only a weak inverse correlation of ozone and spore counts. Weak associations with particle acidity and mass were found in the same study. Neas *et al.* (1995) found a significant negative effect on mean deviation in PEF which became stronger when weighted by proportion of hours spent outdoors. However, the association became non-significant when adjusted for particle strong-acidity.

Table 6 24 hour, 15 hour and 12 hour average ozone concentrations and peak expiratory flow

Author (date)	Subjects	Season, time of day, lag and averaging time	Mean ozone (24 hr)	Ozone range	Estimate L/min/10 μg/m^3	Lower CI	Upper CI	Notes
Gold *et al*. (1999)	Children (cross sectional)	All year, afternoon, lag 0, 24 hr	52 ppb	8-103 ppb	-0.4	-0.89	0.09	Mexico city
Naeher *et al*. (1999)	Adult women (new mothers)	Summer, afternoon, lag 1, 24 hr	35 ppb	17-88 ppb	-0.27	-0.70	0.16	Virginia, asthmatics included
Higgins *et al*. (1995)	Adults with asthma/COPD	Summer, minimum of PEFs at 2 hour intervals, lag 0, 24 hr	Not given	Max 27 ppb, min (from graph) approx 6ppb	-0.14	-0.27	-0.01	Widnes/Runcorn Greater effect in bronchoreactive asthmatics
Jalaludin *et al*. (2000)	Children (asthmatic)	All year, afternoon, lag 0, 15 hr	12 ppb	Max 43ppb	-0.46	-0.87	-0.05	Sydney, greater effect in bronchoreactive asthmatics
Neas et al. (1995)	Children (cross-sectional)	Summer, evening, lag 0, 12 hour	50 ppb	Max 88 ppb IQR (day or night 12 hour 30 ppb)	-0.37	-0.74	-0.01	Uniontown, Pennsylvania, asthmatics excl., resp. symptoms incl.
Neas *et al*. (1999)	Children (cross-sectional)	Summer, evening, lag 0, 12 hr	56,57 ppb	Interquartile range 20,22ppb	-0.28	-0.71	0.16	2 summer camps in Philadelphia, asthmatics included.

Neas *et al*. (1996)	Children (cross-sectional)	Summer, evening, lag 0, 12 hr	55 ppb	IQR 22 ppb, upper decile 75ppb, max 92ppb	0.10	-0.24	0.44	Pennsylvania, children with asthma medication excluded, resp. symptoms included

Table 7 Forced vital capacity and 8 hour average ozone concentrations

Author (date)	Subjects	Season	Ozone mean (8 h)	Ozone range (8h)	Estimate l/10 ìg/m^3	Lower CI	Upper CI	Notes
Berry *et al*. (1991)	Healthy children	Summer, lag 0	Not given	6 days > 100 ppb; max 131 ppb	0.0065	0.0016	0.0113	Suburban New Jersey summer camp, severe ozone episode at start may have changed baseline
Scarlett 1996	Children, cross-sectional	Summer, lag 1	51 ppb	7 to 128 ppb	0.0003	-0.0004	0.0011	Surrey schoolchildren
Cuijpers *et al*. (1995)	Children, cross-sectional	Summer, lag 1	Not given	25 to 82 ppb	-0.01	-0.0197	0.0024	Netherlands, schoolchildren
Berry *et al*. (1991)	Healthy adults	Summer, lag 0	Not given	6 days > 100 ppb; max 131 ppb	0.0014	-0.0084	0.0111	Suburban New Jersey summer camp, severe ozone episode at start may have changed baseline

2. Forced vital capacity (FVC)

2.1 8-hour average ozone and forced vital capacity

24. As with peak expiratory flow, there are few studies using 8-hour average ozone concentrations. The studies are shown in Table 7. No significant decrease was found in any of the studies. Berry *et al* (1991) found no effect of acid aerosol on FVC so this was not a confounder. Scarlett *et al* (1996) found that ozone had no effect on FVC. PM_{10} but not NO_2 had effects on FVC in the same study. None of the studies looked at thresholds.

25. The study of hikers (Korrick *et al* 1998) described in paragraph 6, found a greater percentage reduction in FVC before and after the hike with increasing ozone concentrations although this became non-significant after adjustment for $PM_{2.5}$ and acidity. A linear model was an acceptable description of the dose-response relationship but a quintile analysis and nonparametric smoothing suggested non-linearity with the steepest changes occurring above 40 ppb (Figure 8). The deviations from linearity were not significant in generalised additive models but in adjusted piecewise models the estimated effects above and below 40 ppb were significantly different. Adjustment for other pollutants still reduced the estimate above 40 ppb but to a lesser extent than below 40 ppb. Only 8 out of 530 hikers had greater than 10% declines in FVC (ozone levels did not exceed 70 ppb). The effect on the decline in FVC was not significantly different in those with and without asthma and wheeze but there was a greater effect in never smokers than former smokers.

2.2 1-hour average ozone and forced vital capacity (healthy children)

26. Studies of FVC and 1 hour average ozone concentrations are shown in table 8. The majority of studies show a negative effect and most of these are statistically significant. The overall random effects summary estimate is -0.003 (-0.006 to 0.001) L/10μg/m^3 (P=0.099) – a decline of borderline statistical significance. Hoek *et al*. (1993b) noted that there was less effect on FVC (2.1% decrease at 120 ppb) than on PEF (8.8% decrease at 120 ppb). Lippmann *et al*. (1983) noted that the range of effects among different children ranged from +3-4 ml/ppb to –7 ml/ppb or more. Of the papers that examined other pollutants, there was either no effect of the other pollutant on FVC or control for the other pollutant did not affect the ozone coefficient.

27. Studies that examined thresholds are summarised in Table 9. With the exception of the study by Higgins *et al* 1990, most studies continued to find effects at lower concentrations, including at less than 60 ppb. Spektor *et al* (1991) also found effects on the change in FVC (from morning to afternoon). This was still apparent below 120 ppb. Castillejos *et al*. (1995) examined the change in FVC before and after exercise and found that the mean percentage decrement in FVC was only significant for the highest ozone quintile (182 to 365 ppb). However, a loess smoothed curve began to drop gradually from about 50 or 60 ppb (Figure 9).

Table 8 Forced vital capacity and 1 hour average ozone concentrations (healthy children)

Author (date)	Season, time of day	Ozone (1 hr mean)	Ozone (1 hr range)	Estimate l/10 $\mu g/m^3$	Lower CI	Higher CI	Notes
Spektor *et al*. (1988a)	Summer, afternoon, lag 0	53 ppb	40 – 113 ppb	-0.0052	-0.0075	-0.0028	Summer camp, New Jersey
Spektor *et al*. (1991)	Summer, afternoon, lag 0	Not given	5 days above 120 ppb; (from graph) max 150ppb, min 40 ppb	-0.0119	-0.015	-0.0088	Summer camp, New Jersey
Lippmann *et al*. (1983)	Summer, afternoon, lag 0	Not given	48-122 ppb	-0.0053	-0.0078	-0.0028	Summer camp, Pennsylvania
Higgins *et al*. (1990a)	Summer, afternoon	123 ppb	20 – 245 ppb	-0.0022	-0.0037	-0.0007	Summer camp, California
Hoek *et al*. (1993b)	Spring/ Summer, morning	55,58,64 ppb	4,13,22 ppb to 107,114,118 ppb	0.0024	-0.0049	0.0001	Schoolchildren in Enkhuizen, Zeist, Deurne, The Netherlands
Berry *et al*. (1991)	Summer, afternoon, lag 0	Not given	8 days above 120 ppb; max 204 ppb	0.0042	0.0004	0.0079	Summer camp, New Jersey
Lioy *et al*. (1985)	Summer, Afternoon, lag 0	Not given	20 to 186 ppb	-0.0006	-0.0028	0.0016	Summer camp, New Jersey

Table 9 Studies of forced vital capacity in healthy children (1 hour average ozone) which examined the possibility of a threshold

Author/date	Cut off or omission specification	Estimate (SE) in ml/ppb	Estimate (SE) in ml/ppb
Lioy *et al*. (1985)	With and without an ozone episode period (135 to 186 ppb) and some days following it	- 0.17 (0.35) (without episode)	-0.12 (0.22) (with episode)
Higgins *et al*. (1990b)	Hourly ozone above 120 ppb in preceding 6 hours	0.23 (0.45) (days below 120 ppb)	-0.88 (0.44)*(days above 120 ppb)
Spektor *et al*. (1991)	Daily 1 hour maximum above 120 ppb	-2.58 (0.38)* (excluding days above 120 ppb)	-2.65 (0.39)* (including days above 120 ppb)
Spektor *et al*. (1988a)	Dataset truncated at 80 ppb ozone I hour average	-1.00 (0.44)* (excluding days above 80 ppb)	-1.03 (0.24)* (including days above 80 ppb)
Spektor *et al*. (1988a)	Dataset truncated at 60 ppb ozone I hour average	-1.75 (0.40)* (excluding days above 60 ppb)	-1.03 (0.24)* (including days above 60 ppb)

** P<0.05*

2.3 1 hour average ozone and forced vital capacity (cross-sectional studies in children)

28. Cross-sectional studies examining the effect of 1 hour average ozone on FVC are summarised in Table 10. <u>The random effects summary estimate was 0.000 (-0.001 to 0.001 (P=0.934) – no statistically significant evidence for a decline although the number of studies is small</u>. Two of the studies showed significant negative results. Hoek *et al*. (1993b) found no effect of adjustment for NO_2, SO_2 and PM_{10}. Kinney *et al*. (1989) noted that the pattern of residuals suggested a fairly consistent linear relationship across 1 hour maximum ozone concentrations.

Table 10 1 hour average ozone and FVC (cross-sectional studies in children)

Author (date)	Season Time of day, lag	Mean ozone	Ozone range	Estimate l/10 $\mu g/m^3$	Lower CI	Upper CI	Notes
Scarlett *et al* 1996	Summer, morning, lag 1	60 ppb	12-159 ppb	0.0006	-0.0001	.0012	Surrey school children
Castillejos *et al*. (1992)	Jan-June Morning, lag 1	182ppb (max 1hr)	51-287 ppb	-0.0005	-0.0009	-0.0001	Mexico city school children
Kinney *et al* (1989)	Spring, morning, lag 0	Not given	7-78ppb (max 1 hr)	-0.0046	-0.0081	-0.0011	Tenessee school children
Hoek *et al*. (1993b)	Spring/ Summer, morning	55,58,64 ppb	4,13,22 ppb to 107,114,118 ppb	0.0024	-0.0049	0.0001	Schoolchildren in Enkhuizen, Zeist, Deurne, The Netherlands

29. Studnicka *et al* (1995) found a non-significant decrease in FVC for daily half hour maximum ozone at a summer camp in Austria. However, a strongly significant decrease in FVC (ten fold greater than across all panels) was found during an episode period (mean 56 ppb, range 41-70 ppb) and not during two other periods (mean 45 ppb, range 30-52 ppb and mean 47 ppb range 35-60 ppb). Acidity was much higher in the episode period than the non-episode period and the authors believed this to be the dominant factor. However, the association between H^+ and decreased FVC in the episode period was not significant. PM_{10} (also increased during the episode) was a more plausible confounder.

30. Braunfahrlander *et al* 1994 found an effect of half-hour average ozone on the change in FVC before and after 10 minutes of intense exercise (-0.0067 litres per 10 $\mu g/m^3$ (-0.0129 to –0.0005). Significant heterogeneity in different children's responses was found.

2.4 1 hour average ozone and forced vital capacity (children with respiratory symptoms)

31. There are no studies in a group of exclusively asthmatic children or just children with respiratory symptoms. However, some of the studies described above included sub-group analyses of children with and without respiratory symptoms. Hoek *et al* (1993b), Studnicka *et al* (1995) and Scarlett *et al* (1996) found no differences in effect between children with and without respiratory symptoms, with and without asthma medication and with and without wheeze respectively. However, Castillejos *et al* (1992) found greater effects in Mexican children with chronic phlegm but not in Mexican children with wheeze.

2.5 1 hour average ozone and forced vital capacity (adults)

32. Studies of FVC in adults are shown in Table 11. Neither group of subjects in Berry *et al* (1991) showed a negative effect. However, the group of farm workers studied by Brauer *et al* (1996) did show a significant negative effect, probably because this group was more active. In this group, the association remained after removing days above 40 ppb but the effect became non-significant after removing days above 30 ppb. The effect on the morning to afternoon change in FVC was negative but non-significant. However, two other studies (Spektor *et al* 1988 and Brunekreef *et al* 1994) examining the change in FVC before and after exercise did find significant decreases (-0.0104 and –0.0113 litres per 10 $\mu g/m^3$ respectively). In the former study, truncation at 80 ppb reduced the size of the coefficient but it remained significant. In the latter study, truncation at 60ppb and 50ppb gave similar coefficients but after truncation at 40 ppb many lung function coefficients were close to zero and insignificant.

33. Brauer *et al* (1996) found no difference in response for subjects with or without hayfever/allergy and Brunekreef *et al* (1994) found no difference in response for subjects with or without chronic respiratory symptoms.

Table 11 1 hour average ozone and FVC (adults)

Author	Season, time of day	Mean ozone	Ozone range	Estimate l/10 µg/m^3	Lower CI	Upper CI	Notes
Berry *et al* (1991)	Summer, pm	Not given	8 days > 120 ppb; max 204 ppb	0.0042	0.0012	0.0072	NJ Y-camp workers
Berry *et al* (1991)	Summer, pm	Not given	8 days > 120 ppb; max 204 ppb	0.00001	-0.0067	0.0067	NJ Rec-camp workers
Brauer *et al* (1996)	Summer, pm	40 ppb (1 hr max)	13-84 ppb	-0.027	-0.033	-0.021	Farm workers mean age 44 yrs range 10 to 69

2.6 24 hour average ozone concentration and FVC

34. Linn *et al* (1996) examined lung function in Los Angeles schoolchildren. 24 hour average ozone had a mean of 23 ppb and a range from 1-16 ppb. A non-significant decrease in afternoon FVC (-0.001 litres per 10 µg/m^3, CI –0.004 to 0.002) was found which became less marked after adjustment for NO_2 and PM_5. A subset of children had personal ozone badges – these suggested lower exposures (mean 5 ppb range 1-16 ppb) but were correlated with the ambient monitoring station (r = 0.61). No information on the correlation between 24 hour average ozone and 8-hour or 1-hour averages was provided. It should be noted that this correlation is not necessarily close as high ozone days can have particularly low ozone levels at night (R. Derwent, personal communication).

35. Linn *et al* (1999) examined lung function in COPD patients in Los Angeles. 24 hour average ozone had a mean of 13 ppb and a range from 0-34 ppb. No effect on FVC was found.

3. Forced expiratory volume in 1 second (FEV_1)

3.1 8-hour average ozone concentration and FEV_1

36. The studies of the effect of 8-hour average ozone concentration on FEV_1 are summarised in Table 12. None of the studies found a significant negative effect. However, Korrick *et al* 1998 did find a significant negative effect on the change in FEV_1 before and after a hike. This became non-significant after adjustment for $PM_{2.5}$ and acidity but did not change in magnitude. As described for FVC, the negative slope became greater above 40 ppb (Figure 8). There was a four fold greater effect in hikers with asthma or wheeze. 11 out of 530 hikers had a greater than 10% decline in FEV_1.

3.2 1-hour average ozone concentration and FEV_1

37. Studies of 1 hour average ozone and FEV_1 are summarised in Table 13. This includes a reanalysis (Kinney *et al*. 1996) of six previous studies (Spektor *et al*. 1988a; Spektor *et al*. 1991; Higgins *et al*. 1990b; Avol *et al*. 1990; Raizenne *et al*. 1989; Burnett *et al* 1990). The same analytical method was used on all the datasets and a combined slope of –2.5ml per 10 $\mu g/m^3$ was derived. The random effects summary estimate including 4 additional studies is –0.002 (-0.003 to –0.001) L/10$\mu g/m^3$ (P<0.001) – a small but statistically significant decline.

38. Studies that examined thresholds are summarised in Table 14. Lioy *et al* (1985) and Higgins *et al* (1990) found the estimate much reduced at lower ozone concentrations but had not found a significant effect at higher concentrations either. The remaining studies found that the decrease remained significant when truncated at 120, 80 or 60 ppb although the estimate reduced in size. Spektor *et al* (1991) found that the effect on the morning to afternoon change in FEV_1 was still apparent below 120 ppb. Castillejos *et al* (1995) examined the change in FEV_1 before and after exercise and found that the mean percentage decrement in FEV_1 was only significant for the third (72-125 ppb) and fifth ozone quintile (182 to 365 ppb). However, a loess smoothed curve began to drop gradually from about 50 or 60 ppb (Figure 10).

Table 12 FEV_1 and 8 hour average ozone concentrations

Author (date)	Subjects	Season	Ozone mean (8 h)	Ozone range (8h)	Estimate l/10 ìg/m^3	Lower CI	Upper CI	Notes
Berry *et al*. (1991)	Healthy children	Summer, lag 0	Not given	6 days > 100 ppb; max 131 ppb	0.0045	0.0003	0.0086	Suburban New Jersey summer camp, severe ozone episode at start may have changed baseline
Scarlett (1996) ($FEV_{0.75}$)	Children, cross-sectional	Summer, lag 1	51 ppb	7 to 128 ppb	0.00003	-0.0006	0.0007	Surrey schoolchildren
Cuijpers *et al*. (1995)	Children, Cross-sectional	Summer, lag 1	Not given	25 to 82 ppb	-0.0045	-0.0140	0.0051	Netherlands, schoolchildren
Berry *et al*. (1991)	Healthy adults	Summer, lag 0	Not given	6 days > 100 ppb; max 131 ppb	-0.0011	-0.0111	0.009	Suburban New Jersey summer camp, severe ozone episode at start may have changed baseline

Table 13 FEV_1 and 1 hour average ozone concentrations (healthy children)

Author (date)	Season, time of day	Ozone (1 hr mean)	Ozone (1 hr range)	Estimate l/10 ìg/m^3	Lower CI	Higher CI	Notes
Kinney *et al*. (1996)	Summer, afternoon	53 ppb	40 – 113 ppb	-0.0025	-0.0041	-0.0009	New Jersey
"	Summer, afternoon	69 ppb	Max 137ppb	-0.0065	-0.0091	-0.0038	New Jersey
"	Summer, afternoon	59 ppb	Max 95 ppb	-0.0010	-0.0053	0.0033	Ontario
"	Summer, afternoon	71ppb	Max 143 ppb	-0.0015	-0.0024	-0.0005	Ontario
"	Summer, afternoon	123 ppb	20 – 245 ppb	-0.0042	-0.0062	-0.0022	California
"	Summer, afternoon	94 ppb	Max 161 ppb	-0.0016	-0.0029	-0.0003	California
Berry *et al*. (1991)	Summer, afternoon	Not given	8 days above 120 ppb; max 204 ppb	0.0041	0.0009	0.0073	New Jersey
Lioy *et al*. (1985)	Summer, Afternoon	Not given	20 to 186 ppb	-0.0014	-0.0035	0.0007	New Jersey
Hoek *et al*. (1993b)	Spring/ Summer, morning	55, 58, 64 ppb	4, 13, 22 to 107, 114, 118 ppb	-0.0021	-0.0033	-0.0009	Schoolchildren in Enkhuizen, Zeist, Deune
Lippmann *et al* (1983)	Summer, afternoon	Not given	48-122 ppb	-0.0039	-0.0068	-0.001	Pennsylvania

(Most estimates are for lag 0)

Table 14 Studies of FEV_1 in healthy children (1 hour average ozone) which examined the possibility of a threshold

Author/date	Cut off or omission specification	Estimate (SE) in ml/ppb	Estimate (SD) in ml/ppb
Lioy *et al*. (1985)	With and without an ozone episode period (135 to 186 ppb) and some days following it	- 0.06 (0.30) (without episode)	-0.28 (0.21)* (with episode)
Higgins *et al*. (1990b)	Hourly ozone above 120 ppb in preceding 6 hours	0.18 (0.43) (days below 120 ppb)	-0.71 (0.37)(days above 120 ppb)
Spektor *et al*. (1991)	Daily 1 hour maximum above 120 ppb	-2.50 (0.30)* (excluding days above 120 ppb)	-2.42 (0.32)* (including days above 120 ppb)
Spektor *et al*. (1988a)	Dataset truncated at 80 ppb ozone I hour average	-0.75 (0.29)* (excluding days above 80 ppb)	-1.42 (0.17)* (including days above 80 ppb)
Spektor *et al*. (1988a)	Dataset truncated at 60 ppb ozone I hour average	-1.19 (0.39)* (excluding days above 60 ppb)	-1.42 (0.17)* (including days above 60 ppb)

* P<0.05

3.3 1 hour ozone concentrations and FEV_1 (cross-sectional studies in children)

39. Cross-sectional studies in children are summarised in Table 15. Three out of four studies found significant negative effects. The overall random effects summary estimate is –0.001 (-0.002 to –0.000) L/10µg/m^3 (P=0.037), similar to that found with healthy children. As with FVC, Kinney *et al* (1989) found the pattern of residuals suggested a fairly consistent linear relationship. Studnicka *et al* (1995) found a non-significant decrease in FEV_1 with increasing half hour daily maximum at a summer camp in Austria. There was a significant decrease in FEV_1 during an 'episode' period (mean 56 ppb, range 41-70 ppb) but this may have been confounded by particles or acidity. Braun-Fahrlander *et al* (1994) did not find an effect on FEV_1 although there was significant heterogeneity amongst the responses of different children.

Table 15 FEV_1 and 1 hour average ozone concentrations (cross-sectional studies in children)

Author (date)	Season Time of day, lag	Mean ozone	Ozone range	Estimate l/10 µg/m^3	Lower CI	Upper CI	Notes
Scarlett *et al* (1996) $FEV_{0.75}$	Summer, morning, lag 1	60 ppb	12-159 ppb	0.0001	-0.0004	0.0006	Surrey school children
Castillejos *et al*. (1992)	Jan-June Morning, lag 1	182ppb (max 1hr)	51-287 ppb	-0.0006	-0.0010	-0.0003	Mexico city school children
Kinney *et al* (1989) $FEV_{0.75}$	Spring, morning, lag 0	Not given	7-78ppb (max 1 hr)	-0.0050	-0.0085	-0.0014	Tenessee school children
Hoek *et al*. (1993b)	Spring/ Summer, morning	55,58, 64 ppb	4,13,22 to 107, 114,118	-0.0021	-0.0029	-0.0013	Schoolchildren in Enkhuizen, Zeist, Deurne,

			ppb				The Netherlands

3.4 1 hour average ozone and FEV_1 (children with respiratory symptoms)

40. Hoek *et al* (1993b), Studnicka *et al* (1995) and Scarlett *et al* (1996) found no differences in effect between children with and without respiratory symptoms, with and without asthma medication and with and without wheeze respectively. However, Castillejos *et al* (1992) found greater effects in Mexican children with chronic phlegm but not in Mexican children with wheeze, although the confidence intervals overlapped. Castillejos *et al* (1995) also found greater effects in children with cough/chronic phlegm although the effects were not significant in this small group of children.

3.5 1 hour average ozone and FEV_1 (adults)

41. There was no effect in the two groups of summer camp workers studied by Berry *et al* (1991). However, there were effects in a group of farmworkers doing heavier work (Brauer *et al* 1996). These effects were maintained with omission of days above 40 ppb but not with omission of days above 30 ppb. This study found no effect on morning to evening change in FEV_1. On the other hand, Spektor *et al* (1988) found a significant negative effect on the change in FEV_1 (-6.8 ml per 10 $\mu g/m^3$) before and after exercise that was still apparent below 80 ppb. Similarly, Brunekreef *et al* (1994) found a significant negative effect (-8 ml per 10 $\mu g/m^3$) before and after cycling that was maintained below 50 ppb and only became non-significant below 40 ppb.

Table 16 1 hour average ozone and FEV_1 (adults)

Author	Season, time of day	Mean ozone	Ozone range	Estimate l/10 $\mu g/m^3$	Lower CI	Upper CI	Notes
Berry *et al* (1991)	Summer, pm	Not given	8 days > 120 ppb; max 204 ppb	0.0023	-0.0025	0.0071	NJ Y-camp workers
Berry *et al* (1991)	Summer, pm	Not given	8 days > 120 ppb; max 204 ppb	0.0029	-0.0007	0.0064	NJ Rec-camp workers
Brauer *et al* (1996)	Summer, pm	40 ppb (1 hr max)	13-84 ppb	-0.019	-0.0229	-0.0151	Farm workers mean age 44 yrs range 10 to 69

42. Brauer *et al* (1996) found no difference in response for subjects with or without hayfever/allergy and Brunekreef *et al* (1994) found no difference in response for subjects with or without chronic respiratory symptoms.

3.6 24 hour average ozone concentration and FEV_1

43. Linn *et al* (1996) examined lung function in Los Angeles schoolchildren as described in paragraph 34. A non-significant decrease in afternoon FEV_1 (-0.001 litres per 10 $\mu g/m^3$, CI –0.003 to 0.002) was found which became less marked after adjustment for NO_2 and PM_5. A significant negative effect on the morning to afternoon change in FEV_1 was found (-0.0029 litres per 10 $\mu g/m^3$, CI –0.005 to -0.001).

44. Linn *et al* 1999 examined lung function in COPD patients in Los Angeles. No effect on FEV_1 was found.

4. FEV_1/FVC ratio

4.1 8 hour average ozone concentration

45. Both studies of 8 hour average ozone concentrations found decreases in the FEV_1/FVC ratio although the effect was not significant.

Table 17 FEV_1/FVC ratio and 8 hour average ozone concentrations

Author (date) and Subjects	Season	Ozone mean (8 h)	Ozone range (8h)	Estimate %/10 ìg/m^3	Lower CI	Upper CI
Scarlett (1996) Surrey schoolchildren, cross-sectional	Summer, lag 1	51 ppb	7 to 128 ppb	-0.0007	-0.0255	0.024
Korrick *et al* (1998) (adult hikers, change in ratio after hike) averaging time duration of hike mean 8 hours range 2 to 12	Summer, lag 0	Not given	21 to 74 ppb	-0.045	-0.221	0.131

4.2 1 hour average ozone concentrations

46. Several of the studies below found significant negative effects on the FEV_1/FVC ratio. The overall random effects summary estimate was –0.062 (-0.103 to –0.021) % per 10 µg/m^3 (P=0.003) i.e. a statistically significant fall in the FEV_1/FVC ratio. *(NB This summary estimate includes studies in both healthy children and cross-sectional groups of children).*

Table 18 FEV_1/FVC ratio and 1 hour average ozone concentrations

Author (date) Subjects	Season	Ozone mean (1 hr)	Ozone range (1 hr)	Estimate %/10 ìg/m^3	Lower CI	Upper CI
Spektor *et al* (1988a) Healthy children, NJ camp	Summer	53 ppb	40 – 113 ppb	-0.06	-0.119	-0.001
Spektor *et al* (1991) Healthy children, NJ camp	Summer	Not given	5 days above 120 ppb, min 40, max 150ppb from graph	-0.09	-0.129	-0.051
Castillejos *et al* (1995) Mexican schoolchildren, cross-sectional, change before and after exercise	?	112 ppb	0 to 365 ppb	-0.025	-0.045	-0.005
Scarlett *et al* (1996) Surrey schoolchildren, cross-sectional	Summer, lag 1	60 ppb	12-159 ppb	-0.01	-0.0315	0.012
Spektor *et al* (1988b) Adults near New York	Summer	Not given	20 to 120 ppb	-0.188	-0.27	-0.106

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