COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

OZONE – FURTHER ANALYSIS OF EFFECTS ON MORTALITY AND HOSPITAL ADMISSIONS – PLOTTING COEFFICIENTS AGAINST MEAN OZONE LEVELS

NB Information on a further study was received after completion of this paper. Readers should also refer to COMEAP/2002/12C ADDENDUM 2. This contains amended versions of all the figures.

1. If there is a threshold it would be expected that the slope below the threshold would be flat and the slope above the threshold would be steeper. Therefore, if the range of ozone concentrations in a study is below or mostly below the threshold, then the regression coefficient for that study should be small. If the range of ozone concentrations in a study is above the threshold, the regression coefficient should be greater.

2. The mean ozone concentrations are already entered on the St George's database. However, there could be difficulties in interpretation if the coefficient were just plotted against the mean concentration as there can be different ranges for the same or very similar mean. For example, a panel study in New Jersey ((Spektor *et al.* (1988); Kinney *et al.*(1996)) quoted a mean of 53 ppb with a range from 40 to 113 ppb whereas a panel study in Tuscon, Arizona with a mean of 55 ppb (SD 14) had a range from 15 to 92 ppb ((Krzyzanowski *et al.* (1992)). In addition, even if the mean were below a putative threshold, the range of values might extend above it.

3. Air pollution data has been extracted from the papers relating 8-hour average ozone concentration and all cause mortality and is shown in Table 1. The first group of studies are ranked by mean ozone concentration and a second group, where means were not given, are ranked by median ozone concentration. The data is represented pictorially in Figures 1a to c.

4. The coefficients are plotted against mean ozone concentration in Figure 2. It can be seen that there is only a slight trend towards higher coefficients at higher ozone concentrations and this may be influenced by a significant negative outlier. *[No trend is found in Addendum 2]* Confidence intervals have been omitted for clarity but are shown separately in Figure 2a. It should be noted that the confidence intervals for 2 or 3 estimates are very wide. For example, the confidence intervals for Zmirou *et al.* (1996) are vary from –1.02 to 2.23, those for Hong *et al.* (1999) vary from –4.5 to –0.29 and those for Tenias-Burillo *et al.* (1999) from –0.15 to 2.53. Thus, the confidence in the size and direction of the trend may be weak.

5. As mentioned earlier, the range of ozone concentrations in each study is quite wide and they overlap extensively. A plot of the studies that gave a

mean and a 10^{th} to 90^{th} percentile is shown in Figure 3. This may suggest that the ranges in ozone concentrations in different studies are not sufficiently distinct to illustrate a threshold even if there is one.

Study	Mean (ppb)	SD	Min	10^{th} percentile	25^{th} percentile	median	75^{th} percentile	90^{th} percentile	Max	Estimate % per 10 mg/m^3 or 5ppb	lower CI	upper CI	Place
Zmirou D 1996	5		0						39.5	0.59	-1.02	2.23	Lyon
Michelozzi P 1998	13	9.8			5.2	10.5	18			0.38	-0.03	0.79	Rome
Hong, YC 1999	15.4	7.4	2.1						49	-2.42	-4.5	-0.29	Inchon
Anderson HR 1996	15.5	10.9	1	4	8	14	21	28	74	0.46	0.21	0.71	London
Wong,C.M. 2001	16.8		0						84.5	0.18	-0.18	0.54	Hong Kong
Bremner SA 1999	17.5	11.5	1.9	4.4		16		30.1	79.9	-0.14	-0.45	0.18	London
Simpson RW 1997	18.1		1.7			16.7			63.4	1.18	0.39	1.98	Brisbane
Galan L 1999	21.1	13.8		4.8		39.6		49.4		0.33	-0.13	0.79	Madrid
Roemer,W.H. 2001	21.5			5.5	12	20.5	28	36.5	110.5	-0.17	-0.52	0.18	Amsterdam
Tenias Burillo, J 1999	22.8		5.1	9.8				35.8	62.5	1.18	-0.15	2.53	Valencia
Anderson 2001	24	13.8	0.4	6.7		24		37.5	89.9	0.5	-0.02	1.02	West Midlands
Saurina C 1999	33.8		0						118	0.35	0.03	0.68	Barcelona
Cadum,E. 1999	36.9	25.5	0.5	4.3				72.3	109.7	0.32	-0.12	0.76	Turin
Zeghnoun,A. 2001					6	13	22			0.28	0.06	0.5	Paris
Zeghnoun,A. 2001					8.5	18.5	36			0.75	0.07	1.43	Strasbourg
Hoek 2000			0.5			23.5		59(P95)	113	0.22	0.13	0.31	Netherlands
Zeghnoun,A. 2001					12.7	26	44.5			0.65	-0.05	1.35	Lyon
Zeghnoun,A. 2001					23	34	45.5			1.58	0.59	2.57	Toulouse
Borja-Aburto VH 1997			16	45 (P5)	74	94	114	139(P95)	179	0.21	0.1	0.32	Mexico City
Klemm R J 2000										-0.2	-1.27	0.88	Georgia

6. Similar results are found if the coefficients are plotted against median ozone concentrations (Figure 4). There is no evidence of a trend. The 10^{th} to 90^{th} percentiles are not shown here but Figure 1 indicates that they do overlap. The only study where the range of ozone concentrations stretches well out of the range of the others is that for Mexico city (Borja-Aburto *et al.* 1997) (median 94 ppb; 5^{th} to 95^{th} percentile 45 to 139 ppb). However, the coefficient in this study is modest 0.21% per 10 $\mu g/m^3$ (0.1 to 0.32).

7. In plotting ranges in Figure 3, the 10^{th} to 90^{th} percentiles representing 80% of the data were used. It was not considered appropriate to use the maximums and minimums because these can represent extreme single days which would not be expected to drive the coefficient to any great extent. However, for interest, the coefficients are plotted against maximum ozone concentrations in Figure 5. Again, there is only slight evidence of an increasing trend *[Addendum 2 shows a slightly greater increasing trend]*.

8. Examination of Table 1 indicates that statistically significant effects were found in:

a) studies with a maximum no higher than 63.4 ppb (mean 18.1 ppb) (Simpson *et al.* 1997),
b) studies with a mean no higher than 15.5 ppb (maximum 74 ppb) (Anderson *et al.* 1996)
c) studies with a median no higher than 13 ppb (75^{th} percentile 22 ppb) (Zeghnoun *et al.* 2001 (Paris)).

Three studies at low ozone concentrations did not find significant positive effects. One study in Korea (Hong *et al*. 1999) found a significant negative effect (this study showed a positive slope above about 25 to 30 ppb see COMEAP/2002/9a). The study by Zmirou *et al.* 1996 had very wide confidence intervals and noted that the ozone monitor was situated in a heavily trafficked urban area which is not ideal for measuring population exposure as it underestimates ozone concentrations away from traffic. The study by Michelozzi *et al.* 1998 (mean 13 ppb, 75^{th} percentile 18 ppb) was only marginally outside statistical significance.

9. It should be noted that even if the coefficients do not vary by the range of ozone concentration, there is still the possibility that the coefficients themselves were a linear representation of a raw dataset which was suggestive of a threshold. In fact, as discussed in COMEAP/2002/9a, it is known that there is a suggestion of a threshold in the studies by Wong *et al.* 2001, Hong *et al.* 1999, Anderson *et al.* 1996 and, possibly, Galan *et al* 1999. The other studies did not report the shape of the dose-response function. The confidence intervals might be expected to be wider if a straight line was being fitted to a 'curved' dataset but there are other reasons why the confidence intervals could be wide. Small sample size is one reason although this could be checked. However, it is also possible that there is not a tight fit to a straight line because the points are just

randomly scattered away from the line. It would not be possible to distinguish this from a loose fit due to trying to fit a straight line to a curve without writing to the authors of the relevant studies to ask about the raw data.

Conclusions

10. The Committee's comments are invited on the following:

a) Is the approach taken in this paper a reasonable one in theory?
b) Do the overlapping ranges of ozone concentrations in this particular case mean that any conclusion is uninterpretable?
c) Does the plot of coefficients against mean ozone concentration provide weak evidence for a threshold (due to a slight increasing trend) or should the plot be taken as evidence against there being a threshold (due to the lack of a marked upward trend)?
d) How serious a drawback is the possibility that the coefficients are masking an indication of a threshold in the underlying raw data?
e) Does the Committee agree that there is evidence for an effect, at some levels at least, below 63 ppb?
f) What is the Committee's view of the three studies that do not find statistically significant increases at low ozone concentrations (paragraph 8) – are the studies sufficient to conclude that there is evidence against effects at these concentrations?
g) Does the Committee consider it would be worthwhile repeating this approach for other health outcomes?

Secretariat
October 2002

References

Anderson, H.R., Bremner, S.A., Atkinson, R.W., Harrison, R.M. and Walters, S. (2001) Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. *Occupational and Environmental Medicine* **58**, 504-510.

Anderson, H.R., Ponce de Leon, A., Bland, J.M., Bower, J.S. and Strachan, D.P. (1996) Air pollution and daily mortality in London: 1987-92. *British Medical Journal* **312**, 665-669.

Borja-Aburto, V.H., Loomis, D.P., Bangdiwala, S.I., Shy, C.M. and Rascon-Pacheco, R.A. (1997) Ozone, suspended particulates, and daily mortality in Mexico City. *American Journal of Epidemiology* **145**, 258-268.

Bremner, S.A., Anderson, H.R., Atkinson, R.W., McMichael, A.J., Strachan, D.P., Bland, J.M. and Bower, J.S. (1999) Short term associations between outdoor air pollution and mortality in London 1992-4. *Occupational and Environmental Medicine* **56**, 237-244.

Cadum, E., Rossi, G., Mirabelli, D., Vigotti, M.A., Natale, P., Albano, L., Marchi, G., Di Meo, V., Cristofani, R. and Costa, G. (1999) [Air pollution and daily mortality in Turin, 1991-1996]. *Epidemiol Prev* **23**, 268-76.

Galan Labaca, I., Aranguez Ruiz, E., Gandarillas Grande, A., Ordonez Iriarte, J.M. and Aragones Sanz, N. (1999) [The short-term effects of air pollution on mortality: the results of the EMECAM project in the municipality of Madrid, 1992-1995. Estudio Multicentrico Espanol sobre la Relacion entre la Contaminacion Atmosferica y la Mortalidad]. *Rev Esp Salud Publica* **73**, 243-52.

Hoek, G., Brunekreef, B., Verhoeff, A., van Wijnen, J. and Fischer, P. (2000) Daily mortality and air pollution in The Netherlands. *J Air Waste Manag Assoc* **50**, 1380-9.

Hong, Y.-C., Leem, J.-H., Ha, E.-H. and Christiani, D.C. (1999) PM_{10} exposure, gaseous pollutants, and daily mortality in Inchon, South Korea. *Environmental Health Perspectives* **107**, 873-878.

Kinney, P.L., Thurston, G.D. and Raizenne, M. (1996) The effects of ambient ozone on lung function in children: A reanalysis of six summer camp studies. *Environmental Health Perspectives* **104**, 170-174.

Klemm, R.J. and Mason, R.M. Jr (2000) Aerosol Research and Inhalation Epidemiological Study (ARIES): air quality and daily mortality statistical modeling--interim results. *J Air Waste Manag Assoc* **50**, 1433-9.

Krzyzanowski, M., Quackenboss, J.J. and Lebowitz, M.D. (1992) Relation of peak expiratory flow rates and symptoms to ambient ozone. *Arch.Environ.Health* **47**, 107-115.

Michelozzi, P., Forastiere, F., Dusco, D., Perucci, C.A., Ostro, B., Ancona, C. and Pallotti, G. (1998) Air pollution and daily mortality in Rome, Italy. *Occupational and Environmental Medicine* **55**, 605-610.

Roemer, W.H. and van Wijnen, J.H. (2001) Daily mortality and air pollution along busy streets in Amsterdam, 1987- 1998. *Epidemiology* **12**, 649-53.

Saurina, C., Barcelo, M.A., Saez, M. and Tobias, A. (1999) [The short-term effects of air pollution on mortality. The results of the EMECAM project in the city of Barcelona, 1991-1995. Estudio Multicentrico Espanol sobre la Relacion entre la Contaminacion Atmosferica y la Mortalidad]. *Rev Esp Salud Publica* **73**, 199-207.

Simpson, R.W., Williams, G., Petroeschevsky, A., Morgan, G. and Rutherford, S. (1997) Associations between outdoor air pollution and daily mortality in Brisbane, Australia. *Archives of Environmental Health* **52**, 442-454.

Spektor, D.M., Lippmann, M., Lioy, P.J., Thurston, G.D., Citak, K., James, D.J., Bock, N., Speizer, F.E. and Hayes, C. (1988) Effects of ambient ozone on respiratory function in active, normal children. *Am.Rev.Respir.Dis.* **137**, 313-320.

Tenias Burillo, J.M., Perez-Hoyos, S., Molina Quilis, R., Gonzalez-Aracil, J. and Ballester Diez, F. (1999) [The short-term effects of air pollution on mortality. The results of the EMECAM project in the city of Valencia, 1994-96. Estudio Multcentrico Espanol sobre la Relacion entre la Contaminacion Atmosferica y la Mortalidad]. *Rev Esp Salud Publica* **73**, 267-74.

Wong, C.-M., Ma, S., Hedley, A.J. and Lam, T.-H. (2001) Effect of air pollution on daily mortality in Hong Kong. *Environmental Health Perspectives* **109**, 335-340.

Zeghnoun, A., Eilstein, D., Saviuc, P., Filleul, L., Le Goaster, C., Cassadou, S., Boumghar, A., Pascal, L., Medina, S., Prouvost, H., Le Tertre, A., Declercq, C. and Quenel, P. (2001) [Surveillance of short-term effects of urban air pollution on mortality. Results of a feasibility study in 9 French cities]. *Rev Epidemiol Sante Publique* **49**, 3-12.

Zmirou, D., Barumandzadeh, T., Balducci, F., Ritter, P., Laham, G. and Ghilardi, J.P. (1996) Short term effects of air pollution on mortality in the city of Lyon, France, 1985-90. *J Epidemiol Community Health* **50 Suppl 1**, S30-5.