

COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

EFFECTS ON HEALTH OF LONG-TERM EXPOSURE TO OZONE

Background: QUARK Report

1. COMEAP commented on the effects of chronic exposure to ozone in the following paragraphs of the 1998 Report on the Quantification of the Effects of Air Pollution on Health in the United Kingdom. Research produced subsequent to the publication of the QUARK Report is presented in the following sections.

Effects of chronic exposure

6.28 Epidemiological evidence for chronic effects of exposure to ozone is scanty. The only adequate cross-sectional study on adults is that reported by Schwarz who used data on adults of 18-65 years from the US National Health and Nutrition Examination Survey II.⁴⁹ Highly significant negative effects on lung function were observed for both ozone and NO₂. However, because too few areas had data on both pollutants their independent effects could not be estimated. The effect of ozone (mean of day time levels over the previous year) became evident at about 40 ppb (80 µg/m³). The regression coefficient was around -3 ml/ppb annual average ozone, in all models examined.

6.29 The other main source of evidence is the cohort study of Seventh Day Adventists in California.⁵⁰ Cumulative exposure to ozone was associated with the severity of asthma and incidence of diagnosed asthma in men only. The relative risk for asthma in all ages associated with asthma was 1.35 (0.93,1.96) per 500h/yr above 100 ppb (200 µg/m³) 1 h average ozone concentration. This was not significant and the finding of a significant effect among men was not based on an a priori hypothesis.

6.30 It is not recommended that these estimates be used for quantitative risk assessment in the UK until there is replication, preferably in Europe. Also, there is the suggestion in both these studies that the effects observed were occurring at higher levels than are likely to occur in the UK.

Studies published between 1997 and 2002*Incidence of asthma*

2. A recent study by McConnell *et al.* (2002) investigated newly diagnosed asthma in 3535 children in relation to number of team sports played and levels of air pollutants (ozone, PM₁₀ and NO₂). Four-year pollutant concentrations were used to class the communities as high or low pollution areas. In children living in high ozone areas and playing three or more team sports, the relative risk of developing asthma was 3.3 (95% confidence interval (CI), 1.9-5.8) compared with children playing no sports. However, overall the risk of developing asthma was no greater in the high ozone area than in the lower ozone area. Ozone was not strongly correlated with any of the other pollutants.

3. A 1998 study by Gong *et al.* investigated long-term lung function in 164 residents of an ozone-polluted community (All hours annual average = 0.04 ppm, daily maximum O₃:

Highest = 0.3-0.4 ppm, Annual Average = 0.1 ppm) over 9 years. They hypothesised that acute respiratory responsiveness to ozone would be a predictor of lung injury from chronic exposure to ozone and co-pollutants. However, no participants reported the development of asthma or respiratory symptoms over the last 4 years of the study.

Respiratory symptoms

4. Ramadour *et al.* (2000) studied the prevalence of rhinitis, asthma and asthmatic symptoms in 2445 children who had lived for at least 3 years in a highly polluted area. They found a positive correlation between prevalence of some asthmatic symptoms and mean 8-hour ozone levels. The second highest prevalence of wheeze in the last 12 months occurred in the area of highest ozone (mean: $52 \pm 15 \text{ } \mu\text{g}/\text{m}^3$) and the lowest prevalence of wheeze in the last 12 months occurred in the area of lowest ozone (mean: $30 \pm 17 \text{ } \mu\text{g}/\text{m}^3$). No association was found with SO_2 or NO_2 .
5. Galizia and Kinney (1999) examined the respiratory effects of long-term ozone exposure by looking at two groups of students. Ozone exposure was considered to be high if students had lived for 4 or more years in an area with a 10-year average summer-season daily 1-h maximum ozone levels greater than or equal to 80 ppb ($160 \text{ } \mu\text{g}/\text{m}^3$). Symptoms of cough, phlegm, wheeze apart from colds and a composite respiratory symptom index (RSI) were examined. Symptoms of phlegm, wheeze apart from colds and RSI were increased in the high-ozone group, with odds ratios of 1.79 (CI, 0.83-3.82), 1.97 (CI, 1.06-3.66) and 2.00 (CI, 1.15-3.46) respectively. Results for wheeze and RSI, but not phlegm, were statistically significant. The authors suggested that the effect could be due to ozone in combination with other pollutants and not ozone alone, as these two possibilities could not be distinguished.
6. A study in Switzerland (Braun-Fahrlander, 1997) looked at the effect of long-term exposure to air pollution and respiratory and allergic symptoms and illnesses in 4470 schoolchildren in 10 different communities. The symptoms recorded included chronic cough, nocturnal dry cough, bronchitis, current wheeze, asthma, sneezing, hay fever and conjunctivitis. They found a small positive correlation between number of hours per year with ozone concentrations above $160 \mu\text{g}/\text{m}^3$ and nocturnal dry cough, bronchitis and conjunctivitis, but there was no correlation between symptom rates and annual mean concentrations of ozone (range: $17\text{-}75 \mu\text{g}/\text{m}^3$). In addition, these results were driven by only two communities, and the measure of ozone was positively correlated with other pollutants. Annual mean ozone was negatively correlated with other pollutants. The authors note that the information on exposure was not detailed enough for inferences about the effects of ozone to be made.
7. A SAPALDIA study by Zemp *et al.* (1999) examined respiratory symptoms in random population samples of adults ($n=9651$) in 8 areas of Switzerland compared to levels of ambient air pollution. Ozone measures included annual average, summer daytime average and excess ozone. Symptoms were in three categories; bronchitic (chronic cough, phlegm or both), asthmatic (wheeze, breathlessness, asthma) and non-specific cardiopulmonary (dyspnea on exertion and chest tightness). No association was found between annual mean ozone levels and respiratory symptoms. Excess ozone was positively associated with chronic phlegm, breathlessness and dyspnea, and negatively associated with current asthma. There was a negative correlation between annual mean ozone concentrations and other pollutants. The authors cautioned that several factors could have led to confounding errors.

8. Kinney and Lippmann (2000) investigated whether respiratory effects could be observed over the course of a summer spent in a high ozone area, where peak hourly concentrations frequently rose above 100 ppb (200 $\mu\text{g}/\text{m}^3$), compared to areas of moderate ozone levels (where peak levels rarely rose above 100 ppb). Levels of SO_2 and PM_{10} were also measured. Respiratory effects included sore throat, cough, phlegm, chest pain, chest tightness, wheeze, stuffy nose, eye irritation, head cold and chest cold. The authors also recorded separate numbers for “any symptoms” and “lower respiratory index”. In all students there was a general increase in all conditions except head cold. In the group of college-age students exposed to high ozone levels, a statistically significant increase in cough, chest tightness, sore throat and “any symptoms” was recorded.

9. Overall, most studies found that increased ozone concentrations had an effect on some respiratory symptoms. However, there was no clear pattern of association between long-term exposure to ozone and particular types of respiratory symptoms. There also seemed to be little correlation with annual mean ozone levels (Braun-Fahrlander *et al.*, 1997; Zemp *et al.*, 1999). Where an association was found, the ozone measurements tended to be maximums:

Galizia and Kinney (1999)	4 or more years with 10-year average summer-season daily 1-hr maximum ozone levels greater than or equal to 80 ppb (160 $\mu\text{g}/\text{m}^3$)
Braun-Fahrlander <i>et al.</i> (1997)	Number of hours per year with ozone concentrations above 160 $\mu\text{g}/\text{m}^3$
Zemp <i>et al.</i> (1999)	Excess ozone: an index of cumulative exposure to ozone concentrations above 120 $\mu\text{g}/\text{m}^3$, defined as the sum of all half-hourly values of ozone concentrations minus 120 $\mu\text{g}/\text{m}^3$ for those half hours when the concentration exceeded 120 $\mu\text{g}/\text{m}^3$
Kinney and Lippmann (2000)	High ozone area defined by peak hourly concentrations frequently rising above 100 ppb (200 $\mu\text{g}/\text{m}^3$)

10. High ozone concentrations were not consistently associated with particular respiratory symptoms. In only two cases were high ozone levels associated with wheeze or asthma (Ramadour *et al.*, 2000; Galizia and Kinney, 1999). In one study an association was found with nocturnal dry cough, bronchitis and conjunctivitis, but not with wheeze or asthma (Braun-Fahrlander *et al.*, 1997). In another case, ozone levels were negatively correlated with prevalence of asthma (Zemp *et al.*, 1999). Finally, an increase in cough, chest tightness and sore throat, but not wheeze, was seen in one group exposed to high ozone levels (Kinney and Lippmann, 2000). Three studies therefore found no positive correlation between prevalence of asthma and any measure of ozone.

Lung function

11. Galizia and Kinney (1999) also examined lung function based on forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1) and forced expiratory flow rate between 25 and 75% of FVC and at 75% of FVC (FEF_{25-75} and FEF_{75}). They found a statistically significant drop in FEV_1 (-3.1%, CI -0.2 to -5.9%) and FEF_{25-75} (-8.1, CI -12.3 to -13.9%) in males in the “high ozone” group.

12. The 1997 SAPALDIA study (Ackermann-Lieblich *et al.*) investigated the long-term effects of several air pollutants (SO₂, NO₂, O₃ and PM₁₀) on 6637 healthy adults living in eight different areas of Switzerland. People reporting respiratory symptoms were excluded from the study. Lung function was measured by FVC and FEV₁. Annual mean values of all pollutants were associated with a decline in lung function, except mean levels of ozone which had a slight positive association with pulmonary function. Summer daytime average ozone and excess ozone (Mean O₃ = 43.1 µg/m³, Mean summer daytime O₃ = 92.0 µg/m³) were both associated with a reduction in pulmonary function. The authors point out that the association with ozone was mainly driven by one study area, and that due to the small range in long-term exposure to ozone concentrations, the results for ozone were of limited value.

13. The 1998 study by Gong *et al.* that examined lung function in residents of highly ozone-polluted areas saw a rapid decline in FVC and FEV₁ over the first 5 years (t1 - t2) (FVC: 4.12 to 3.86 litres; FEV₁: 3.49 to 3.24 litres). However, over the following 4 years (t2 - t3) there was little additional deterioration of lung function, such that the overall decline over 9 years (t1 - t3) was not abnormal. The rate of decline from t1 to t3 was only half that from t1 to t2. The study therefore found no convincing evidence of long-term health effects of ozone.

14. In the group of students exposed to high ozone levels in Kinney and Lippmann's study (2000), there was a decline in lung function over the summer (measured as FVC, FEV₁ and FEF₂₅₋₇₅). The largest decline was in FEV₁ (-0.078 litres, standard error (SE) = 0.041, p=.07) although the result was only "almost statistically significant."

15. As with studies of respiratory symptoms, no clear pattern emerges from studies of lung function. Two studies showed an association between ozone levels and a decline in lung function (based on FEV₁, FEF₂₅₋₇₅ and FEF₇₅), though this was not statistically significant in all measures of lung function (Galizia and Kinney, 1999; Kinney and Lippmann, 2000). These studies both used ozone measures involving maximums rather than means (see chart). Another study found an association between reduced lung function and summer daytime average ozone and excess ozone, but not annual mean ozone (Ackermann-Lieblich *et al.*, 1997). Finally one study found no abnormal decline in lung function over the 9-year period studied (Gong *et al.*, 1998). Although some associations were found, these were inconsistent, and the possibility of confounding could often not be dismissed.

Mortality

16. A 1998 study (Beeson *et al.*) looked at the relationship between air pollutant concentrations, including ozone, and the risk of lung cancer. Over 6000 white Seventh-day Adventist adults were included in the study, which took place from 1977 to 1992. The authors found an increased relative risk of lung cancer in males, but not in females, with an interquartile range increase in 100 ppb (200 µg/m³) ozone (Relative risk (RR) = 3.96; CI 1.35-9.42). The gender difference in this study was thought to be due to males spending more time outdoors and engaging more vigorous exercise than females. The authors also added that the associations occurred at exceedance frequencies for O₃ thresholds as low as 80 ppb (160 µg/m³) and that this could have implications for current standards for O₃ concentrations.

17. The HEI reanalysis of two earlier studies, the Six Cities Study and the American Cancer Society Study looked at the effects of air pollutants on mortality. They found that concentrations of ozone has no effect on the risk of death due to lung cancer (RR = 0.94, CI 0.56-1.59), cardiopulmonary disease (RR = 0.78, CI 0.64-0.95) or all cause mortality (RR =

0.87, CI 0.76-1.00) in the Six Cities Study. Likewise, they found no association between ozone and lung cancer (RR = 0.81, CI 0.69-0.94) in the American Cancer Society Study, though a small increased risk of death from cardiopulmonary disease (RR = 1.08, CI 1.01-1.16) and all cause mortality (RR = 1.08, CI 0.96-1.07) was seen. These results were calculated in the summer period (April-September), when mean ozone levels were approximately 30 ppb (60 $\mu\text{g}/\text{m}^3$). Relative risks were even lower during the winter period when ozone levels were lower.

18. Due to limited and contradictory data on the relationship between ozone concentrations and mortality, no firm conclusions can be made at this time.

UK ozone concentrations

19. Maximum hourly concentrations (ppb) 1998-2001

Min - North Kensington mean 14.6 (1-58 range)

Max - Swansea mean 41.1 (21-88 range)

Daily average concentrations (ppb) 1998-2001

Min - North Kensington mean 6.6 (0-32 range)

Max - Swansea mean 34.9 (14-67 range)

Concentrations from 10:00 to 18:00 (ppb) 1998-2001

Min - Marylebone Rd mean 8.6 (0-58 range)

Max - Straith Vaich mean 35.9 (5-88 range)

20. The means are over all 4 years. The range is from the minimum value in any one of the 4 years to the maximum value in any one of the 4 years. Note that higher maximum values can be found at other sites with lower mean values over all 4 years.

21. Compared with some of the values measured in the above studies, values for the UK tend to be lower. Most of the associations found with respiratory and lung function effects occurred with maximum ozone concentrations rather than daily means. The maximums at which effects were seen were generally 80 ppb or above. Maximum hourly concentrations in the areas of the UK with the highest ozone measurements were around 41 ppb, with the range extending only up to 88 ppb. In some of the above studies, maximums rose to 300 or 400 ppb.

Conclusions

22. The Committee is asked:

- (i) To note the 2 studies on ozone and incidence of asthma, which have been included for completeness. These will be discussed with a separate paper (COMEAP/2002/10).
- (ii) For their views on the effects of long-term exposure to ozone on respiratory symptoms.

Each study showed some association between ozone and respiratory symptoms but the type of respiratory symptoms affected was not constant.

The Committee may wish to consider how much the following factors affect their views:

- lack of consistency in the type of respiratory symptoms affected
- difficulties distinguishing the effect of ozone from those of other pollutants

(iii) For their views on the effects of long-term exposure to ozone on lung function.

Overall, the studies seemed to show some association between ozone and lung function, but different studies found associations with different measures of lung function, and the effect was generally small.

(iv) For their views on the effects of long-term exposure to ozone on mortality.

One study found an effect on lung cancer but this was contradicted by two other studies. There was a small increased risk of death from cardiopulmonary disease in one study.

(v) For their views on the relevance of these studies to the UK, given the above comparison between ozone concentrations (paragraphs 19-21).

**COMEAP Secretariat
May 2002**

Ozone measurements used in studies from 1997 to 2002

Authors	Date	Ozone Measurements
Ackermann-Liebrich <i>et al.</i>	1997	Annual average (24-hour); summer daytime average; excess ozone
Braun-Fahrlander <i>et al.</i>	1997	Number of hours per year with ozone concentrations above 160µg/m ³ , annual mean
Gong <i>et al.</i>	1998	All hours annual average; highest daily maximum; annual average daily maximum
Beeson <i>et al.</i>	1998	Interquartile range increase in 100 ppb (200 µg/m ³) ozone
Galizia & Kinney	1999	4 or more years with 10-year average summer-season daily 1-hr maximum ozone levels greater than or equal to 80 ppb (160 µg/m ³)
Zemp <i>et al.</i>	1999	Annual average (24-hour); summer daytime average; excess ozone
Kinney & Lippmann	2000	Peak hourly concentrations frequently rising above 100 ppb (200 µg/m ³)
Ramadour <i>et al.</i>	2000	Annual mean (8-hour average)
McConnell <i>et al.</i>	2002	Annual means calculated from 24 hr mean, daytime mean (10am – 6pm) and maximum 1 hr ozone

References

Quark Report

⁴⁹ Schwartz J. Lung function and chronic exposure to air pollution: a cross-sectional analysis of NHANES II. *Environ Res.* 1989 Dec; 50(2): 309-21.

⁵⁰ Abbey DE, Mills PK, Petersen FF, Beeson WL. Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. *Environ Health Perspect.* 1991 Aug; 94: 43-50.

Ackermann-Liebrich U, Leuenberger P, Schwartz J, Schindler C, Monn C, Bolognini G, Bongard JP, Brandli O, Domenighetti G, Elsasser S, Grize L, Karrer W, Keller R, Keller-Wossidlo H, Kunzli N, Martin BW, Medici TC, Perruchoud AP, Schoni MH, Tschopp JM, Villiger B, Wuthrich B, Zellweger JP, Zemp E. Lung function and long term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. *Am J Respir Crit Care Med.* 1997 Jan;155(1):122-9.

Beeson WL, Abbey DE, Knutsen SF. Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: results from the AHSMOG study. *Environ Health Perspect.* 1998 Dec;106(12):813-23.

Braun-Fahrlander C, Vuille JC, Sennhauser FH, Neu U, Kunzle T, Grize L, Gassner M, Minder C, Schindler C, Varonier HS, Wuthrich B. Respiratory health and long-term exposure

to air pollutants in Swiss schoolchildren. SCARPOL Team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen. *Am J Respir Crit Care Med*. 1997 Mar;155(3):1042-9.

Galizia A, Kinney PL. Long-term residence in areas of high ozone: associations with respiratory health in a nationwide sample of nonsmoking young adults [dsee comments] *Environ Health Perspect*. 1999 Aug;107(8):675-9.

Gong H Jr, Simmons MS, Linn WS, McDonnell WF, Westerdahl D. Relationship between acute ozone responsiveness and chronic loss of lung function in residents of a high-ozone community. *Arch Environ Health*. 1998 Sep-Oct;53(5):313-9.

Health Effects Institute. Special Report: Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. July 2000.

Kinney PL, Lippmann M. Respiratory effects of seasonal exposures to ozone and particles. *Arch Environ Health*. 2000 May-Jun;55(3):210-6.

McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, Avol E, Margolis HG, Peters JM. Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002; 359(9304): 386-91.

Ramadour M, Burel C, Lanteaume A, Vervloet D, Charpin D, Brisse F, Dutau H, Charpin D. Prevalence of asthma and rhinitis in relation to long-term exposure to gaseous air pollutants. *Allergy*. 2000 Dec;55(12):1163-9.

Zemp E, Elsasser S, Schindler C, Kunzli N, Perruchoud AP, Domenighetti G, Medici T, Ackermann-Liebrich U, Leuenberger P, Monn C, Bolognini G, Bongard JP, Brandli O, Karrer W, Keller R, Schoni MH, Tschopp JM, Villiger B, Zellweger JP. Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). *Am J Respir Crit Care Med* 1999; 159(4 Pt 1): 1257-66.