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NATIONAL AMBIENT AIR QUALITY OBJECTIVES FOR GROUND-LEVEL OZONE

SCIENCE ASSESSMENT DOCUMENT

A Report by
the Federal-Provincial Working Group
on Air Quality Objectives
and Guidelines

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This document has been divided into a series of files for easier downloading from our web site.

Part 6 of 7

Canada

12 HUMAN HEALTH EFFECTS—EPIDEMIOLOGY STUDIES

There has been, in the past several years, an increase in scientific study of the epidemiology of air pollution, especially as it relates to mortality and morbidity as expressed by hospitalizations and emergency department visits. Although the primary concern of many of the papers was the adverse health effects of ambient particulate pollution, a large number also investigated the effects of ozone, which often co-occurs with particles as a part of the air pollution mixture. The U.S. EPA Criteria Review (U.S. EPA, 1996a) and the accompanying Staff Paper of the Office of Air Quality Planning and Standards (OAQPS) (U.S. EPA, 1996b) give an excellent review of papers published to 1993. They also include a summary review of older papers included in their previous Criteria Review of 1986 (U.S. EPA, 1986). However, a number of relevant papers were published between 1994 and 1997, including several on Canadian populations. For this reason, an independent assessment was undertaken for this document, emphasizing studies on mortality, hospitalizations, and emergency department visits from 1990 to 1997.[1]

12.1 DESIGN ELEMENTS

12.1.1 Time-series Studies vs. Cross-sectional Studies

Most of the recent epidemiological studies considering acute and short-term effects of air pollution on human health have been time-series studies in which the timing of an adverse health event (for example, hospitalizations) is studied in relation to short-term time trends in air pollution within a defined geographic area. Cross-sectional studies, in which rates of chronic disease or mortality are compared across geographic locations, have often been applied to examination of long-term or chronic effects and their relationship to air pollutants. Both types of studies are denoted as 'ecological', since they are both observational; that is, no control of the experimental conditions is possible, and both consider very large groups of people (thousands or millions) rather than individuals. No individual exposure analysis is usually available or possible due to the impracticality of obtaining information on so many people, and exposure is inferred from centrally located outdoor ambient monitoring stations.

A time-series analysis is by definition longitudinal in nature. Changes over time in an adverse health endpoint in a single population are followed as changes occur in concentrations of a pollutant over time (usually a very short time as in the studies included in this review, but long-term changes could also be followed by this method). The hypothesis being tested in the time-series study is that differences in time related to the pollutant levels are also associated with the outcome. In the cross-sectional study, differences between two or more populations in different locations exposed to different pollutant mixes are examined for changes in health outcome. The time-series analysis is less likely than the cross-sectional analysis to give biased results since the study population is the same over time, and acts as its own "control". However, other

[1] Some 1998 and 1999 references are noted in the text. These were incorporated in the review as "1997 in press" peer reviewed papers, and have been published since. Hence, the 1998 / 1999 dates.

environmental factors and other causes of illness can confound the results and must be taken into account in the time-series as well as the cross-sectional analysis. There are relatively few confounders of exposure from one day to the next in a single population for time-series studies. There are many more opportunities for confounding in cross-sectional analyses. For instance, in cross-sectional analyses, local emissions can affect neighbourhoods differently. In addition, for cross-sectional analyses, other differences between two or more populations are harder to discern and control (e.g., differences in socioeconomic status, 'natural' illness rates unrelated to the substance being investigated, and in lifestyles between communities). The time-series analysis is therefore considered, despite its ecological nature, to be potentially a relatively stronger indicator of effects on public health than the cross-sectional study.

The major weakness of ecological studies with respect to judgments regarding causality is the lack of a direct link between personal exposure to the toxic agent and the resulting health outcome on the individual. Ecological studies such as the time-series studies tell us the risk that a particular endpoint (e.g., hospitalizations) will be increased for the entire population if the average exposure for the entire population is increased by a certain amount. They do not tell us anything about individual exposure or individual risk. Inferences about causality are suggested, strengthened or weakened, but not directly proven (see Section 12.7.6. for discussions of causality). In compensation for this lack, the strength of the time-series study is its ability to examine the overall population responses of very large numbers of individuals to the agent under investigation and, thereby, gain an understanding of the public health impacts and risks to the population as a whole. Causality must be judged by making use of the sum of all the information available from all epidemiological, clinical, and toxicological studies to weigh the evidence.

12.1.2 Statistical Issues, Confound Factors and Co-variates

Observational studies try to find relationships between population or community health responses and some characteristic of the environment, in this case air pollution from ozone. The relationship is often expressed as relative risk. This estimate of risk describes an increase in, for example, non-accidental mortality of 0.9% **above** baseline non-accidental mortality rates. Therefore, it is often referred to as a **relative risk** estimate and the value reported as 1.009 (for a 10 ppb increase in ozone), where a value of 1.000 represents the baseline risk rate. An alternative expression of this estimate of mortality risk for ozone is .09% increase in risk per 1 ppb increase in ozone; this simple conversion is possible because, as stated above, the concentration-response relationship is linear. 95% confidence levels are used to measure the statistical significance and uncertainty of the RR. Since the observed relationships are often weak from a statistical point of view, and are vulnerable to confounding from factors such as seasonal cyclic variations and co-pollutants, a rigorous statistical analysis is necessary in order to detect an effect.

Daily mortality and morbidity (hospitalizations, emergency department visits, etc.) are usually highly cyclic, and undergo strong seasonal fluctuations, with events such as hospitalizations highest on very cold and very hot days. Ambient ozone concentrations also are highly seasonal, with their highest levels in summer, and lowest levels in winter. Such seasonal trends could

bias the results, and they require some means of adjustment in order to study the question of whether there is any association or effect of ozone on these health endpoints. Otherwise the 'signal' would be indistinguishable from the background 'noise'.

A common method of removing cyclic variations in the data is prefiltering through the use of a multiday (e.g., 15-day or weighted 19-day) moving average, by subtracting this average from each data point prior to analysis. This is called a 'high pass' filter because it allows high frequency fluctuations (daily or weekly) to remain while removing the longer cycles from the data. Regressions with sine and cosine functions of various periodicities are also effective in removing seasonal variations in data. Seasonal dummy variables have been used, but they do not always control for within-season variability. Restriction of the analysis to one season or to a part of a season (one or two months) is another method to overcome seasonal variability (Kinney et al. 1995). A fourth method is the use of a nonparametric smoothing technique, using the LOESS (locally optimal estimating and smoothing scatter plots) method for estimation. This method is termed the STL method (Seasonal and Trend decomposition using LOESS) (Schwartz, 1995; Cakmak et al. 1998). By analyzing Toronto data on hospital admissions for 11 years using various techniques, Cakmak et al. (1998) showed that the ozone-hospitalization relationship was highly sensitive to the presence or absence of temporal adjustments for seasonal and day-of-week effects. The method of adjustment was not a critical factor; the STL/LOESS method gave the best fit to the data, followed by the high pass filter.

For ozone, the control of weather variables (temperature, humidity) has also proven to be very important. Ambient ozone is often highly correlated with temperature, and correlation coefficients can be greater than 0.6. Temperature can therefore be a prime confounding factor. Because of its high correlation with ozone, the separation of the two effects is often difficult to establish. If temperature is removed too early in the analysis before examining the relationship of ozone to the outcome, some part of the ozone effect is removed with it, and the relationship of ozone with the endpoint will be severely reduced or eliminated altogether (U.S. EPA, 1993; Lipfert, 1994). Inclusion of temperature in the regression analysis (rather than filtering it out beforehand) avoids this problem. On the other hand, because temperature is often independently associated with adverse health outcomes in a U-shaped dose response, with both very low and very high temperatures resulting in adverse health effects, some researchers have tried to adjust the effects of temperature by using non-linear models. This methodology has proven to be effective in teasing out the confounding effect of temperature (Moolgavkar et al., 1995; Anderson et al., 1996, Touloumi et al., 1997). Other variables include lag time, the duration between the exposure and the effect, should be included in the analysis, and most authors have investigated this aspect. Autocorrelation (pollution on one day is not independent of pollution the next day) is also likely to occur, and statistical methods are available to overcome this.

The detrended data are then examined using correlation analysis, regression analyses, or a combination of the two. Regression analysis has commonly been used in recent papers, preceded by correlation analysis in order to give some direction to the regression analysis. It is

not obvious at this time which regression model best fits the data, and no one model has been selected as preferential. As stated by Thurston & Kinney (1995), "in time-series analysis no model is perfect, but some models are more wrong than others". Poisson regression has been extensively used in the mortality data because mortality is a rare event, following a Poisson distribution. Log normal distributions, and Ordinary Least Squares (OLS) regressions are also common for hospitalization data. The results do not appear to be very sensitive to which of these is used (Kinney et al., 1995; Lipfert, 1994).

Many of the most recent papers using administrative databases have made use of these more sophisticated statistical techniques, to good effect. Those studies that have not, must be weighed more lightly in view of the strong possibility that the findings are spurious, due to confounding.

Additionally, airborne pollution always occurs as a mixture of agents, of which ozone is only one. Particulate matter (PM) has been the co-occurring pollutant of greatest concern with respect to confounding of the relationship between ozone and adverse health endpoints. PM is independently associated with adverse health outcomes including mortality, hospitalizations and Emergency Department visits, from cardiovascular as well as respiratory causes. PM is sometimes also correlated with ozone concentrations. The degree of correlation between the various metrics of PM and ozone is somewhat dependent on the location, (i.e. importance of local sources versus long-distance transport via movement of entire air masses, seasonal effects, etc.). Additional difficulties in the inclusion of PM in analyses are presented by the variety of metrics that have been used to measure it, and some controversy over which size of particles is responsible for the observations of adverse health effects. Total suspended particles (TSP) was used most frequently in the past, but has been replaced in some U.S. locations and complemented in some Canadian locations by PM_{10}, $PM_{2.5}$ or sulphates. Coefficient of Haze (COH) was also formerly measured. Visibility has also been used as a predictor for fine particles ($PM_{2.5}$). The sulphate fraction of particles is valuable as a surrogate for fine particles. Particle strong acidity has been suggested as the species that is partly responsible for the effect of particles on health, but direct measurements are available in very few localities. In addition, the presence of ammonia, which can change the acidity, is almost never measured. Further major difficulties are presented by the 6-day monitoring schedule for PM followed almost universally throughout North America, which has made it difficult or impossible to include PM in regression analyses for daily changes in pollutants compared to daily changes in adverse health outcomes. Similarly, other co-occurring pollutants often, but not always, have long-term fluctuations in levels. Many authors have not investigated the modifying effects of one or more of NO_2, SO_2, or CO on outcomes associated with ozone, although measurements were often available.

12.1.3 Selection Criteria For Quantitative Analysis (Meta-Analysis)

Many studies have attempted to determine the influence of ozone pollution on human health, which involves estimation of a parameter [such as relative risk (RR)] in a concentration-response function, along with a measure of the uncertainty of the estimate [such as 95% confidence interval (95% CI)]. Because uncertainty decreases as sample size increases,

combining data sets is expected to yield more reliable estimates of relative risk. Combining data from several comparable studies in order to analyze them together is often referred to as meta-analysis. A meta-analysis of the published studies is presented in this document for each category of health outcomes, based on the availability of the data, in order to evaluate whether they collectively indicate statistically significant associations for that outcome.

A list of criteria is used in this document to select studies for inclusion in the quantitative analysis, and, within selected studies, to select from among several reported results. A study is included in the quantitative analysis only if it:

1. measures daily mortality or hospitalization (i.e., is a time series study);

2. reports quantitative results for ozone;

3. is an original study (rather than a review paper or an abstract) in a peer-reviewed publication;

4. considers the entire population (rather than only a subset of the population) in the study location;

5. adjusts effects of some measure of seasonal cycle, temperature and relative humidity;

6. reports results from a co-pollutant model, including PM or some proxy for PM in the model with ozone; PM_{10} or $PM_{2.5}$ is preferable to other measures of particulate matter, and more pollutants in the model is preferable to fewer pollutants;

7. considers summer results when there are results from a whole year and from several seasons in the same study.

Reporting a statistically significant positive result for ozone is not a criterion for study selection, nor does statistical significance or size of relative risk affect the criteria for result selection within a study.

For meta-analysis, it is reasonable that a pooled estimate that combines the estimates from all selected studies, should give more weight to estimates from studies with smaller variances than those with larger variances. Variances provide an indication of the uncertainty associated with an estimated parameter. It also takes into account both the consistency of data and the sample size used to obtain the estimate, two key factors that influence the reliability of results.

12.2 MORTALITY STUDIES—ACUTE EFFECTS

Past acute episodes of air pollution, as in the London fog episodes of the early 1950s, have been linked to increased mortality due to the presence of particulate matter accompanied by sulphur dioxide. But until very recently, there have been only a few suggestive reports of associations between mortality and ozone pollution. Twenty-three studies reported as of April, 1997, were reviewed in detail (see Table 12.1a). The primary purpose of most of the studies was to examine the possible association of mortality with particulate matter, and relationships with ozone (or other co-pollutants) were reported as secondary findings. A summary of the results is presented in Table 12.1b for a more straightforward demonstration of the results.

Table 12.1b also lists the final selection of studies on mortality and the rationale for exclusion of some studies. During the analysis, reported RRs were converted as necessary so that all RRs were expressed in terms of a 1-hour maximum averaging period, so that they are directly comparable. The conversion was based upon the ratio of the mean concentrations experienced for each averaging time in that study area. If this concentration information was not available from a specific study, a conversion of 2.5 was used to convert 24-hour average RRs, and a conversion of 1.33 was used to convert 8-hour average RRs, based on past experience (Schwartz, 1997).

Sections 12.2.1 and 12.2.2 in this chapter discuss the merits and weaknesses of specific studies, and Section 12.2.3 discusses the effects of co-pollutants. Section 12.2.4 reports the results of meta-analysis of mortality studies.

Table 12.1a Ambient ozone and association with mortality

REFERENCE LOCATION TIME OF STUDY	OZONE, PPB	OTHER VARIABLES	STUDY DESIGN	RESULTS COMMENTS
Schwartz 1991 Detroit, Mich. (pop. 2,340,000) 10 years, 1973-82	Means of 1-h max. and daily mean (values not given) 2-3 monitors	TSP: 87 ug/m^3 (24-h mean) (daily TSP est. based on 6-day monitoring) SO_2: 12 ppb weather var. (temp, visibility, dew point) mean daily deaths 53/d	-daily deaths, excl. non-residents, accidents -Poisson regression analysis -author stated that included in regression (no details given) were terms for time trends in mortality, year, seasonal variation in weather, over dispersion, serial correlation, dummy variables for hot and cold days. -ozone, TSP and SO_2 regressed with a 1-day lag	"ozone was highly insignificant as a predictor of daily mortality" -Reanal. excl. winter months (not defined) did not improve correlation of ozone -TSP lagged 1 day was highly associated with daily mortality ($p<.0001$), and was independent of SO_2 Association of mortality with O_3 may have been attenuated because of method of accounting for seasonality in measurement and outcome variable. -TSP and SO_2 were both moderately high.O_3 was probably also moderately high, in the range 60-70 ppb for 1-h daily max., but TSP most important as predictor of mortality -No CO or NOx included in monitoring or analysis
Kinney & Ozkaynak 1991 Los Angeles Co. (pop. 7,477,000) 10 years, 1970-79	75 ± 45 (mean daily 1-h max.) (O_x –total oxidants) 8 monitors, whole county	KM (measure of particulates) 25±11 SO_2 15 ppb NO_2 69 ppb CO 8 ppm Weather var. (temp, rel. humidity, extinction coeff.) total deaths 152 ± 18/d respiratory 8 ± 4/d cardio-vasc. 87 ± 13/d	-total daily deaths excl. suicides, accidents daily deaths from cardiovasc., respiratory causes -multiple regression analysis -weighted 19-d filter (high-pass) for removal of seasonal trends in deaths and pollution vars. -day-of-week dummy variables, -autoregression terms, -carried out sensitivity analyses, different filtering, supplemental regressions	-oxidants (O_3) lagged 1 d were associated with total and cardio-vascular mortality ($p=0.001$) but not respiratory mortality (possibly because of small no. of respiratory deaths (cf. CV or total deaths)) -O_x, temp. and NO_2 explained 4% of total mortality. -NO_2, CO, KM all correlated, but less strongly than temp, O_3 -statistical analysis appeared adequate, exhaustive. -TSP or PM_{10} not used; KM may be poor substitute (compare results of 1995 study where relationship of O_3 was attenuated to non-significance when PM_{10} was included in regression (Kinney et al. 1995)

Table 12.1a Ambient ozone and association with mortality

REFERENCE LOCATION TIME OF STUDY	OZONE, PPB	OTHER VARIABLES	STUDY DESIGN	RESULTS COMMENTS
Dockery et al. 1992 St. Louis, Mo. (pop. 2,356,000) 1 year, Sept 85-Aug 86 Kingston-Harriman, TN (pop. 641,000) 1 year, Sept 85-Aug 86	St. Louis 22.5 ± 18.5 (24-h mean, approx. equiv. mean of 1-h daily max. = 68) K-H, Tenn. 23.0 ± 11.4 (as above) 1 monitor in each site	~~St. Louis~~ (24-h means) PM_{10} 27.6 ug/m^3 SO_4 —8.0 ug/m^3 H^+ —9.7 nmole/m^3 SO_2—5.1 ppb NO_2—20 ppb deaths 20,449 (8.6/1000 person-y) ~~K-H, Tenn.~~ PM_{10} 30.0 ug/m^3 SO_4 8.7 ug/m^3 H^+ 36.1 n/mole/m^3 SO_2 5.1 ppb NO_2 12.6 ppb deaths 5670 (8.8/1000 person-years) temp., dew point temp., both locations	-daily deaths, excl. accidents, non-residents -Poisson regression -model included seasonal indicators, weather variables for same day and previous day	-Ozone not associated with mortality in St Louis ($p>0.3$) or in Tennessee -PM_{10} (a 100 ug/m^3 increase) was associated with a 16% increase in mortality in St. Louis, but did not reach statistical significance in Tennessee. -$PM_{2.5}$, SO_4, and H^+ had a weaker association with mortality in St. Louis -no gaseous pollutant was significant in St Louis -No association of mortality with any of the measured pollutants was observed in Kingston-Harriman, Tennessee -Since association of PM_{10} remained strong, despite a relatively low level, we conclude that if associated at all, ozone is a much weaker predictor than PM_{10} -No CO measurements or inclusion in regression -A seasonal indicator is too coarse to act as a filter for within-season variations in ozone and in mortality; this would also hide an association with a weaker variate such as ozone. -using a 24-h mean value reduces significance of ozone, since it occurs in high daily peaks with low concentrations at night (usually)
Kinney & Ozkaynak 1992 (abstract) New York City (pop. 8,000,000) 6 years, 1971-76	56 (mean of 1-h daily max.) (April-Sept only for O_3 - 36 months total)	CoH, SO_2, (values not given) Weather (temp. RH, visibility) deaths 163/d	-analysis was similar to their Los Angeles study (K&O 1991) -daily deaths, excluding accidents, suicides -daily cardiovascular and respiratory deaths -multiple regression analysis, using weighted 19-day filter for removal of seasonal trends in deaths and pollution variables	-Model including daily temp., RH, CoH (a measure of fine particles) and ozone (lagged 1 day) explained 10% of variation in total mortality -Slope of regression line for ozone was 0.55 deaths/ppb ($p<0.001$) -no details of monitoring were available (no. of stations, mean values, etc.) -analysis was thorough, based on statement that analysis was similar to LA (Kinney & Ozkaynak 1991) -CoH may be poor indicator of particulates; no SO_4 measurements

Table 12.1a Ambient ozone and association with mortality

REFERENCE LOCATION TIME OF STUDY	OZONE, PPB	OTHER VARIABLES	STUDY DESIGN	RESULTS COMMENTS
Li & Roth 1995 Philadelphia (pop. 1,642,000) 18 years, 1973-90	19.8 ± 14.4 (24-h mean, equiv. 1-h max. = approx. 60)	TSP 68.5 ug/m^3 SO_2 16.98 ppb ~~deaths~~ <65y ≥65y total 19.1/d 35.2/d cancer 5.7/d 7.8/d COPD 0.23/d 0.75/d card-v 5.2/d 17.6/d pneum. 0.38/d 1.31/d other 7.58/d 7.75/d	-daily deaths, except accidents -subdiv. by age, <65 y; ≥65 y -subdiv by cause: cancer, COPD, card.-vasc dis. (CV), pneumonia, other -compared a variety of stat models and methods -Poisson regression, incl. log transform & sq. root form -multiple regression -autoregression -smoothed out cyclic variations by trigonometric fit, terms for day of year filtered by unweighted moving averages gave only t-values	-Authors concluded that (I) effects of pollution on mortality are dependent on weather, and (ii) results are not consistent between models -Results appear to have reasonable internal consistency: O_3 signif. related to mortality for age ≥65, in 7 of 8 t-tests when TSP, SO_2 also incl. (8th test used only a 7-d moving average, too short) -O_3 not related to deaths for people <65 y in most tests -O_3 reduced correlation between TSP & deaths -TSP highly sign. by itself, but not with other pollutants -SO_2 signif. in 6/8 analyses, with TSP, O_3 included. -analyses did not include filtering for mortality data, also highly seasonal. -No CO, Nox in model -number of deaths too small for analysis in most subcategories -results agreed qualitatively with Moolkavgar study on Philadelphia
Moolkavgar et al. 1995 Philadelphia (pop. 1,642,000) 16 years, 1973-88	22.4, yearly av. (24-h mean, equiv. 1-h max = approx. 65-70) (summer) (spring) (fall) 11.9 (winter)	~~TSP, ug/m^3~~ 74 (su.) 210 max 67 (sp) 338 max 65 (fall) 215 max 66 (w) 205 max ~~SO_2, ppb~~ (su) 156 max (sp) 101 max (f) 100 max (w) 103 max ~~daily deaths~~ 54.3 (yearly mean) (51.0, 54.4, 52.6, 59.3; Su, Sp, F, W)	-daily deaths, except accidents and suicides (includes residents and commuters) -Poisson regression analysis -no evidence of autocorrelation -analysis by each 3-m season -correlation analysis of pairs of pollutants -treated each day separately in another model (may have acted as a kind of filter) -pollutants were lagged 1 day, combined with same day temp. -also analyzed entire year a single series with indicator variables for year, season, and quartile of temperature.	-ozone was assoc. with mortality in summer only (RR= 1.15, CI 1.07-1.24) when TSP, SO_2, weather incl. In model -When ozone was discretized into quintiles, only highest gave a pos. assoc. (>47.7 to 154 ppb) -SO_2 associated in spring, fall and winter (RR=1.19, 1.14, 1.21) -TSP not signif. If ozone included into model in summer, or SO_2 in other seasons -No CO in analysis -results showing O_3 most strongly related to mortality, followed by SO_2, agreed with Li & Roth (1995)

Table 12.1a Ambient ozone and association with mortality

REFERENCE LOCATION TIME OF STUDY	OZONE, PPB	OTHER VARIABLES	STUDY DESIGN	RESULTS COMMENTS
Kinney et al. 1995 Los Angeles Co. (pop. 7,901,000) 6 years, 1985-90 (only every 6th day for ozone, total 364 days)	70± 41 (1-h max.) range 3-201 8 monitoring sites (only used data for days when PM_{10} available, N= 364)	~~PM_{10}, ug/m^3~~ 58± 23 (range 15-177) 4 sites, every 6th day (N= 364) ~~CO, ppb~~ 4.7±2.9 (range 1-13) 8 sites Weather- max. temp, mean RH deaths: 153±20/d	-daily deaths, excl. suicides, accidents, non-residents -the object was comparison of a range of statistical methods to derive RR for PM_{10} -OLS regression, log-linear anal., Poisson regression all tested (made little difference -cyclic data variations treated with dummy variables, season by season, 10-stage sine-cosine waves (couldn't use high-pass filter because had data for only every 6th day) -weather variables included -effects of other pollutants O_3 and CO tested with PM_{10}	-RR for O_3 only was 1.02 (1.00-1.05) when PM_{10} was included as a covariant, the RR for ozone was reduced to 1.00 (CI: 0.94-1.06). Ozone had no independent association with mortality; the data set for ozone was considered by the authors to be too small to draw any conclusions in view of expected weakness of association (N= 364 -RR of 1.05 for PM_{10} was unchanged when lag 1d O_3 and CO were included in the model -CO was also significant, with RR 1.05, same magnitude as PM_{10} (RR for PM_{10} reduced to 1.04 with CO in the regression)
Ozkaynak et al. 1995 (abstract) Toronto, Ont. (metro area) (pop. 3,000,000) 19 years, 1972-90	36 (mean of 1-h daily max.) (95th percentile approx. 66, Burnett et al. 1996)	Daily pollution data on TSP, SO_4, CoH, SO_2, CO, NO_2, from 16 monitoring stns. weather variables temp, RH. PM_{10} estim. from TSP Deaths 40/d	-daily plus cause-specific mortality, all ages categorized, for Metro Toronto -PM_{10} estimated from TSP data -multiple regression analysis including weather and air pollution variables -aggressive detrending of cyclic variations in both mortality and pollution data, using weighted 19-day linear filter -preliminary results only -preliminary results only	-Total estimated contribution of ozone plus particles to total daily mortality was approx. 3.8%, from model incl. temp, RH, same-day max O_3, TSP or PM_{10} -Ozone calc to contribute 1.5% and TSP 2.3% at the respective means (or 0.34% per 10 ppb of O_3 -slope for O_3 0.017 deaths/ppb -slope for TSP or PM_{10} 0.011/ug/m^3 (couldn't distinguish TSP from PM_{10})

Table 12.1a Ambient ozone and association with mortality

REFERENCE LOCATION TIME OF STUDY	OZONE, PPB	OTHER VARIABLES	STUDY DESIGN	RESULTS COMMENTS
Saldiva et al. 1995 Sao Paulo, Brazil (pop. 16,000,000) 1 year, May 90-Apr.91	38.5 (year), 17.7, (spr., sum.) (24-h means) (equiv. To approx. 36 as yearly mean of 1-h max) 38.3 max. year) 38.4 max. (spr, su) 4 monitoring stns	PM_{10} 82.4 ug/m^3 SO_2 6.5 ppb NOx 127 ppb CO 6.2 ppm PM_{10}, SO_2, CO at 8 monitoring stns., NOx at 3 stns. Deaths: 62.5/d (54.4/d in spr, sum.)	-daily mortality, persons >65y, within metro area -multiple and Poisson regression -controls, dummy variables for month of year, day of week, temp., rel. humidity -lagged moving averages of various lengths applied to air data (but not to mortality data) -autocorrelation adjustment -sensitivity analysis conducted	-Ozone (any measure) was not related to mortality when PM_{10} included as covariate -PM_{10} (100 ug/m^3 incr.) was assoc. with a 13% increase in mortality after inclusion of other covariates -linear relationship of quintiles from 45 to 130 ug/m^3, with RR=1 up to approx 60 ug/m^3 -assoc. of SO_2, NOx, CO disappeared after inclusion of PM_{10} in model (CO alone was stronger than PM_{10}) -Statistical analysis thorough, but mortality data unfiltered; makes difference in results obtained (Thurston & Kinney 1995) -Ozone levels were comparatively low while PM_{10} levels were very high; if both are involved in mortality increases, PM_{10} would act to obscure effect of ozone in this city.
Dockery et al. 1996 (abstract) Philadelphia (Pop. . 1,642,000) 1992-1993	N/A	$PM_{2.5}$, PM_{10}, SO_2 No data on values	-daily mortality, daily non trauma deaths-adjusted parametrically for trend, season, temperature and dew point -non parametric regression	-positive association between O_3 (0.9% increase in death for every 10µg/m^3 increase in O_3)—independent and additive to the $PM_{2.5}$ associations. O_3 was not consistent by season, since RR was lowest in summer. -association between daily non trauma deaths and $PM_{2.5}$ concentrations of the previous day (2% increase in death associated to 10µg/m^3 increase in $PM_{2.5}$ and to a lesser degree with PM_{10} (1.2% for 10µg/m^3 PM_{10}) -no association with coarse particles, total aerosol acidity, SO_2 and negative association with CO
Ito and Thurston 1996 Cook County (Chicago) (pop. 5.3 million in 1986) 1985-1990	38 ± 19.9 6 year average, 5 sites, average of all sites, missing data regressed from other sites	PM_{10} 40.7 ± 19.1 µg/m^3, CO 2.05 ± 0.95 ppm, SO_2 24.5 ± 14.7 ppb, Weather (T, RH, Bar. Pres., wind speed, B_{ext})	-daily mortality (two race categories: black and white, 3 age categories: 15-60, 60+ and all ages, male and female) -five death categories: total deaths excluding injury and poisoning, circulatory, respiratory, cancer and residual (total minus circulatory-respiratory-cancer) -Poisson regression or a log-linear Generalized Linear Model -adjusted for temperature, time-trend, day of week (dummy variables), long-wave cycles	-positive association between O_3 and total mortality with both single and two-pollutant models (RR=1.10; CI: 1.06-1.15 and RR=1.07; CI: 1.01-1.12 per 100 ppb increase of O_3 respectively) -positive associations were found also between O_3 and circulatory or cancer deaths, but not for respiratory or residual mortality (RR . 1.13; CI: 1.06-1.2, 1.09; CI: 0.99-1.18, 1.1; CI: 0.95-1.28, and 1.08; CI: 0.98-1.2 per 100 ppb of O_3 respectively) -correlation of PM_{10} and O_3 coefficients was -0.37, higher correlation between O_3 and T than PM_{10} and T, suggesting some degree of sharing of effects between PM_{10} and O_3, and O_3 and temperature -PM_{10} was associated with total, cancer, and respiratory mortality but not with circulatory or residual mortality (RR=1.05; CI: 1.03-1.08, 1.12; CI: 1.06-1.18, 1.14; CI: 1.04-1.25, 1.03; CI: 0.98-1.07, and 1.01; CI: 0.95-1.08 per 100 µg/m^3 PM_{10} respectively)

Table 12.1a Ambient ozone and association with mortality

REFERENCE LOCATION TIME OF STUDY	OZONE, PPB	OTHER VARIABLES	STUDY DESIGN	RESULTS COMMENTS
Anderson et al. 1996 London (England) April 1987 - March 1992	15.5 ± 10.9 (8 h average) 20.6 ± 13.2 (1 h maximum) Single background monitor	BS (black smoke): 14.6 ± 7.0 µg/m^3 (24h average) NO_2 37.2 ± 12.3 ppb (24 h average), 57.2 ± 23.0 ppb (1h max.) SO_2 32.0 ± 11.7 µg/m^3 (24h average) Temperature, Relative Humidity	-Poisson regression analysis of daily counts of deaths with adjustment for effects of secular trend, seasonal and other cyclical factors, day of week, holiday, influenza epidemic, temperature, humidity, and autocorrelation (lagged 0-3 days) -RR of death from all causes (excluding accidents), respiratory disease, and cardiovascular disease.	-positive association between O_3 and increase in all cause, cardiovascular, and respiratory mortality (same day) with greater effects in warm season -O_3 effects independent of other pollutants -during warm season, increase of 8 h O_3 concentration from 10th percentile to 90th percentile of the seasonal range (7-36 ppb) was associated RR=1.0348; 95% CI:1.0173-1.0526, RR=1.0355; CI: 1.0104-1.0613, RR=1.0541; CI: 1.0035-1.1073 respectively for all cause, cardiovascular and respiratory mortality - similar results of positive associations between O_3 and mortality were observed for 1 h maximum all year and warm season data -positive association between PM_{10} and all cause mortality (lag one day), independent of other pollutants, significant for all year, warm and cool season, but greater effect in warm season(RR= 1.0245; CI: 1.0088-1.0405 for warm season)
Sunyer et al. 1996 Barcelona (Spain) 1985-1991	28.1 (3.6-96.4)[2] in winter (w) 44.1 (4.8-144.4) in summer (s) 1h maximum	BS w=49.7µg/m^3 (11.4-66.7); s=35 µg/m^3 (10.6-125.6) 24h mean SO_2 w=46 µg/m^3 (2.2-160); s=36.4 (5.4-116.5) 24h mean NO_2 w=88.4 µg/m^3 (8.3-339.2); s=97.3 (8-336.4) Temperature, Relative Humidity,	-Autoregressive Poisson regression model analysis of daily variation in total mortality, mortality in subjects >70 years, and cardiovascular and respiratory mortality; -control for temperature, relative humidity, influenza epidemic, seasonality, day of week, holidays, long term trends	-positive association between O_3 and total mortality (lag 0), mortality >70 years (lag 1), cardiovascular mortality (cv) (lag1) for both all year (ay) and summer data (s) but not for winter (w): Total mortality (95%CI) RR: ay=1.048;(1.012-1.086), s=1.058; (1.017-1.101), Elderly mortality ay=1.042; (1.003-1.082), s=1.059; (1.016-1.105), cv mortality ay=1.058; (1.009-1.111), s=1.088; (1.028-1.152), correlation coefficient –0.33 (BS) to 0.3 (NO_2) -also positive associations between NO_2 and total mortality (lag1), mortality >70y (lag 1), and cardiovascular (lag 1) for ay, s but not w -strongest associations between SO_2 and total mortality (lag1), mortality >70y (lag 1), and cardiovascular (lag 1) for ay, s and w and also for summer and respiratory mortality (lag 0) -also strong associations between particles (BS) and total mortality (lag1), mortality >70y (lag 1), and cardiovascular (lag 1) for ay, w but not s, and possibly significant for ay & w for respiratory mortality (lag3) -all data are RR per 100 µg/m^3 increase in air pollutant

[2]Data provided in µg/m^3 and transformed in ppb

Table 12.1a Ambient ozone and association with mortality

REFERENCE LOCATION TIME OF STUDY	OZONE, PPB	OTHER VARIABLES	STUDY DESIGN	RESULTS COMMENTS
Verhoeff et al. 1996 Amsterdam (pop. 716,000 in 1992) 1986-1992	21.9 [3] (1h max.; percentiles:10 %=4.1, 25%=10.2, 50%=19.9, 75%=30.1, 90%=41.3, maximum value=153.3	BS=12 µg/m^3 (max=81) PM_{10}=38 µg/m^3 (max=163) SO_2=13 µg/m^3 (max=139) CO= 973µg/m^3 (max=9057) Temperature, Relative Humidity,	-Poisson regression analysis of total mortality and age stratified mortality (Municipal population register--no data on cause of death) study may be bias because of this oversight -control for seasonal and long-term temporal patterns (year of study, month, day of the week, epidemic of influenza-type illnesses, weather terms) -current day, lag 1, 2 days data	-positive association between O_3 and total mortality (lag 2 d), single pollutant model: RR=1.049 (95% CI: 1.001-1.100) for 100 µg/m^3 increase (or 50 ppb), or RR=1.098 (CI:1.002-1.200) for 100 ppb increase. -positive association between BS and total mortality with one pollutant (current day) RR=1.187; CI: 1.020-1.380, and two pollutant models +SO_2-RR=1.265; CI: 1.073-1, +CO-RR=1.203; CI: 1.005-1.441, +O_3-RR=1.178; CI: 1.011-1.373 - inclusion of O_3 and BS together reduced RR of O_3 to 1.029 (CI: 0.967-1.096) per 50 ppb increase, while BS remained stable; -inclusion of O_3 and PM_{10} together in the model reduced the RR of each pollutant. Ozone RR=1.050 (CI: 0.947-1.165) per 50 ppb increase. - warm season (May – October) RR for ozone (single-variate model) was 1.04 (95%CI 0.99-1.09) per 50 ppb. -Mortality data: accidental death included
Zmirou et al.1996 Lyon (France) pop. 410,000 1985-1990	7.75 (0-77) (1h max.) 5.1 (0-40.2) (8-h mean) One site (urban centre)	SO_2 (5 sites)24h mean=46.76 (2.16-314.57); 1 h max. 100.22 (4.71-635.69) PM_{13} (3 sites) 24h mean 38.05 (2.67-179.81) NO_2 (1 site) 24h mean = 70.17 (3.50-323.75); 1h max. 132.73 (9.55-737.26) Temperature, Relative Humidity	-Poisson regression of total mortality (accidental deaths excluded), respiratory, cardiovascular and digestive causes (control) controlling for best fit time patterns and weather factors (trends, day of week, holiday, temperature, humidity, autocorrelation)	-no association between mortality and O_3 ; RR (1-h max.)=1.16 (95% CI: 0.76-1.64); RR (8-h mean)= 1.12 -only one site for O_3 monitoring in urban centre, potential scavenging, may not reflect actual population exposure -ozone concentrations very low, + number of deaths/day also low, leading to instability on results -SO_2 is the only pollutant that shows a clear association with mortality in the city of Lyon (total, respiratory, cardiovascular) -PM_{13} was associated with cardiovascular and respiratory mortality (marginal for cv mortality) -no association was found between any of the pollutants and digestive mortality (control) (0.80-1.48).

[3] Data provided in µg/m^3 and transformed in ppb.

Table 12.1a Ambient ozone and association with mortality

REFERENCE LOCATION TIME OF STUDY	OZONE, PPB	OTHER VARIABLES	STUDY DESIGN	RESULTS COMMENTS
Ostro et al. 1996 Santiago, Chile (pop. 4.4 million) 1989-1991	1h (max.) 52.8 ppb (11-264)	PM_{10} 24h mean: 112.9 (32-336), 119.5 (30-367), 113.4 (35-308) $\mu g/m^3$ respectively for each year; daily max: 147.2 (35-500), 143.5 (35-424), 132.9 (39-340) NO_2 1h max. 55.6 (10-258) ppb SO_2 1h max. 59.9 (4-363) ppb Temperature, Relative Humidity	Poisson regression of specific mortality, and least square regression and parametric tests were used for total mortality (results from both distribution techniques are reported) controlling for temperature, month, season, day of the week	-positive association between total mortality and O_3 for summer months only using both methods (RR=1.02; CI: 1.00-1.05 and RR=1.04; CI: 1.00-1.09 per 100 ppb using least square and Poisson regression respectively) -O_3 was well correlated with max. temperature (r=0.68) and to a lesser degree with min. temperature (r=0.42) -positive association between PM_{10} and mortality (total, specific, age stratified)--association remained significant all two pollutant models -authors conclude that O_3 may have an independent effect on mortality as it had a stronger association with mortality (based on p-value) than did PM_{10}
Dab et al. 1996 Paris France (pop. 6.1 million) 1987-1992	22.3 (3-75) 5th-95th%(1-h max.) 14.1 (10-56)(8-h mean) (5th-95th)	SO_2 29.7 (24-h) 59.9 (1-h) BS 31.9 (24-h) PM_{13} 50.8 (24-h) NO_2 45.0 (24-h) 73.8 (1-h)(all Fg/m^3)	Poisson autoregression models Respiratory mortality only Controls for best fit models including long term trends, seasonal, weekly + daily patterns, holidays, influenza epidemics and weather (temperature, humidity)	The ozone RR for respiratory deaths was elevated, but 95% confidence limits were wide and included the null value. RR 1.16 (95% CI 0.87-1.62) (1-h max, 100 ppb increase) RR 1.29 (95% CI 0.87-1.94) (8-h mean, 100 ppb)
Touloumi et al. 1997 6 APHEA cities 3 additional cities	Athens 48 Barcelona 37 Koln (no data) London 21 Lyon 7.6 Paris 23 Amsterdam 22 Basle (not given Zurich (A @)	 BS 84.4 NO_2 135 ($\mu g/m^3$) BS 46.6 NO_2 97.8 BS 14.6 NO_2 109.4 BS 31.6 NO_2 70.1	Data were analysed by each city separately following a standardised methodology to ensure comparability of results. Poisson autoregressive models were used for control of seasons, temperature, humidity, and influenza epidemics. Fixed effects models were used to pool the individual regression coefficients when there was no evidence of heterogeneity among the cities and random effects models otherwise. For meta-analysis, Amsterdam, Basel, Geneva and Zurich were added.	-Positive associations between daily deaths and NO_2 and ozone. Increases in 50 $\mu g/m^3$ in NO_2 (1-hr max.) or 25 ppb ozone (1-hr max.) were associated with a 1.3% (95% CI 0.9 – 1.8%) and 2.9% (95% CI 1.0- 1.9%) increase in the daily number of deaths, respectively. - RR of ozone in the model including NO_2 was 3.2% (95% CI – 0.3 to 6.8%). RR of NO_2 in the model including ozone was 1.5% (95% CI 0.9 to 2.0%). Stratified analysis of NO_2 effects by low and high levels of black smoke or ozone showed no significant evidence for an interaction within each city. -The pooled estimate of RR for ozone effect was slightly reduced [2.8% (95%CI 0.5 to 5.0%)], whereas the one for NO_2 was almost halved but remained significant[0.6% (95%CI 0 to 1.2%)], when two pollutant models including black smoke were applied.

Table 12.1a Ambient ozone and association with mortality

REFERENCE LOCATION TIME OF STUDY	OZONE, PPB	OTHER VARIABLES	STUDY DESIGN	RESULTS COMMENTS
Loomis et al., 1996 Mexico City (5 sub-areas) 1990-1992 3 years, 1990-1992	O_3 daily 1-h maximum: 154 ppb (range 26-319 ppb) The 1-h max. value of ozone was above 120 ppb, approximately 75% of the days. O_3 24-h mean: 62 ppb (range 12 -130 ppb)	TSP: every 6 th day as a 24-h mean: 168 µg/m^3 (86-460 µg/m^3) SO_2 as an 24-h mean: 54 ppb (9-135 ppb) Also monitored: temperature (daily minimum and maximum, daily average and difference between min. and max.) 9 monitoring stations Total deaths: 31/d	-Number of daily deaths in the 5 sub-areas -Deaths were grouped by age (<5yr, 5-64y, ≥65y) and causes (respiratory diseases, cardiovascular diseases, accidents and other causes) -Poisson regression analysis (controlling for potentially confounding covariates: temperature, periodic phenomena related to the year, the months, the day of the week and holidays -Same day and lagged 1 day checked -Temperature indices with lags of one to nine days were tested	When reviewed only single pollutants in the statistical model: -daily deaths increased 5.4% for each 100 µg/m^3 increase in TSP -daily deaths increases 7.5% for each 100 ppb increase in SO_2 -daily deaths increased 2.9% for each 100 ppb increase in O_3 (RR=1.029, 95% CI= 1.015-1.044) (this excess mortality was greater for people aged ≥65 years) -When O_3, TSP and SO_2 were included in the model, only the association with TSP with the observed increase in daily mortality was statistically significant [RR=1.052 (95% CI= 1.034-1.072)] -Bivariate of O_3 and SO_2 not given

Table 12.1a Ambient ozone and association with mortality

REFERENCE LOCATION TIME OF STUDY	OZONE, PPB	OTHER VARIABLES	STUDY DESIGN	RESULTS COMMENTS
Kelsall et al., 1997; Samet et al., 1997 Philadelphia, PA 15 years, 1974-1988	O_3 24-h mean 19.8 ± 14.6 ppb 8.3-28.5 IQR (=20.2)	Other pollutants were measured over a 24-h period (mean): TSP: 37.3 $\mu g/m^3$ SO_2: 17.3 ppb NO_2: 39.6 ppb CO: 17.4 ppb (x100) Total deaths: 46.7/d Respiratory: 2.5/d Cardiovascular: 20.2/d Other 24.0/d	-Number of deaths of Philadelphia residents (mortality data were stratified by age (<64y, 65-74y, ≥75y) and causes of deaths (respiratory, cardiovascular and others) -Estimation of the percentage change in daily mortality per interquartile change in each of the air quality variables, controlling for day of the week and long-term and weather-related trends -Poisson regression analysis with fitting generalized additive models (GAM) -Study of the effect of each pollutant individually (with controlling for time trends, season and weather) and then in pairs and finally all pollutants together	-O_3 was weakly correlated with the concentrations of other pollutants -Mortality significantly increased with increasing TSP, and O_3. -1.1% increase in mean mortality attributable to a 10 ppb increase in mean daily ozone in univariate analysis (2% increase for 20.2 ppb ozone). -TSP remained statistically significant in the model along with O_3 -When TSP and SO_2 considered together: their effect dropped by approximately 40% -O_3, TSP, SO_2, NO_2 and CO together: significant effects of SO_2 and O_3 -TSP effect was strongest in spring and summer and O_3 effect was greatest in winter and fall -TSP effect tended to be greatest in the oldest category (≥75y) - O_3 effect was positive across all cause-of-deaths categories with no consistent variation by age groups -Results agreed with Moolkavgar and Li & Roth studies

Table 12.1a Ambient ozone and association with mortality

REFERENCE LOCATION TIME OF STUDY	OZONE, PPB	OTHER VARIABLES	STUDY DESIGN	RESULTS COMMENTS
Wietlisbach et al., 1996 Zurich, Basle and Geneva, Switzerland, 1984 – 1989.	Mean ± SD (presumably 24-h average), µg/m^3: Zurich: 26.9 ± 21.0; Basle: 23.9 ± 19.4; Geneva: 0	Total mortality, mortality for people >65 y, respiratory mortality, cardiovascular mortality. TSP, SO_2, NO_2, CO, temperature, RH	1. Standard Poisson regression model to evaluate time trends, seasons and weather variables (temperature and RH) alone with pollutants. 2. Semi- and fully-nonparametric Poisson models, locally weighted regression smoothing. Data reported using this model. 3. Gaussian regression models; co-variates in the models.	• Association of mortality with ozone was weak and inconsistent. • Mortality was associated with TSP, SO_2, and NO_2. • When all five pollutants were in the model, regression coefficients on the pollutants were unstable and statistically insignificant: -For total mortality, regression coefficient (± SE) for Zurich was 0.012 (0.027), for Basle 0.075 (0.074), and no data for Geneva. -For mortality of people >65 years of age, regression coefficient (± SE) for Zurich was 0.005 (0.030), for Basle 0.145 (0.083, $p<0.05$), and no data for Geneva. -For respiratory mortality, regression coefficient (± SE) for Zurich was -0.151 (0.067, $p<0.05$), for Basle 0.193 (0.155), and no data for Geneva. -For cardiac mortality, regression coefficient (± SE) for Zurich was –0.003 (0.040), for Basle –0.163 (0.116), and no data for Geneva
Burnett et al., 1998 Canada (11 cities) (pop. 10,800,000) 12 years (4383 days), 1980-1991	O_3 24-h average of 11 cities: 16.2 ppb Data were averaged over all monitoring stations in each city (data not given)	Monitored as an 24-h period (mean): NO_2: 23.5 ppb SO_2: 5.4 ppb CO: 1.0 ppm Also monitored: daily 1-h maximum and minimum temperature, daily average dew point and relative humidity Non-accidental deaths: 816 991 deaths; 196.5/d	-Number of daily deaths for non-accidental causes: (ICD-9, codes 1-799) -Multiple regression analysis, using a 19-weighted linear filter to remove city-specific long term trends, seasonal, sub-seasonal, day of study, day of the week effects and weather	-Day to day variations in O_3 were negatively correlated with NO_2, SO_2 and CO -CO and NO_2 were highly correlated; NO_2 and SO_2 were also positively correlated, CO and SO_2 were positively associated too. -Based on a single pollutant model, a 0.9% ($p \leq 0.05$) increase in mortality was associated with a 10 ppb increase in 24-h mean O_3 -NO_2 had the largest effect on mortality with a 4.1% increased risk ($p<0.01$) followed by O_3 at 1.8% ($p<0.01$), SO_2 at 1.4% ($p<0.01$) and CO at 0.9% ($p=0.04$). in a multiple pollutant regression models. -All pollutants together: association of 8.2% of premature deaths -$NO_2 > O_3 > SO_2 > CO$ -When cities were analyzed separately: 24-h O_3 was a significant predictor of mortality in 6 cities

12.2.1 Studies reporting significantly positive associations between ozone and mortality

Seventeen of the 23 mortality studies reported statistically significant positive associations between increases in mortality and ground level ozone pollution, using single- or multiple-pollutant models. These associations could not usually be explained on the basis of yearly trends, day-to-day variations, epidemics, or weather. The latter is the most important source of variation with respect to the ozone-mortality association because ozone is often correlated with temperature in summer, while both minimum and maximum temperatures have also been associated with increased mortality. All studies adjusted temperature and relative humidity in some way in their regressions, and also included other cyclic factors that were shown to influence the results during preliminary analyses. These associations were found in cities across North America, in 4 U.S. and 13 Canadian locations, in Santiago Chile and three European cities, and in a meta-analysis including seven European cities, demonstrating consistency of results despite widely varying climatic conditions and pollutant mixtures.

These associations were reported for cities with mean ozone concentrations (reported as the one-hour maximum) between 20 and 75 ppb, i.e. below, and in most cases well below the current Canadian objective for ozone of 82 ppb. However, some lack of predictability using this criterion alone was noted due to negative results in several cities with mean concentrations from 22 ppb [Paris (Dab et al., 1996), Amsterdam (Verhoeff et al., 1996)] to as high as 154 ppb in Mexico City.

Twelve of these studies with significant results provided quantitative estimates of risk based on regressions including ozone as the only air pollutant in the model, adjusted for weather, season and other cyclic variables. The relative risks (RR) for all-cause mortality (excluding accidents in many studies) varied between 0.24% and 1.16% per 10 ppb increase in ozone, measured as the 1-hour maximum. The mean RR (from studies with significant results, n=12) was an increase in daily mortality of 0.65% (standard deviation 0.36%) per 10 ppb increase in ozone, and the median was 0.53%. The multi-pollutant analysis data will be discussed in Section 12.2.3.

In terms of the impact of particulate matter on the association between ozone and mortality, in Los Angeles (Kinney & Ozkaynak, 1991) and New York (Kinney & Ozkaynak, 1992), the particulate pollution did not have a completely satisfactory surrogate. KM (an optical measurement) was used in Los Angeles while COH (another optical reading of carbonaceous soot) was used in New York (no sulphate measurements were given in either location). Particulate matter was not strongly associated with mortality in either location, and the possibility exists that at least some of the relationship seen with ozone could have been due to particulate matter. In a later analysis of pollution data from Los Angeles (1985-90), in which PM_{10} measurements were available, ozone was not found to be related to mortality after inclusion of PM_{10}. The authors cautioned that too few co-occurring data points were available (n=364) to separate their effects (Kinney et al., 1995). In Toronto, the small but significant relationship of ozone (estimated to account for 1.5% of additional mortality at 36 ppb) and the somewhat stronger association of TSP and PM_{10} (2.3%) to daily mortality (at 42 ug/m^3 PM_{10}) may be a reasonably accurate reflection of the true relationship between these two pollutants and daily mortality in this location (Ozkaynak et al., 1995). Ozone was relatively lower than in Los Angeles (36 ppb, mean of 1-h daily max.); daily TSP and sulphate measurements were available, and PM_{10} was estimated from these.

Li and Roth (1995), Moolkavgar et al. (1995), Samet et al. (1997) and Kelsall (1997) all looked at data from Philadelphia which were extensions and reanalyses of data from earlier studies (Shumway et al., 1988; Schwartz & Dockery, 1992) showing a relationship of TSP to daily mortality. Li and Roth (1995) were most interested in testing a wide variety of statistical models for comparison purposes, and presented only t-values for TSP, SO_2, and ozone, showing considerable model-dependent variability. In the summer only, ozone was significantly associated with mortality in people over age 65, in 7 of 8 models, with t-values ranging from 2.8 to 3.8 for 6 of the 7 positive tests (the seventh was highly significant at 5.8). The first two studies were remarkably consistent (considering differences in methodology) in finding ozone to be most strongly related to mortality, with SO_2 also related, although less strongly, and in finding the association between TSP and mortality to be insignificant after ozone and SO_2 were included in the analysis.

The study by Moolkavgar et al. (1995) treated each day of the year separately (18 years), and used indicator variables in their regression for year, season, and temperature. The reason for the lack of significance of TSP in Philadelphia was unclear. The recent extensive re-analysis of the Philadelphia data by the Health Effects Institute (Samet et al., 1997, Kelsall et al., 1997) confirmed that ozone was an important element of the air pollution mixture associated with mortality in Philadelphia. There was an estimated 1.1% increase in mean mortality attributable to a 10 ppb increase in mean daily ozone in univariate analysis and also 1.0% in a multipollutant analysis that included all five “criteria” pollutants. The coefficients for TSP and SO_2 were about half that for ozone, while NO_2 and CO were not found to have a positive association in univariate analyses, thus confirming the previous Philadelphia findings on the role of O_3 and SO_2 , but adding TSP as an important predictor of mortality. The reversal of the roles of NO_2 and TSP in the bivariate regression is a reflection of the high correlation coefficient between these pollutants.

Subdivision of total deaths into respiratory and cardiovascular causes was investigated by Kinney & Ozkaynak (1991) for Los Angeles. Oxidants (mostly ozone) were associated with total and cardiovascular deaths, but not with respiratory deaths, contrary to expectations based on morbidity studies and clinical studies in which the only effects were respiratory in nature. However, the number of respiratory deaths per day (8) was very low, and was less than one-tenth the cardiovascular deaths (87/day), quite possibly accounting for the observed lack of association with respiratory deaths.

More recently, studies by Dockery et al.(1996), Ito and Thurston (1996), Loomis et al. (1996), Sunyer et al.(1996), Anderson et al.(1996), Verhoeff et al.(1996), Ostro et al. (1996), Touloumi et al. (1997), Kelsall et al. (1997), Samet et al., (1997), and Burnett et al. (1998), examined 7 cities plus two groups of cities (one in Europe and one in Canada) and found positive associations between ozone and total mortality.

Dockery et al. (1996) is only an abstract with limited information on ozone. The authors state that there is a specific effect of fine particles (PM_{10} and $PM_{2.5}$) with a possible additional effect of ozone. A 0.9% increase in mortality per 10 ppb ozone was estimated in a bivariate regression including $PM_{2.5}$, which remained significantly associated with mortality. The association of ozone with mortality is considered to be independent and additive to the $PM_{2.5}$ association.

Ito and Thurston (1996) looked mainly at the association of PM_{10} and mortality. Three categories of deaths (cancer, respiratory, circulatory) plus total non-accidental and residual deaths (total minus the three categories) were included in the data. It was found that both PM_{10} and ozone

were associated with increases in total and cancer mortality (using single and two-pollutant models). A 1% increase in total non-accidental mortality was predicted for a 10 ppb increase of O_3; this estimate was reduced to a 0.7% increase (95% CI: 0.1-1.2%) when PM_{10} was included in a bivariate regression. Respiratory mortality was associated only with PM_{10} and circulatory mortality only with ozone. The total number of deaths per day was 9.8 for respiratory causes this resulted in a larger standard deviation (SD) than that for circulatory causes, which might explain the lack of significance for ozone. The authors stated that the relative risk (RR) were more uniform among the categories for ozone when compared to PM_{10}. The interpretation of the results for PM_{10} and breakdown by race, gender and cause specificity were not conclusive because of large standard errors for these small-count sub-categories. The authors concluded that in this study, both ozone and temperature showed no cause-specificity, while PM_{10} was more cause-specific for respiratory and cancer deaths. The authors also suggested that some residual confounding of the ozone results by temperature may have occurred.

A study on a second large Latin America city, Mexico City (Loomis et al., 1996), demonstrated a very small positive association between O_3 and mortality, with a 0.24% (95% CI 0.1-0.4%) increase in mortality per 10 ppb increase in ozone, measured at the 1-hour maximum. Ozone related mortality was increased for the elderly, aged $\geq$65y, and for cardiovascular disease (CVD), but not for respiratory diseases, possibly because of low numbers of deaths from respiratory diseases (3/day) compared to death from CVD. PM_{10} was a much more important predictor of mortality than ozone in this location, and bivariate analysis including both pollutants resulted in loss of association between O_3 and mortality. Further discussion of these results follows in section 12.2.3.

In the study by Sunyer et al., (1996) in Barcelona, a 10 ppb increase in ozone (1-h max) was associated with a 0.96% increase in mortality (95% CI 0.24-1.72%), and the risk was increased to 1.16% when summer months only were included. In this study, SO_2 was the pollutant that was most highly associated with mortality (all categories except respiratory) and the only one associated with respiratory mortality. RRs for this pollutant were all higher than for any of the other pollutants. No co-regressions with combination of pollutants were performed because of high colinearities between pollutants. It is, therefore, impossible to determine if the effects attributed to ozone were truly independent of other pollutants. The interaction between pollutants and season were assessed. Some correlation was found between the following pollutants and physical variables: between ozone and temperature (r=0.415), PM_{10} and SO_2 (r=0.634), PM_{10} and ozone (r=-0.334).

Only one monitor was used for ozone in the Anderson et al. (1996) study in London (UK), which may not properly reflect the levels in London because of its central urban location and greater probability for scavenging effect, and may have caused misclassification of exposure. A positive association was found between ozone and total mortality, as well as cardiovascular mortality and respiratory mortality. These effects were greater during the warm season. The ozone effects were also independent of other pollutants, particularly British Smoke Shade (BS), which was not found to be associated with mortality after accounting for the ozone effect.

In the study by Verhoeff et al. (1996), the authors used the Municipal Population Registry which does not provide the cause of death. This limitation in the study may have introduced a slight bias since information on accidental deaths is included in the mortality data (accidental deaths were roughly five percent of total deaths). The study found a positive association between ozone and total mortality, with an estimated 0.98% increase in premature deaths per 10 ppb increase in O_3

(95% CI 0.02-2.0). In bivariate regressions with BS or PM_{10}, the confidence limits of the regression coefficient for O_3 were broadened and included the null value. The study is nonetheless considered to provide support for the association of ozone with mortality for the reasons outlined in section 12.2.3.

Ostro et al. (1996) used two different regression models, the Poisson model and the ordinary least squares (OLS) model, to study the association of mortality and pollutants in Santiago, Chile. When applied to ozone, both models demonstrated a significant association with total mortality only during the summer months with an estimated 0.4% (95% CI 0.0%-1.0%) increase for each 10 ppb increase in O_3 in single-pollutant analysis (Poisson model, 0.2% increase from OLS model). The authors concluded that ozone may have an independent effect on mortality, as ozone correlated weakly with PM_{10}, NO_2 and SO_2 (r was –0.23, -0.06 and 0.00, respectively), and ozone retained its significant association with mortality when both PM_{10} and ozone were included in bivariate analyses.

In the recently published European APHEA (Air Pollution and Health – A European Approach) study (Touloumi et al., 1997), six cities (Athens, Barcelona, Koln, London, Lyon and Paris) spanning Central and Western Europe, were examined. The mean of the hourly maximum of ozone varied from 93.8 ppb in Athens to 15.2 ppb in Lyon. Particulate pollution was measured as BS. The data were analyzed by each center separately following a standardized methodology to ensure comparability of results. Poisson autoregressive models allowing for overdispersion were fitted to remove seasonal and long-term trends from the mortality series, day of the week patterns, local characteristics such as holidays, and influenza epidemics. Meta-analyses were conducted using fixed effects models to pool the individual regression coefficients when there was no evidence of heterogeneity among the cities, and using random effects models otherwise. Data reported a significant association between daily mortality and ozone levels, and nitrogen dioxide as well. Stratified analysis of nitrogen dioxide effects by low and high levels of BS or ozone showed no significant evidence for an interaction within each city. The association was such that the authors concluded that an increase of 50 $\mu g/m^3$ (25 ppb) in ozone for the hourly maximum would result in a 2.9% increase in the number of deaths from all causes.

The authors (Touloumi et al., 1997) further conducted a meta-analysis adding four more European cities (Amsterdam, Basle, Geneva and Zurich), which resulted in a virtually identical estimate. It is of interest to note that the risk estimates for the cities of Paris, Amsterdam, Zurich and Basle were of marginal significance when considered individually, but treatment as a unit narrowed the confidence limits and increased the statistical significance. These two groups of cities were admirable candidates for meta-analysis because they all used similar protocols.

Burnett et al. (1998) have shown a positive association between O_3 and total non-accidental mortality in 11 Canadian cities. Based on a single pollutant model, a 0.86% ($p \leq 0.05$) increase in mortality was associated with a 10 ppb increase in 24-h mean ozone, in the 11 cities considered together (population 10.8 million studied over the 12-year period 1980-1991). NO_2 had the highest contribution to the air pollution effect on mortality (5.3% for a 23.5 ppb mean increase) followed by CO (2.5%) and SO_2 (1.8%) for 1 ppm and 5.4 ppb mean increases respectively. When all gaseous pollutants were included simultaneously, it was estimated that a total of 8.2% premature deaths were associated with the gaseous air pollutants, of which ozone contributes approximately one-fifth, NO_2 one-half, SO_2 one sixth, (all at $p \leq 0.01$) and CO one tenth ($p \leq 0.05$). When individual cities were analyzed separately, 24-h ozone was a significant predictor of mortality in 6 of the eleven cities.

Two potential problems with this study concern the lack of data on particulate matter and its effect on the risk estimates, and the problems created by including moderately or highly collinear pollutants together in multivariate analysis. In a previous paper on hospitalization data by the same group of authors (Burnett et al., 1997a) the entire air pollution effect was claimed to be explained by a combination of the gaseous pollutants, with no additional increase in model fit after adding particulate matter. The present paper attributes about an additional 1% to particles (+8% from the gases) in a separate analysis of the effect of reduction of sulphur in gasoline on mortality in 5 of the 11 cities.

The problem of collinearity appears to be a reasonable explanation of the inconsistency of effects of ozone and other pollutants, in individual cities. Although the average correlation coefficients were low or low-moderate ($r \leq 0.35$), they were much higher in some cities (e.g. $r=0.7$ for NO_2-CO in Edmonton).

In an analysis conducted for the Working Group on Air Quality Objectives and Guidelines (WGAQOG) of CEPA/FPAC, Burnett (1998) expanded the 11-city analysis to 13 cities, including Halifax and St-John to represent the Atlantic Region. In this case, 1-hour maximum ozone was used to examine the relationship between ozone and non-accidental mortality. Both the mortality data and the daily variations in 1-hour maximum ozone levels were adjusted using pre-filtered non-parametric smoothed functions of day of study and day of week differences for each city, which also acted to normalize data among cities. City-specific weather effects were also removed by adjusting temperature, daily average dew point temperature, and average relative humidity in non-parametric smoothed functions. Current day, and lag one to 4 days were considered. (See Appendix A for detailed methodology and results).

Data from this analysis (Burnett, 1998) demonstrate that the risk of premature mortality attributable to a 10 ppb increase in (1-h maximum) ozone was 0.79% (95% CI: 0.59-0.99%) for current day exposure (lag 0 d) and 0.65 ± 0.11% for the previous day exposure (lag 1 d). The risk decreased for each successive lag day, and the confidence intervals included the null value for lag days 3 and 4. The results were obtained using the combined data from the 13 cities, in order to utilize information from all regions of the country as well as to increase statistical power. The concentration-response curve appeared to be linear (not shown). A sensitivity analysis was undertaken to find the lowest ambient ozone concentration that could be statistically associated with mortality, by progressively removing days when the concentration was above 50, 45, 40, 35, 30, 25, 20, 15, and 10 ppb, respectively. The risk remained essentially constant (0.77 to 0.92% per 10 ppb increase) for all concentrations at 20 ppb and above, at the 99% confidence level ($p<0.01$. There was no evidence for a threshold in the mortality data. A difficulty with this analysis is the lack of accounting for the potentially confounding effect of other air pollutants. However, a similar analysis with most of the same data set demonstrated that CO, NO_2, and SO_2 did not confound the effect of ozone on mortality (Burnett et al., 1998). Fine particles are also a possibility for confounding effects, but daily measures of particulate mass were not available for the 13 cities in this analysis. Since ozone and fine particles are not correlated when the entire year is examined, and since fine mass (as sulphates) did not confound this association between ozone and hospitalization in Southern Ontario (Burnett et al., 1994, 1995), this provides some assurance that ozone acts independently in its effects on mortality in the Burnett (1998) analysis.

12.2.2 Studies reporting non-significant associations between ozone and mortality

In six studies (7 locations), no significant relationship of ozone to mortality was found (Schwartz, 1991; Dockery et al., 1992; Saldiva et al., 1995; Zmirou et al., 1996; Dab et al., 1996 and Wietlisbach et al. (1996)). In the first five of these six, groups of investigators used similar methodology (Schwartz, 1991, 1996; Dockery et al., 1992), applying a number of techniques to smooth out seasonal variability, and temperature/weather effects, though not a high-pass filter such as the 19-day weighted moving average. A problem associated with the use of a dummy variable as a seasonal filter, as in the Detroit MI (Schwartz 1991), St. Louis MO and Harriman TN (Dockery et al., 1992) studies, would be that the dummy variable would not act as a complete filter, being too coarse to allow detection of a weak ozone signal. Another problem of the Dockery et al. (1992) study, which was pointed out in the U.S. EPA Criteria Summary (1993), was the adjustment for the short-wave influences of temperature on mortality as a separate step prior to consideration of ozone. Since ozone is usually correlated with temperature, this would tend to pre-filter out the signal of interest, and might (improperly) remove all short-wave ozone-mortality association that is correlated with temperature. In addition, monitoring was conducted poorly in this study, and the single monitor in each large area might lead to considerable error in estimating population exposures, thus leading to misclassification.

Saldiva et al. (1995) performed a statistical analysis that included only 3 dummy variables for temperature and a monthly correction for season. This might not be adequate to demonstrate an association of mortality with ozone due to its high correlation with temperature and season. In Sao Paulo, ozone levels (38 ppb 1-h maximum) were low for a large Latin American city, while PM_{10} levels were very high (82 $\mu g/m^3$ annual mean), such that any weak effect of ozone could have been overwhelmed by the much stronger association of PM_{10}.

In the study by Dab et al. (1996) in Paris France, only respiratory mortality was examined, which had very low rate (9 deaths/day) compared with total mortality (37 deaths/day). This was probably insufficient to detect a significant association with ozone, although associations with mortality were found for PM_{13} and SO_2. In this study, temperature was treated as a linear variable although it is not the case, which could result in an underestimate of the ozone effects. In addition, the Paris analysis was carried out using only one of three ozone-monitoring networks, the one that was not representative of areas of high population density. This would result in more serious misclassification for ozone than for particulate matter, since large differences in ozone have been found between central-city and suburban monitors, while particulate matter concentrations usually are highly correlated across the region.

In the study by Zmirou et al. (1996) for Lyon France, only one monitoring site, in the urban centre, was available for ozone. This would increase the potential for scavenging of ozone by NO_2, and may not reflect actual population exposure to ozone. Ozone concentrations were much lower in this study (mean of 1-h maximum 7.75 ppb) than in any other locations listed in Table 12.1b. The relative risk of death (given originally for 50 $\mu g/m^3$ increases in pollutants or approximately 25 ppb for ozone) was 1.6% (95% CI: -2.4% to 6.4%) for a 10 ppb increase in ozone (1-h max). In this study, the only pollutant that showed a clear association with mortality was SO_2, although PM_{10} was associated with cardiovascular and respiratory mortality (to a lesser degree than SO_2). Interestingly, the authors used digestive mortality data as a control, since no prior association reported between air pollutants and digestive mortality. As expected, none of the pollutants showed any association with digestive mortality.

Wietlisbach et al. (1996) investigated the association between ozone and mortality in years 1984 to 1989 in Zurich and Basle, Switzerland. Semi-nonparametric Poisson regression models were

used that included the pollution variables, a LOESS smooth of time to account for trend and seasonality, and a LOESS smooth of daily minimum temperatures. The authors reported a weak and inconsistent association between ozone and mortality in a single pollutant model. A significant association was found only in elderly population (>65 years) in Basle, but not in Zurich, and not in other age groups. When respiratory and cardiovascular mortalities were examined separately, ozone was not found to be associated with either of these, probably because of the low mortality rates. No adjustment for potential confounders was reported. The authors did not specify which ozone data (1-h maximum verse 24-h average) were used. Results were expressed as regression coefficients, but no standard deviation, or confidence interval or t values were reported.

Table 12.1b Summary of relative risk estimates in daily mortality for each 10 ppb increase in ozone, in univariate and multi-variate models

Location and reference	Ozone mean, ppb (range)(1-h max., unless indicated)	Percent increase (95% CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Ozone only models	% increase (95%CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Multi-pollutant models	Inclusion or exclusion in meta-analysis (S: Significant NS: Non-significant)
Detroit, MI (Schwartz 1991)	not given	no increase	----	**Results NS** Excluded, no quantitative results.
Los Angeles Co. CA (Kinney, Ozkaynak 1991)	75 ± 45	Increased, % not given	4%, O_3 and NO_2	**Results S** Excluded, no quantitative results for multi-variate model.
St. Louis MO Harriman TN (Dockery et al. 1992)	22.5 ± 18.5 (24-h mean) 23.0 ± 11.4 (24-h mean)	24-h ozone: St. Louis: 0.29% (-1.18% to 2.94%),. Harriman: -0.64% (-3.93% to 3.29%)	---	**Results NS** Excluded, no quantitative results for multi-variate model.
New York City NY (Kinney, Ozkaynak 1992)	56 (range not given)	[5.5 deaths per 10 ppb]	10%, O_3 and COH	**Results S** Excluded, no quantitative results for multi-variate model
Philadelphia PA (Li & Roth 1995)	19.8 ± 14.4 (24-h mean)	Increased for age 65y+ not increased for age <65	---	**Results S** Excluded, no quantitative results for multi-variate model
Philadelphia PA (Moolkavgar et al. 1995)	19.9 (year) (24-h mean) 35.5 (summer) (1.3-159)	Yearly data not given separately Summer: 1.5% (0.9-2.1%), 24-h ozone	Yearly: 0.62% (0.18- 1.04%) Summer: 1.5% (0.7-2.4%) +TSP, SO_2, 24-h ozone	**Results S** Included
Los Angeles CA (Kinney et al 1995)	70 ± 41 (3-201), yearly	0.2% (0% - 0.5%), yearly ozone	0% (-0.44 to 0.4%) +PM_{10}	**Results S** Included
Toronto ON (Ozkaynak et al. 1995)	36 (95th centile 66)	(not given separately)	0.34% to 0.42% (+TSP)	**Results S** Excluded, an abstract
Sao Paulo Brazil (Saldiva et al. 1995)	38.3 + 29.7 (1-h max.), 12.5 + 11.5 (24-h mean)	For age 65+ years. 1-h: 0.4% (-0.42% to 1.03%); 24-h: -1.31% (-4.15% to 1.75%)	---	**Results NS** Excluded, no data
Philadelphia PA (Dockery et al. 1996)	not given	(not given separately)	0.9% (+$PM_{2.5}$)	**Results NS** Excluded, an abstract

Table 12.1b Summary of relative risk estimates in daily mortality for each 10 ppb increase in ozone, in univariate and multi-variate models

Location and reference	Ozone mean, ppb (range)(1-h max., unless indicated)	Percent increase (95% CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Ozone only models	% increase (95%CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Multi-pollutant models	Inclusion or exclusion in meta-analysis (S: Significant NS: Non-significant)
Chicago IL (Ito & Thurston 1996)	38 ± 19.9, yearly, 2-d average.	1.0% (0.6-1.5%), yearly ozone, 2-d average	2-day average ozone. 0.68% (0.08-1.16%) (+PM_{10})	**Results S** Included
Santiago Chile (Ostro et al. 1996)	52.8 (11-264)	Yearly: OLS model: -0.57% (-0.75 to –0.38%); Poisson: 0% (-0.19% to 0.38%) Summer: OLS model: 0.20% (0-0.50%) Poisson: 0.4% (0-1.0%)	Yearly: OLS model: -0.56% (-0.92 to 0%); Poisson: -0.20% (-0.56 to 0.20) Summer: OLS model: 0.38% (-0.57 to 1.32%); Poisson: 0.4% (0-0.9%) +PM_{10}	**Results S** Included
Mexico City DF (Loomis et al. 1996)	154 (26-319) (1-h max) 62 (12-130) (24-h mean), yearly	Yearly, 1-h max. ozone: 0.24% (0.11-0.39%) Yearly, 24-h max. ozone: 0.58% (0.22-0.94%)	Yearly, 1-h max. ozone: -0.18% (-0.52 to 0.16%) (+TSP and SO_2)	**Results S** Included
London UK (Anderson et al. 1996)	Yearly: 20.6 ± 13.2 (1-h max.), 15.5 ± 10.9 (8-h mean); summer: 7-36 (8-h) 11-45 (1-h)	Yearly ozone: 1-h max: 0.83% (0.42-1.25%) 8-h mean: 1.01% (0.46-1.57%); Summer: 1-h max. 1.03%(0.53-1.53%) 8-h mean: 1.2%(0.6-1.8%)	Yearly, 8-h average ozone: 1.14% (0.59 –1.69%) with black smoke. Summer, 8-h average ozone: 1.45% (0.7-2.19%) with BS. No 1-h max. data reported.	**Results S** Included
Barcelona Spain (Sunyer et al. 1996)	28 (3.6-96) winter 44 (4.8-144) summer	Yearly: 0.96% (0.24-1.72%) Summer: 1.16% (0.34-2.02%)	---	**Results S** Excluded, no quantitative results for multi-variate model
Amsterdam NL (Verhoeff et al. 1996)	21.9 (4-41; 10-90th %), yearly	yearly ozone 0.98% (0.02-2.0%),	Yearly: 0.58% (-0.67 to1.9%) + BS 1.0% (-1.1 to 3.3%) + PM_{10}	**Results S** Included
Lyon France (Zmirou et al. 1996)	7.75 (0-72) (1-h max) 5.1 (0-40.2) (8-h mean), yearly	Increase not significant 1-h max.: 1.6% (-2.4% to 6.4%) 24-h avg.: 1.2% (-2.0% to 4.8%), yearly ozone	--- ---	**Results NS** Excluded, no quantitative results for multi-variate model
Paris France (Dab et al. 1996)	22.3 (3.1-74.8) (1-h max 14.1 (10-56) (8-h mean), yearly	Respiratory mortality only; Yearly ozone; 1-h max.: 0.8% (-1.3% to3.1%) 24-h avg.: 1.5% (-1.2% to 4.6%),	--- ---	**Results NS** Excluded, no quantitative results for multi-variate model

Table 12.1b Summary of relative risk estimates in daily mortality for each 10 ppb increase in ozone, in univariate and multi-variate models

Location and reference	Ozone mean, ppb (range)(1-h max., unless indicated)	Percent increase (95% CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Ozone only models	% increase (95%CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Multi-pollutant models	Inclusion or exclusion in meta-analysis (S: Significant NS: Non-significant)
4 APHEA cities: Athens Barcelona London Paris 3 additional cities: Amsterdam Basel Zurich (Touloumi et al. 1997)	47.7 ± 21.8 (all 1-h max) 36.8 ± 17.8 21.0 ± 13.2 23.5 ± 16.7 21.9 (4-41; 10-90th %) no 1-h values given for Basle or Zurich (8-h means 12 (B) and 14 (Z)), yearly ozone	Meta-analysis pooled estimate (random effects): For a single day: 1.16% (0.40-1.96%); Average of 2-5 day cumulative ozone: 0.96% (0.48 - 1.48%) Plus 4 non-APHEA cities: 1.16% (0.40% to 1.96%) (1-h max.) All yearly ozone data,1-h max. ozone	Meta-analysis (random effects): 1.12% (0.20-2.00%) +BS 1.28% (-0.12% to 2.72%) +NO_2 Pooled estimates with non-APHEA cities not included in bivariate analysis	**Results S** Included for 4 APHEA cities.
Philadelphia PA (Kelsall et al. 1997, Samet et al., 1997)	19.9 ± 14.6 (2-day average) 8.3-28.5 IQR (=20.2)	2-d average ozone: 1.13% (0.4% - 1.9%)	2-d average ozone: 1.01% (0.02-2.0%)+TSP 1.11% (0.38-1.84%)+SO_2 1.12% (0.73-1.84%)+NO_2 1.17% (0.40-1.94%)+CO_2 0.96% (0.33-1.59%) + all four	**Results S** Included
Zurich, Basle and Geneva, Switzerland, 1984 – 1989. (Wietlisbach et al., 1996)	Mean ± SD (presumably 24-h average): Zurich: 13.4 ± 10.5; Basle: 12.0 ± 9.7; Geneva: 0	Data are expressed as regression coefficients; no SD or confidence interval reported. No ozone data for Geneva. For total mortality, no association in Zurich or Basle. For mortality of people >65 years of age, no association in Zurich, significant association in Basle ($p<0.05$). For respiratory and cardiac mortalities, no association in any cities.	---	**Results NS** Excluded, no relative risk data reported; exposure data not detailed (1-h max. vs. 24-h average).
11 Canadian cities (Burnett et al. 1998)	16.2 (24-h mean of 11 cities) IQR 13 3-35 (5-95th centile), yearly ozone	24-h ozone: 0.86% (0.35-1.37%), yearly ozone	24-h average ozone: 1.11% (0.66-1.56%) (+NO_2. SO_2, CO) (particles contribute another 1%)	**Results S** Included
13 Canadian cities [Burnett 1998 (special analysis for WGAQOG)]	31 (1-h max) (25-38 range of means, 13 cities) 32.9 ± 16.7 (16 cities)	0.79% (0.59-0.99%), yearly ozone	---	**Results S** Excluded, no data on multi-variate analysis; not in a peer reviewed journal

Ozone-only analyses, mean increase (%) in mortality ± SD = 0.613% ± 0.467% (n=17), per 10 ppb increase in ozone (1-h max.), 95% CI: -0.302% to 1.53%, $p>0.05$.

Table 12.1b Summary of relative risk estimates in daily mortality for each 10 ppb increase in ozone, in univariate and multi-variate models

Location and reference	Ozone mean, ppb (range)(1-h max., unless indicated)	Percent increase (95% CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Ozone only models	% increase (95%CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Multi-pollutant models	Inclusion or exclusion in meta-analysis (S: Significant NS: Non-significant)
Multi-pollutant analyses, mean increase (%) in mortality ± SD = 0.523% ± 0.444% (n=10), per 10 ppb increase in ozone (1-h max.), 95% CI: -0.347% to 1.39%, p>0.05. Meta-analysis of multi-pollutant analyses, weighted mean increase (%) in mortality ± SD = 0.399% ± 0.105% (n=10), per 10 ppb increase in ozone (1-h max.), 95% CI: 0.193-0.604%, p<0.05.				

12.2.3 Effects of co-pollutants (Multi-pollutant studies)

Air pollution is always composed of a mixture of pollutants, often co-varying, and it is frequently difficult or impossible to separate the effects of one agent from the others. The statistical methods in time-series analysis make an assumption of independent action of the various pollutants in the atmosphere, which may not be the case. The net result with respect to association between pollutants and health endpoints may be due to a combination of ozone and PM, or ozone and one or more of the other pollutants that frequently co-occur with ozone.

Fourteen studies reported results using multi-variate models [Philadelphia (Moolkavgar et al. 1995, Kelsall et al., 1997, Samet et al. 997, Dockery et al. 1996), Chicago IL (Ito & Thurson 1996), Los Angeles (Kinney and Ozkaynak, 1991, Kinney et al., 1995), New York City (Kinney and Ozkaynak , 1992), Mexico City (Loomis et al., 1996),Toronto (Ozkaynak et al. 1995), 11 Canadian cities considered together (Burnett et al. 1998), London UK (Anderson et al. 1996), Amsterdam (Verhoeff et al., 1996), and a meta-analysis of 4 European cities (Touloumi et al. 1997)]. Eleven of these studies demonstrate a statistically significant positive association between ozone and mortality, with seven of them providing quantitative data. After adjusting for the effects of other pollutants, the relative risk (RR) for an increase in all-cause mortality varied between 0.27% and 1.12% per 10 ppb increase in ozone, measured as the 1-hour maximum. The mean RR (from studies with significant results, n=7) was an increase in daily mortality of 0.70% (standard deviation 0.35%) per 10 ppb increase in ozone, which is similar to single pollutant data [mean mortality increase is 0.65% per 10 ppb ozone ($\pm$0.36%), range 0.24% - 1.16%]. In almost all the cases with significant results, with particulate matter or SO_2 or NO_2 in bivariate analyses, ozone appeared to act independently from other air pollutants in the association of air pollution with increased mortality. Results for the individual co-pollutants are discussed in more detail below.

Three of these studies using multi-variate models reported a loss of the significance in the association between ozone and mortality when other pollutants were adjusted (Kinney et al. 1995, Verhoeff et al 1996, and Loomis et al. 1996). These three studies had reported positive associations between ozone and mortality in single pollutant analyses.

In the Verhoeff et al. (1996) study in Amsterdam, the Netherlands, the positive association between ozone and mortality was attenuated about 40% when particles as BS were included in a bivariate analysis. The RR for ozone declined from 1.05 to 1.03 (95% CI 0.97 to 1.10 for a 100 $\mu g/m^3$ or 50 ppb increase) while the RR for BS (100 $\mu g/m^3$) declined only 5% from a RR of 1.187 to RR of 1.178. The confidence limits for BS broadened considerably while the RR remained slightly above 1.0. With PM_{10} as the particle metric, the RR for ozone retained its magnitude while the RR for PM_{10} was reduced by 82%, from 1.187 to 1.034, and the confidence intervals for both pollutants included the null value (RR=1.0). When taking a closer look at the correlation analysis data, ozone was very weakly correlated with BS (r=-0.15) and PM_{10} (r=0.06), implying that ozone might have an independent relationship to mortality.

The statistical analysis in the Kinney et al. (1995) study for Los Angeles was thorough. However, the authors stated that the database on ozone was too small (every sixth day for six years or 364 days), and thus severely limited the power of the study to be able to discern an ozone effect when it was included with PM_{10} in a bivariate regression. Moreover the correlation coefficients between PM_{10} and ozone were high in this location (r=0.5) making it impossible to separate out their effects on mortality in this reduced data set.

The study by Loomis et al. (1996) in Mexico City ran into similar problems. As pointed out by the authors of this study, the associations found in ozone-only models were based on 715 days of monitoring, while the TSP plus ozone bivariate regressions were based on only 129 days of simultaneous monitoring, too few to provide consistent results. (Even 715 days provides a fairly small number of data points for a time-series analysis). In this particular case, total non-accidental mortality showed a much stronger association with 24-h average ozone concentration (RR=1.058, 95%CI 1.022-1.094%) than with current day 1-h maximal ozone concentration (RR=1.024; 95% CI 1.011-1.034 for 100 ppb increase) in models including temperature or seasonal adjustments. Moving average ozone and 10-h average ozone also had stronger associations with total mortality (RR= 1.043, 95% CI 1.021-1.064; RR=1.040, 95% CI 1.018-1.062, respectively) than 1-h maximum ozone. However, all bivariate or multi-pollutant analyses were undertaken using 1-h maximum ozone lagged 0 day, rather than any other measurement times (24-h, daytime maximum, and moving average, and a 1-day lag time). Had other ozone markers been used instead of the current-day 1-h maximum in multi-variate analyses, the associations might have been strengthened. Therefore this study provides inconclusive results regarding the attenuation of the ozone effect by TSP, or the independent effects of the two pollutants.

Although SO_2 had been associated with mortality in many of the early pollution episodes such as the London Fogs, bivariate regressions with ozone were performed only in a few studies. In the Moolkavgar et al. (1995) report on Philadelphia, SO_2 was associated with mortality in both an all-year and a summer-only analysis. When both summertime ozone and summer SO_2 were regressed together, both retained their positive associations equally, but inclusion of TSP as a third variable resulted in the decline of the regression coefficient for SO_2 and TSP, with retention

of the association for ozone. Later analyses of the Philadelphia data (Kelsall et al. 1997, Samet et al., 1997) qualitatively agreed with the previous findings. In these studies, the relative risks for ozone were reduced but still significant and the relative risks for SO_2 increased from 1.011 to 1.023. In Mexico City (Loomis et al., 1996), the significant association of mortality with ozone from single-pollutant analysis was no longer seen when ozone was included in a three-pollutant regression with SO_2 and TSP (the results of a bivariate regression with SO_2 were not given). In London UK, both ozone and SO_2 were positively associated with premature mortality in single-pollutant analyses, and the text stated that both retained their associations when regressed in bivariate regressions, but no values were provided (Anderson et al., 1996). In an analysis conducted in 11 Canadian cities, Burnett et al. (1998) reported that a 5.4 ppb increase in 24-hour mean SO_2 (average of 11 cities) contributed a 1.4% increase (95% CI 1.1% to 6.2%) to premature deaths, when all other pollutants including ozone were included in a multivariate regression. This was approximately one-sixth of the estimated 8.2% of all non-accidental deaths ascribed to air pollution. In the same analysis, a 16.2 ppb rise in 24-h ozone (average of 11 cities) contributed 1.8%, or about one-quarter of the total 8.2% ascribed to air pollution. The average correlation between ozone and SO_2 was low (-0.2) and varied between -0.3 and 0.0 in the 11 cities individually. Overall, based on the evidence from all the available studies, it appears that the associations of both ozone and SO_2 with premature mortality are independent of each other in locations where both are associated with mortality in single regressions.

Regressions including both ozone and NO_2 have been conducted in five studies, in Los Angeles (Kinney & Ozkaynak, 1991), Philadelphia PA (Kelsall et al., 1997, Samet et al., 1997), London UK (Anderson et al., 1996), a meta-analysis on 4 European cities (Touloumi et al., 1997), and a study on 11 Canadian cities (Burnett et al., 1998). Kinney & Ozkaynak (1991) reported that ozone and NO_2 together accounted for 4% of all deaths in Los Angeles. In Philadelphia, ozone was strongly and independently associated with premature mortality in bivariate regression, while NO_2 was not. The ozone coefficient was virtually unchanged in bivariate regressions, while NO_2 did not associate with mortality in either single-variate or bivariate models (Kelsall et al., 1997; Samet et al., 1997). When ozone was included in a multi-variate regression with all five of the air pollutants including NO_2, its coefficient was only slightly reduced, and for a 10 ppb increase in ozone, mortality increased 0.96% (95% CI: 0.3-1.6%). In a meta-analysis (Touloumi et al. 1997) which included four European cities, both ozone and NO_2 were independently associated in bivariate regressions. The relative risk for ozone declined only slightly from 1.029 to 1.025, and the RR for NO_2 rose slightly from 1.013 to 1.015. In the 11-Canadian city study, Burnett et al. (1998) reported that a 23.5 ppb increase in 24-hour mean NO_2 (average of 11 cities) contributed a 4.1% increase (95% CI 1.1% to 6.2%) to premature deaths. This was observed when all other pollutants including ozone were included in a multi-variate regression analysis. This was approximately 50% of the estimated 8.2% of all non-accidental deaths ascribed to the gaseous component of air pollution. The average correlation between ozone and NO_2 was low (-0.1) but varied between -0.5 and 0.2 in the 11 cities individually. The evidence from these five studies

supports the independent associations of both ozone and NO_2 with premature mortality when the two are examined together.

Only limited numbers of studies (Kelsall et al., 1997, Samet et al. 1997, Burnett et al. 1998) have examined the relationship of ozone to mortality in multi-pollutant analyses with more than two air pollutants normally considered, i.e. PM, SO_2, NO_2, and CO. In the Philadelphia analysis by Samet et al. (1997, also in Kelsall et al., 1997), the ozone coefficient remained stable and significant when regressed together with TSP, SO_2, NO_2 and CO. In this study, the correlation coefficients between ozone and other pollutants were moderate (r for TSP, SO_2, NO_2 and CO were 0.12, -0.02, 0.001 and –0.2, respectively), indicating that ozone acts independently on mortality. In the study by Burnett et al. (1998), the ozone coefficient also remained a significant predictor of mortality when regressed together with NO_2, SO_2, CO, and particles (stated in text but data not shown). In this study the correlation coefficients between ozone and other pollutants were generally moderate (below 0.2 to 0.3), but correlation coefficients in individual cites and between other pollutants were as high as 0.6. Some caution is therefore warranted in the attempt to establish the role of ozone or of the other pollutants in prediction of premature mortality from the results of this study.

Overall, a majority of studies that conducted bivariate and multi-variate analyses have confirmed the association between ozone and premature mortality that was seen in the single-pollutant analyses. The independence of this assocation from associations with particles, SO_2 and NO_2 was established in various locations with different pollutant mixes, thus giving external consistency to the results.

12.2.4 Summary of mortality data and meta-analysis

On balance, the time-series studies reviewed here, most of which received extensive statistical treatments, indicate that the association between ozone and mortality is positive, consistent, and independent of other co-occurring air pollutants including particulate matter. Seventeen of the 23 studies reviewed reported statistically significant positive associations using single pollutant models. Fourteen studies reported results using multi-pollutant models, eleven of which demonstrated statistically significant independent associations between ozone and mortality. These associations were found in cities across North America, in four U.S. and 13 Canadian locations, in Santiago Chile and three European cities, and in a meta-analysis including seven European cities, demonstrating consistency of results despite widely varying climatic conditions, pollutant mixtures, population compositions, and life styles.

These associations were reported for cities with mean ozone concentrations (expressed as the one-hour maximum) between 20 and 75 ppb, i.e. below, and in most cases well below the current Canadian Air Quality Objective for ozone of 82 ppb.

For meta-analysis, there are two basic models by which variances are used to weight the estimates from different studies in a pooled estimate. One is the fixed effects model, which assumes that there is a single true concentration-response relationship, and therefore a single true value for the relative risk. The second model is the random effects model, which assumes that the relative risk from different studies may in fact be estimates of different risks, rather than just different estimates of a single underlying parameter. The reason for this assumption is that the behavior or susceptibility of populations varies among study locations, resulting in a potential difference in the relationship between health effects and ambient ozone concentrations. In this document, ten mortality studies that met the criteria in Section 12.1.4 were included (Table 12.1b) in a meta-analysis, and the random effects model was assumed when the null hypothesis of a single underlying relative risk parameter {expressed as [(RR-1) x 100]} was rejected using a test statistic, Q_w.

A pooling of ten studies with adjustments for seasonal cycles and weather terms, and with a simultaneous inclusion of co-pollutants, reveals that the weighted relative risk of total non-accidental mortality is 1.040 (95% CI 1.019 – 1.060) for 100 ppb 1-h maximum ozone [or 0.40% increase in mortality (95% CI 0.19 – 0.60%) per 10 ppb increase in ozone]. This value is in line with the relative risks from other meta-analyses reported by Thurston and Ito (1999)(RR=1.036 per 100 ppb increase in 1-h maximum ozone, 95% CI 1.023-1.050), and by the US EPA (1997)(RR=1.029 per 100 ppb increase in 1-h maximum ozone).

Using the data from 13 Canadian cities (Burnett, 1998, in Appendix A) to conduct single-pollutant regression analyses, the results show that the risk for non-accidental mortality is 0.79% per 10 ppb increase in daily one-hour maximum ozone (95% CI: 0.59-0.99%). The Lowest observed adverse effect level (LOAEL) with statistical significance is 20 ppb ($p<0.001$). The data continue to show a trend of positive association with ozone values as low as 10 ppb. There appears to be no threshold for mortality.

Six studies did not find any association between ozone and mortality. Although similar methodology was used for each of these studies, some differences in the statistical treatment and/or shortfalls (e.g. small ozone sample size, or data from only one monitor, or respiratory mortality data only) were identified. These differences might explain the lack of association between ozone and mortality for some of the studies.

Although less information was available on the concentration-response characteristics for mortality than for hospitalization data, several studies indicate that the relationship is more or less in a linear pattern, down to less than 10 ppb without evidence of any threshold or flattening out of the response curve at low concentrations. Only a few studies provided evidence of a more specific cause of death; cardiovascular deaths were associated with ozone increases in several

studies while respiratory deaths were not, possibly because of proportionally fewer deaths in this category.

12.3 MORBIDITY STUDIES—ACUTE EFFECTS: HOSPITALIZATIONS

The short term effects of ambient air pollutants on morbidity have been investigated in a number of studies, using administrative data on hospital admissions or emergency room visits. These are advantageous in providing an objective measure of adverse effects, particularly in Canada where the cost of medical care is not a deterrent to seeking hospitalization, due to universal free medical coverage. Despite the fact that hospitalizations represent only the serious outcomes, and are the tip of the iceberg with respect to the number of people adversely affected by a pollutant, hospitalizations as an endpoint have proven to be surprisingly sensitive indicators of adverse health outcomes. This is due to the extremely large size of some of the populations studied and to the advanced statistical methods employed. This has allowed for detection of small effects in susceptible subpopulations that would not be detected in clinical studies, partly because of ethical considerations. Table 12.2a contains detailed information on hospital admission studies. The data are summarized in Table 12.2b to assist in understanding the information.

Table 12.2a Ambient ozone and association with hospitalizations

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Burnett et al., 1994 Southern Ontario (pop. 8,700,000) 1983-1988 (6 years; 2191 days) 168 hospitals	Respiratory admissions: -Asthma (39%) -COPD (25%) -Infection (36%) All ages categorized into group: <2y (12%), 2-34y (30%), 35-64y (22%), 65 +y (36%) 235,532 respiratory visits; 107/d	O_3 1-h max: 52 ppb (May-Aug) 95th percentile was 92 ppb (range 62-118 ppb) <40 ppb (other months) 22 monitoring sites (correl high: r=0.68)	Daily mean of some pollutants were measured (data not given): SO_2 (24 sites) NO_2 (18 sites) SO_4 (9sites) daily mean: 5.34 ?g/m^3 Also monitored temperature, relative humidity and pressure	-Multiple regression analysis, using weighted 19-weighted linear filter for removal of seasonal cyclic variations -Dummy variables for day-of-week effects and for inter-hospital differences -Same day and lag days 1,2 and 3 were checked	-There is a highly significant relationship (p<0.001) between 1-h peak O_3 concentrations recorded previous day an respiratory admissions during the summer months of May-August -Respiratory admissions for all ages were significantly increased by air pollution (ozone + sulphates): Asthma= 7%, COPD= 6% and Infection=4%, all diseases=5.8%. -Increase of 5% of admissions was associated with a increase in ozone from 0 to 50 ppb. -Association with sulphates (lagged 1 day) was also positive for hospital admissions (RR= 1.003-1.035 for a 5 ?g/m^3 increase in sulphates). -Asthma was the most significantly affected in children (<14y), an 8.2% increase in asthma admission per 50 ppb increase (p=0.005) -No correlation for negative control -Neither SO_2 or NO_2 are considered to be a strong confounder for ozone or sulphates
Burnett et al., 1997a 16 cities across Canada (pop. 12,600,000) April 1981 to December 1991 (10 years; 3927 days) 134 hospital	Respiratory admissions (not broken down into subcategories) Mean admissions: 720,519 respiratory visits; 183/d	O_3 1-h max: Spring: 40 ppb Summer: 38 ppb Fall: 21 ppb Winter: 26 ppb Whole year: 31 ppb (95th percentile 60 ppb)	Average on available data on an hourby hour basis: SO_2: 14.4 ppb NO_2: 35.5 ppb CO: 2.2 ppm CoH: 0.64 (1000 in ft) Dew point and temperature (daily maximum and minimum) also recorded	- Multiple regression analysis using a 19-weighted linear filter to detrend seasonal cyclic variations -Dummy variables for hospitals effects, day to day variations, location and weather -Looked at different lag times, considered admissions same day and lag 1, 2 day	-1-h max, 30 ppb incr. Of ozone (single variate): Winter: 0.994 (95% CI 0.964-1.025); Spring: 1.042 (1.012-1.073); Summer: 1.05 (1.026-1.074); Fall: 1.028 (0.998-1.059). -Single-variate model, the ozone risk for hospital admissions (for respiratory diseases) for 16 cities, April-Dec. is: 1.042%/30 ppb increase in daily 1-h maximum ozone (t=5.12, p<0.05). -Multi-variate models, RR (t ratio): 1.043 (4.45), +CO 1.031 (3.04), +CO, dew point temperature 1.024 (p=0.0258), +CO, dew point temperature, PM (soiling index), in 11 cities with available PM data. -O_3 levels measured on the day previous to admission were more strongly related to respiratory hospitalizations. Associations were also observed on the same day and lags 2 days -No association for control negative. -The RR (30 ppb increase) for elderly (>65 y, RR=1.040, 95%CI 1.01-1.072) was similar to that for younger patients aged <65 y (RR=1.045, 95%CI 1.021-1.068).

Table 12.2a Ambient ozone and association with hospitalizations

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Burnett et al., 1997b Toronto, Ont. 1992-1994	Total respiratory admissions (ICD-9 464-466, 490, 480-486, 491-494, 496) Cardiac admissions (ICD-9 410-414, 427, 428)	Daily 1-h max. 41.2 ppb (5^{th}-95^{th} percentile 22-69 ppb) When regression was done, used 3 day average levels.	PM_{10}: 28.4 µg/m^3 $PM_{2.5}$: 16.8 µg/m^3 Sulphate: 57.1 nmol/m^3 H^+: 5 nmol/m^3 NO_2:38.5 ppb SO_2:7.9 ppb CO: 1.8 ppm.	Logistic regression models were used for associations of hospitalizations with pollutants. Seasonal cycle and day of the week were controlled using nonparametric smoothed curve using LOESS. Multi-variate models were used to control co-pollutants. Temperature was co-regressed with pollutants.	-The study focused on PM effects. -Single pollutant models, not controlled for temperature and dew point temperature, at 11.5 ppb ozone (3-d avg.); lag 1 day: respiratory admissions: RR=1.068 (t ratio=6.19) cardiac admissions: RR=1.057 (3.52) -Single pollutant models, controlled for temperature and dew point temperature (11.5 ppb, 3-d avg.), lag 2 days: respiratory admissions: RR=1.064 (t ratio=5.13) cardiac admissions: RR=1.074 (3.85) -multi-variate analysis not done for ozone, but for PMs -Correlation of ozone was: with sulphate (r=0.53), PM_{10} (r=0.23), $PM_{2.5}$ (r=0.32) and H^+ (r=0.34).

Burnett et al., 1997c
 	
10 Canadian cities (1981-1991)
	Congestive heart failure (ICD-9 427) in the elderly >65 y.	Daily 1-h max.: 32 ppb (5^{th} –95^{th} percentile: 10-64 ppb)
		
		24-h avg.: 16 ppb (5^{th}-95^{th} percentile 3-35 ppb)
			Coefficient of haze (CoH): 0.7 10^3 ln ft
			NO_2:39 ppb
			SO_2: 13.1 ppb
			CO: 2.32 ppm.
				Logistic regression models were used for associations of hospitalizations with pollutants.
				
				Seasonal cycle and day of the week were controlled.
				
				Multi-variate models were used to control co-pollutants.
				
				Temperature was co-regressed with pollutants.
					-The study focused on CO effects.
					
					For ozone effects (24-h average ozone) on congestive heart failure, lag 2 d, at 16 ppb ozone:
					-Single pollutant models, not controlled for temperature and dew point temperature: log-RR coefficient=0.0021 (t ratio=2.2);
					-Single pollutant models, controlled for temperature and dew point temperature:
					log-RR coefficient=00.0022 (t ratio=1.8);
					-multi-variate analysis, controlled for temperature, DP temperature, and all the pollutants:
					log-RR coefficient=0.0021 (t ratio=2.0);
					-City-specific RR was also calculated, but only for CO.
					-Correlation of ozone was negative with other pollutants (r=-0.36 to –0.15).

Table 12.2a Ambient ozone and association with hospitalizations

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Bates and Sizto, 1987;1989 Southern Ontario (smaller area than the Burnett et la. 1994 study) (pop. 5,900,000) 1974 and 1976-1983 (9 years) Winter (Jan.-Feb.) Summer (July-Aug.) 79 hospitals	All respiratory admissions All ages separated into groups: -0-14y -15-60y -61+y 1,282,064 visits in winter where 2.9% for respiratory visits 1,223,054 visits in summer where 1.8% for respiratory visits	O_3 1-h peak: Winter: 23.34 ppb Summer: 56.07 ppb 17 monitoring stations	Monitored every hour: SO_2 CoH SO_4= winter: 9.51 µg/m^3 and summer: 10.31 µg/m^3 on a basis of 24-h period every 6th day Also monitored daily temperature and relative humidity 17 monitoring stations	-Multiple regression analysis -They compared the number of admissions on each day only with the average number of admissions for the same day of the week (Tuesday), in the same season, of the same year.	-Significant association ($p<0.001$) between respiratory admissions and 1-h peak O_3 in summer (lagged 1 or 2 days) -O_3 correlated with respiratory admissions minus asthma, but lagged 2 days only -O_3 correlated with total asthma admissions in all ages except with asthma in children aged 0-14y -SO_4 and SO_2 were correlated to the same three endpoints with about the same lad times for SO_4 and a lag of 2 days only for SO_2 -CoH was not correlated to any of the respiratory admissions - O_3, SO_4 and temperature together, all lagged 0,1,2 days: 5.6% of variability in respiratory admissions (temperature alone accounts for less than 1% of the variance and SO_4 accounts for about 3%)
Delfino et al., 1994. May-Oct. and Aug.-July, 1984-1988, Montreal (population about 3 million in 1986).	All age respiratory admissions (ICD-9); all age non-respiratory admissions; ages 0-18 non-respiratory admissions.	Ozone 1-h max.: May-Oct. 36 (90th: 59.2); July and Aug.: 41 (90th: 65.8). Ozone 8-h max.: May-Oct. 30.4 (90th: 51.5); July and Aug.: 35 (90th: 57.3)	PM_{10}: 24-h mean May-Oct. 29.5 (90th 45.7) µg/m^3; July and Aug. 31.5 (90th 48) µg/m^3. SO_4: 24-h mean: May – Oct: 4.2 (90th 8.2) µg/m^3; July and Aug. 4.9 (90th 9.7) µg/m^3	-A High-pass filter (19-d moving average) used to eliminate yearly seasonal trends in the data; -day-of week trends controlled by prefiltering the outcome variables prior to analysis; -Ordinary least-squares used to regress single air pollutants on the outcome; -Coregressions of ozone with PM.	-Respiratory admission regression coefficient (t ratio) for 8-h average ozone was 0.025 (2.6) per µg/m^3 ozone increase, 0.676%±0.26% increase in respiratory admissions per 10 ppb ozone. -Ozone and temperature were both non-significant when entered into regression model simultaneously. Regression coefficient for ozone (8-h average) was 0.015 (t ratio 1.22) when temperature was regressed simultaneously, 0.405%± 0.332% increase in respiratory admission per 10 ppb ozone. -Asthma admissions when ozone was co-regressed with PM_{10}, regression coefficient for ozone (1-h max.) was 0.004 (t ratio 0.89), 0.175%±0.197% increase in asthma admissions per 10 ppb ozone. -Respiratory non-asthma admission when ozone was co-regressed with sulphate, coefficient for ozone (1-h max.) was 0.04 (t ratio 0.07), 1.65%±23.61% increase in non-asthma respiratory admissions per 10 ppb ozone.

Table 12.2a Ambient ozone and association with hospitalizations

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Thurston et al., 1994 a,b Toronto (pop. 2,400,000) July-Aug 1986-1988 (3 summers; 117 days) 22 hospitals	Total respiratory (mean 13.77 admissions/d) and asthma hospital admissions (mean 8.94 admissions/d)	O_3 1-h max: 49.3 ppb (1986) 53.4 ppb (1987) 69.7 ppb (1988) Mean 57.5 ppb (3 years) 2 days > 120 ppb 22 days > 80 ppb	Daily maximum 1-h: SO_2: 1.7 pphm NO_2: 4.73 pphm Daily 24-h average: SO_4: 7.5 µg/m^3 H^+: 28.77 nmole/m^3 PM_{10}: 32.9 µg/m^3 $PM_{2.5}$: 18.6 µg/m^3 TSP: 71.73 µg/m^3 Also monitored daily temperature Three sites	-Detrend for hospitalization, pollutant and temperature data, and controlling for day-of-the week effects -Bivariate correlation analysis -Same days and lagged/followed 1,2,3 were checked	-Only the O_3, H^+, and SO_4 associations with respiratory/asthma admissions remained significant after controlling for temperature. Admissions increased 3.83%±1.43% for 10 ppb ozone, 1.68% for 10 µg/m^3 H^+, 0.77% for 10 µg/m^3 sulphate, single-pollutant models + temperature. -In two pollutant models, ozone associations were still significant, and admissions increased 3.64%±1.48% per 10 ppb ozone (+ H^+), 3.68%± 1.5% (+sulphate), 2.93%±1.69% (+fine particles), 2.81%±1.75% (+PM10), and 2.61%±1.65% (+TSP). Only H+ (1.11% increase in admission per 10 µg/m^3) and sulphate (4.5% increases in admissions per 10 µg/m^3) remained significant when co-regressed with ozone. -O_3 was still strongly significant after excluding days with maximum 1-h O_3 > 120 ppb -Summertime haze air pollution was associated with 24% of all respiratory admissions (21% with O_3, 3% with H^+) -The slope for all 117 days was 0.051 admission/ppb ozone. It decreased to 0.048 when the 2 days > 120 ppb were removed, and to 0.045 when all days above 80 ppb were removed. -Temperature, NO_2 and SO_2 associations with respiratory/asthma admissions were weaker and less definitive -The highest correlations among the pollution variables, and between the pollution and temperature, almost occurred with zero lag -The authors concluded that there was no clear discrimination of a single pollutants as the responsible agent, but the regression suggest that O_3 was the summertime haze constituent of greatest relevance to hospital admissions

Table 12.2a Ambient ozone and association with hospitalizations

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Thurston et al., 1992 Albany (991,477); Buffalo (2, 047,669); White Plains (1,956,695) and New York City (7,322,564) June-Aug. 1988-1989 (2 summers; 92 days)	Total respiratory and asthma admissions Respiratory admissions: -Albany: 12.5/d -Buffalo: 24.35/d -NYC: 136.95/d -White Plains: 24.9/d Asthma admissions: -Albany:2.55/d -Buffalo: 6.85/d -NYC: 52.15/d -White Plains: 6.55/d	O_3 1-h max (ppb): 1988 -Albany: 64-148 -Buffalo: 75-164 -NYC: 69-206 -White Plains: 84-179 1989: -Albany: 55-112 -Buffalo: 65-128 -NYC: 53-111 -White Plains: 60-123	Also monitored: H^+ SO_4 Also monitored: daily temperature	-Daily counts of unscheduled (emergency) hospital admissions with a primary diagnosis of respiratory illness -Detrend for the summer admissions and environmental data, and also controlling for day-of-the week effects -Multiple regression analyses and cross-correlation analyses -Same day and lagged/followed 1,2 and 3 days were checked.	-Strong associations between elevated summer haze pollution (O_3, H^+, SO_4) and increased total respiratory and asthma admission on the same day and/or subsequent days in Buffalo and New York City, especially during the summer 1988. -For Buffalo and NYC, RR of total respiratory admissions is 1.22 ±0.12 (89 ppb) and 1.19±0.04 (137 ppb) respectively for ozone (based on the 1988 high-pollution summer, +temperature). - For Buffalo and NYC, RR of asthma admissions is 1.29 ±0.12 (89 ppb) and 1.23±0.10 (137 ppb) respectively for ozone (based on the 1988 high-pollution summer, +temperature). -Lag times were 0-3 days with lad 2 days most highly correlated with ozone -Pollution-admissions remained significant ($p<0.05$) even after the simultaneous inclusion of lagged daily maximum temperature.
Schwartz, 1994a Birmingham, Alabama (pop. 590,591) 1986-1989 (4 years)	Hospital admissions of elderly: -pneumonia (5.93/d range 5.08 to 7.85) -COPD (2.16/d range 1.82 to 2.55)	O_3 24-h avg.: Winter:- Spring: 28 ppb Summer: 28 ppb Fall: 18 ppb Mean: 25 ppb (10-90% 14-25 ppb)	PM_{10}: Winter: 40 $\mu g/m^3$ Spring: 47 $\mu g/m^3$ Summer: 49 $\mu g/m^3$ Fall: 44 $\mu g/m^3$ Also monitored weather variables: temperature and dew point	-Daily counts of pneumonia and COPD admissions -Poisson regression analysis (controlling for time trends, seasonal fluctuations and weather)	-No association with pneumonia admissions and ozone concentrations on the same day. -Weak association with pneumonia admissions and ozone 2 days before the admissions (RR= 1.14, 95% CI 0.94-1.38 for 50 ppb increase in ozone, 24-h avg.). The association was not due to the coincidence of high ozone with high-temperature days, since it persisted when they were excluded (days> 120 ppb)) -Weak association with COPD admissions and ozone 1-day lag (RR=1.17, 95% CI 0.86-1.60 for 50 ppb increase in ozone, 24-h avg.). -1-h max. ozone: pneumonia: 1.04 (95%CI 0.97-1.12) for 50 ppb; COPD: 1.07 (95%CI 0.96-1.20) -For an increase of 100 $\mu g/m^3$, inhalable particules were a risk factor for pneumonia admissions (RR=1.19, 95% CI 1.07-1.32) and for COPD admissions (RR=1.27, 95% CI 1.08-1.50) -Temperature correlated for both PM_{10} and ozone -Correlation between PM_{10} and ozone (correl. low: r=0.29) -Results not sensitive to methods of analysis or to extremes temperature

Table 12.2a Ambient ozone and association with hospitalizations

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Schwartz, 1994b Detroit, Michigan (pop. 4,382,000 were 517,000 are 65yr of age or older) 1986-1989 (4 years)	Hospital admissions, 65 yr of age or older -Pneumonia (15.7/d) -COPD (5.8/d) -Asthma (0.75/d)	O_3 mean 24-h average: 21 ppb (10-90% 7-36 ppb) O_3 mean peak (1-h max.): 53 ppb 1986-1989: 9 monitoring sites 1987-1988: 8 monitoring sites O_3 data were available for 85% of the days during the study period	PM_{10} collected over a 24-h period: mean 48 $\mu g/m^3$ Monitoring stations in operation for PM_{10}: 1986: 2; 1987: 6; 1988: 7; 1989: 4 PM_{10} data were available for 82% of the days during the study period Also monitored weather variables: daily temperature and dew point	-Daily counts of pneumonia (ICD-9, 480 to 486) and COPD (ICD-9, 490 to 496) admissions of persons aged 65 years or older -Poisson regression analysis -Dummy variables for each months (controlling for seasonal and other long-term temporal trends, temperature and dew point)	-Asthma admissions were not associated with either pollutants -Pneumonia: PM_{10} (RR=1.012, 95% CI 1.019-1.004) and 24-h ozone concentrations (RR=1.026, 95% CI 1.040-1.013) were associated with daily admissions for pneumonia. The relative risk is for 10 $\mu g/m^3$ increase in PM_{10} and 5 ppb increase in 24-h ozone concentrations, two-pollutant models. A similar but weaker effect was found for 1-h max. ozone. -COPD were associated with PM_{10} (RR=1.020, 95% CI 1.032-1.009) and ozone (RR=1.028, 95% CI 1.049-1.009). The relative risk is for 10 $\mu g/m^3$ increase in PM_{10} and 5 ppb increase in 24-h ozone concentrations, two-pollutant models. -Controlling for one pollutant did not effect the magnitude of the association with the other pollutant -Correlation between PM_{10} and O_3: r=0.35 -Correlation between O_3 and temperature: r=0.67 -Concentration-response relationship for pneumonia admissions for PM is linear, while for ozone it shows a potential threshold at 25 ppb. When PM exceeding 150 $\mu g/m^3$ and ozone exceeding 120 ppb were eliminated in the regression models, the associations remain significant, RR 1.012 (95%CI 1.019-1.004) for PM, and RR 1.026 (95%CI 1.040-1.013) for ozone; both for pneumonia, two-pollutant models. -Same treatment for COPD, when PM above 150 $\mu g/m^3$ and ozone above 120 ppb were eliminated in the regression models, the associations remain significant, RR 1.018 (95%CI 1.033-1.004) for PM, and RR 1.032 (95%CI 1.056-1.008) for ozone; both for pneumonia, two-pollutant models.

Table 12.2a Ambient ozone and association with hospitalizations

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Schwartz, 1994c Minneapolis-St. Paul, Minnesota (pop. 2,460,000) 1986-1989 (4 years; 1461 days)	Hospital admissions, 65 years and older -Pneumonia (6/d) -COPD (2.2/d)	O_3 mean 24-h: 26 ppb 6 monitoring stations in 1986 and only four in 1987-1989 O_3 data were available for 99% of the days during the study period	PM_{10} collected over a 24-h period: 36 µg/m^3 PM_{10} data were available for 86% of the days during the study period 2 sites in 1986 through 88 and four sites in 1989 Also monitored weather variables: temperature and dew point.	-Daily counts admissions, by admit rate, for pneumonia (ICD-9, 480-487) and COPD (ICD-9, 490-496) of persons aged 65 years or older -Poisson regression analysis with dummy variables for each 48 months and for 8 categories each of temperature and dew point. Linear and quadratic time terms were also included	-PM_{10} was a risk factor for pneumonia admissions. For single pollutant model, RR =1.17 (95% CI=1.33-1.03). For multi-pollutants model with ozone and temperature, RR=1.18 (95% CI=1.03-1.36), for 100 µg/m^3. -Ozone was also associated with pneumonia admissions. For single pollutant model, RR=1.19 (95% CI=1.02-1.40), 50 ppb, 24-h avg. For multi-pollutant with PM and temperature, pneumonia RR=1.22 (1.02-1.47) for 50 ppb, 24-h average. -When days exceeding 150 µg/m^3 PM10, and 120 ppb ozone were excluded, the association remained for pneumonia (RR=1.17, 95% CI=1.35-1.02 for PM_{10}, and RR=1.15, 95% CI=1.37-0.96 for ozone). -Association between PM10 and COPD was also significant. -Correlation between PM_{10} and O_3: r=0.18 -Correlation between O_3 and temperature: r=0.51.
Schwartz, 1995 New Haven, Connecticut Tacoma, Washington 1988-1990 (3 years; 1096 days)	Respiratory admissions (ICD-9, 460-519) for 65 years of age or older New Haven: 8.1/d Tacoma: 4.2/d.	O_3 April to October, 24-h avg. New Haven : 28.6 ppb (10-90%, 15.8-45.4 ppb). Tacoma: 24.5 ppb (10-90% 13.3-35.7 ppb).	Pollutant measured on a 24-h period New Haven: PM_{10}: 41 µg/m^3 SO_2: 78 µg/m^3 Tacoma: PM_{10}: 37 µg/m^3 SO_2: 44 µg/m^3 Also monitored weather variables: temperature and relative humidity	-Daily counts of respiratory admissions of person aged 65 years or older. -Multiple regression analysis using a 19-day weighted linear filter (as Burnett and co-workers)	-All three pollutants were associated with respiratory hospital admissions of the elderly -For total respiratory admissions, ozone in single pollutant model RR =1.06, 95% CI=0.99-1.13 in New Haven, and RR=1.21, 95% CI=1.06-1.38 in Tacoma, for a 50 µg/m^3 ozone (25.5 ppb). -In two-pollutant models, for a 25.5 ppb increase in ozone, in New Haven, RR=1.07, 95% CI=1.00-1.15 with PM, and RR=1.05 (0.98-1.13) with SO_2. in Tacoma, RR=1.20 (95% CI=1.06-1.37) with PM, and RR=1.21 (1.06-1.37) with SO_2.

Table 12.2a Ambient ozone and association with hospitalizations

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Schwartz, 1996 Spokane, WA. Jan. 1988 – Dec. 1990	Respiratory admissions of patients 65 years or older, (ICD-9 460-519) (ICD-9 480-487, pneumonia, and ICD-9 490-496, COPD, were the largest subcategories). Total 4241 respiratory hospitalizations, 1137 for COPD; 267 for asthma, 2049 for pneumonia. Elderly (≥65 y)	1-h max. (converted from µg/m^3): 40.3 ppb (10-90% 29.6-55.6 ppb); 24-h average (converted from µg/m^3): 28.6 ppb (10-90% 20.4-37.2 ppb).	PM_{10} Daily average: 37 (10^{th} to 90^{th}: 16-83) µg/m^3	-Generalized additive model to remove long wavelength correlations between air pollution and morbidity. -Linear Poisson regression for daily number of admissions on smooth functions of day of study, temperature, dew point temperature, and day of week indicators.	-Correlation of ozone with temperature was 0.436, with PM10 was 0.259, regarded as low. -Per 25.5 ppb increase of ozone (1-h max. or 24-h average), for all respiratory admissions (single pollutant models): 1-h max.: RR 1.244 (95%CI: 1.002-1.544); 24-h avg: RR 1.284 (95%CI: 0.926-1.778). -For pneumonia: 1-h max. RR: 1.279 (95%CI: 0.947-1.727) -for COPD: 1-h max. RR: 1.125 (0.764-1.656). -Without extreme temperature days (excluding 2.5% of days of coldest weather and 2.5% of days of hottest weather): 1-h max. RR: 1.133 (0.901-1.442). -Including a 2-demensitoal smooth vs temperature and humidity: 1-h max. 1.241 (1.001-1.538). -Including smooth functions of temperature on the same day and 4 preceding days: 1-h max. RR: 1.38 (1.09-1.749).
Moolgavkar et al., 1997 Minneapolis-St. Pau, MN Birmingham, AL Jan. 1986-Dec. 1991	Total respiratory Pneumonia COPD Elderly (≥65 y)	24-h ozone: mean (10^{th} to 90^{th} percentile): Minn: 26.2 ppb (13.5-40.1 ppb), data avaliable for all seasons Birm: 25.1 (13.5-37.6 ppb), data not available in winter.	PM10 (µg/m^3): Minn:33.98; Birm: 43.44 SO2 (ppb): Minn: 4.82; Birm: 6.58 NO2 (ppb): Minn: 16.3; Birm: no data CO (ppm): Minn: 1.6; Birm: 1.23	Semiparametric Poisson regression models were used for analyses of the data. Temperature and day of study (to adjust for temporal trends and variations in hospital admissions not attributable to pollution or weather) were adjusted by nonparametric smoothers. PM_{10}, NO_2, SO_2 and CO were concurrently adjusted using multi-variate regression models.	-Single pollutant model: -Minn: for total respiratory admission, ozone lag 1 d, 15 ppb increase was associated with 6% (95% CI 3.3-8.7%) increase in admission. -Birm: for total respiratory admission, ozone lag 2 d, 15 ppb increase was associated with 0.27% (95% CI –0.2 to 0.74%) increase in admission, not significant. -Multivariate models: -Minn: for total respiratory admission, ozone lag 1 d, 15 ppb increase was associated with 5.15% (95% CI 2.36-7.94%) increase in admission; for pneumonia, 6.6% (3.4-9.8%) increase; for COPD, 4.5% (-0.5% to 9.5%) increase. -Birm: 0.27% (-0.2% to 0.74%) increase, not significant. ;

Table 12.2a Ambient ozone and association with hospitalizations

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Anderson et al., 1997 Europe: 6 APHEA cities: Amsterdam (1977-1989), Barcelona (1986-1992), London (1987-1991), Milan (1980-1989), Paris (1987-1992), Rotterdam (1977-1989)	Hospital admissions for all ages: -COPD (ICD-9, codes 490,491, 492 and 496): A: 1.1/d B: 11/d L: 20/d M: 4/d P: 11/d R: 1.1/d The proportion of COPD admissions for patients aged ≥ 65 years ranged from 48% in Paris to 70% in Barcelona	O_3 1-h mean all year (converted from µg/m^3): A: 39.5 ppb B: 32.8 ppb L: 19.5 ppb M: - P: 18.5 ppb R: 36.4 ppb 8-h avg. all year (converted from µg/m^3): A: 35.2 ppb B: 28.6 ppb L: 14.3 ppb M: - P: 10.2 ppb Rotterdam: 31.1 ppb	SO_2 et NO_2: 24-h and 1-h max. means for each day TSP et BS: 24-h period Also monitored weather variables: temperature and relative humidity	-Daily counts of COPD admissions -Lag days 1,2,3 checked (up to 5 days for O_3) -Poisson regression analysis controlling for seasonal and other cycles; influenza epidemics; days of the week; temperature and humidity -autocorrelation checked	-Significant association between ozone and hospital admissions for COPD -For all ages, the relative risk (RR: 95% CI) for a 50 µg/m^3 (25.5 ppb for ozone) increase in mean level of pollutants (lagged 1 day) were: -SO_2: 1.02 (0.98, 1.06) -BS: 1.04 (1.01, 1.06) -TSP: 1.02 (1.00, 1.05) -NO_2: 1.02 (1.00, 1.05) -O_3 (8h): 1.043 (1.022, 1.065) lag one day; 1.056 (1.027-1.086) for 5 cumulative days. -O_3 (1 h): 1.029 (1.011, 1.047) lag one day; 1.049 (1.024-1.075) for 5 cumulative days. -For 8-h avg. ozone, RR cool season 1.03 (1.00-1.07), warm season 1.04 (1.02-1.07). For 1-h max. ozone, RR cool season 1.01 (0.98-1.05), warm season 1.03 (1.01-1.05).

Table 12.2a Ambient ozone and association with hospitalizations

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Schouten et al., 1996 Europe : 2 APHEA cities in the Netherlands: -Amsterdam (pop. 694,700) -Rotterdam (pop. 576,200) 1977-1989	Hospital admissions: -Respiratory A: 6.7/d R: 4.79/d) -COPD A: 1.74/d R: 1.57/d -Asthma: A: 1.13/d R: 0.53/d	converted from $\mu g/m^3$: O_3 8-h mean: -for May-Oct. (5-95%): A: 44.1 ppb (14.3-77.6); R: 42 ppb (12.8-81.1) -for whole year: A: 35.2 ppb (2.55-68.4 ppb); R: 32.6 ppb (3.1-71.4). O_3 1-h max.: -for May-Oct.: A: 49.7 ppb (21.4-88.3); R: 49.2 ppb (18.4-94.9). -whole year: A: 40.3 ppb (5.1-77.0); R: 38.8 ppb (5.6- 83.7)	SO_2: 24-h period (mean of all year) A: 28 $\mu g/m^3$ R: 40 $\mu g/m^3$ BS: 24-h period A: 11 $\mu g/m^3$ R: 26 $\mu g/m^3$ NO_2 :24-h period A: 50 $\mu g/m^3$ R: 54 $\mu g/m^3$	-Daily number of admissions for the three classifications -Poisson regression model with and without autoregressive terms -Dummy variable for the winter and its interaction with the pollutant was included in the model with a dummy variable for the summer and the pollutant	-No correlation with summer O_3 8-h and respiratory admissions in people aged > 65 years in Amsterdam (RR=1.127, 95% CI 0.983-1.292, 1-d), but a significant positive association in Rotterdam (in 1977-81, RR=1.344, 95% CI=1.097, 1.647, in 1982-89, RR=0.950, in 1985-1989, RR=1.05) for a 100 $\mu g/m^3$ (51 ppb) increase in O_3 8-h. -1-h max. ozone, summer, 1-d: in Amsterdam, respiratory admission, age 15-64 y, 0.976 (95% CI 0.876- 1.088), age 65+ 1.109 (95% CI 0.987- 1.247); COPD: 1.049 (95% CI 0.923 - 1.193); asthma: 0.995 (0.834 – 1.186), for 51 ppb increase. -1-h max. ozone, in Rotterdam, summer, 1-d: respiratory admission, age 15-64 y, 1.026 (0.940– 1.120); age 65+, 1.346 (1.133- 1.598)(in 1977-1981); COPD, 1.038 (0.927 -1.163) , for 51 ppb increase. -SO_2 and NO2 did not show any clear effects in Amsterdam and Rotterdam -BS did not show any clear effects in Amsterdam; in Rotterdam it was positively but not significantly related to the number of admissions

Table 12.2a Ambient ozone and association with hospitalizations

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Ponce de Leon et al., 1996 London (pop. 7,300,000) April, 1987 to February 1992	Respiratory admissions (ICD-9, 460-519), all ages separated into categories: -0-14y:45.4/d -15-64y:33.6/d -65+ y: 46.7/d	O_3 8-h mean: Whole year: 15.6 ppb (10-90% 3-29 ppb); summer 7-36 ppb. O_3 1-h max: 20.6 ppb (5-95% 2-46 ppb) Only 4 monitored stations with moderate correlation between them (data not given)	Other pollutant measured as an daily average: BS: 14.6 µg/m^3 SO_2: 32.2 µg/m^3 NO_2: 37.3 ppb	-Poisson regression analysis, adjusting for effect of trend, seasonal and other cyclical factors, day of the week, holidays, influenza epidemic, temperature, humidity. -Autocorrelation check -Same day and lagged 1,2,3 w ere checked	-O_3 (lagged one day) was significantly associated with an increase in daily admissions among all age groups, except for the 0-14y -This effect was stronger in the “warm” season (April-September) -Very few significant associations were observed with the other pollutants -In summer the RR (95% CI) in 8-h O_3 levels of 29 ppb were (single pollutant models): 1.0483 (1.0246, 1.0726), all ages 1.0294 (0.9930, 1.0672), 0-14y 1.0751 (1.0354, 1.1163), 15-64 y 1.0616 (1.0243, 1.1003), >65 y --Whole year RR in 8-h O_3 levels of 26 ppb were (single pollutant models): 1.0293 (95% CI=1.0113, 1.0477), all ages 1.0269 (95% CI=0.9995, 1.0551), 0-14y 1.0536 (95% CI=1.0232, 1.0849), 15-64y 1.0455 (95% CI=1.0172, 1.0746), 65+ y. -1-h max. ozone effects effects (RR 1.00084/ppb, SE 0.000282/ppb, p<0.01) are smaller than effects of 8-h avg. ozone. Threshold for 1-h ozone may be at 40 ppb. -Whole year ozone (8-h, 26 ppb) + other pollutants models, RR±SE: 1.0292 ±0..0091, +NO_2 1.0292 ± 0.0091, + BS 1.0285 ± 0.0091, +SO_2

Table 12.2a Ambient ozone and association with hospitalizations					
REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Burnett, 1998 (Special analysis for WGAQOG) 13 Canadian cities (pop. 10,800,000) April 1, 1981 to December 31, 1991	Daily number of admissions to hospital (respiratory diseases) for: -Acute bronchitis (ICD-9, 466) -Pneumonia (ICD-9, 480-486) -COPD (ICD-9, 490-496)	O_3 1-h max: 31 ppb Range: (25-38 ppb) Data were average over all stations in each cities (data not given)	Also monitored: daily readings of maximum and minimum temperature, daily average dew point temperature and daily average relative humidity Even Rate/Day for admissions: 13.0	-Estimation of a "National Reference Level" for ozone in Canada date -Number of daily admissions rates for respiratory diseases -Poisson regression analysis were both the respiratory admissions data and the daily variations in 1-h maximum O_3 levels were adjusted using pre-filtered non-parametric smoothed functions of day of study and day of the week differences for each cities - O_3 levels recorded same day and lagged 1,2,3,4 day prior to the event	-Single pollutant model, increase of hospitalizations for 10 ppb ozone: 1.04% (95% CI 0.78-1.30%). -This risk tended to decrease slightly if ozone values above 25 ppb are not included in the analysis (0.74%) -The risk is clearly reduced if days above 20 ppb are excluded -Risk of respiratory admissions increases from 0-2 days lagged and then decreased to 4 days lagged -The LOAEL is 25 ppb based on respiratory admissions (0.74%) -Evidence of a threshold between 15 and 20 ppb

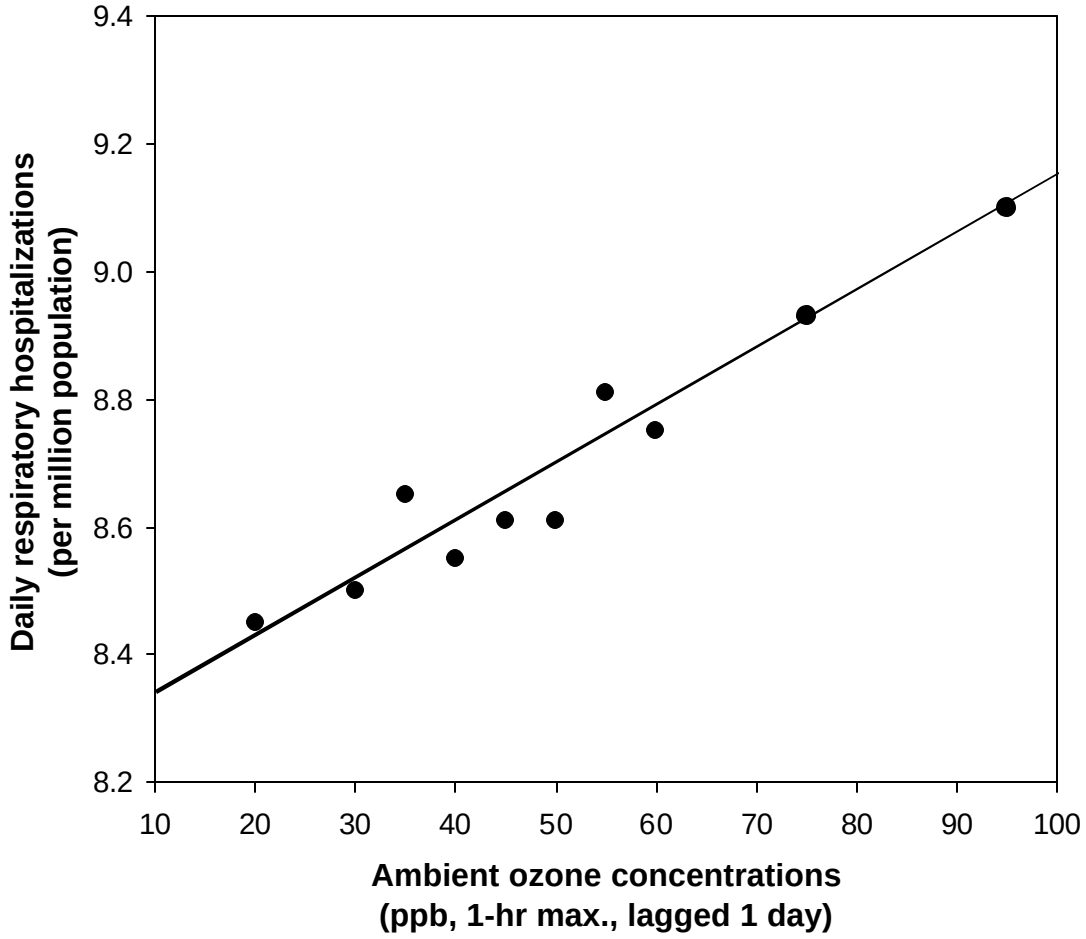
12.3.1 Canadian studies

Two recently completed large scale Canadian studies investigated the effect of short-term high ozone concentrations on respiratory morbidity, utilizing hospital admissions as an objective measure. In a study which covered all of Southern Ontario (and a little of Northern Ontario– Sudbury, Algoma) and included data from a population base of 8.7 million people over a period of 6 years (1983-88), a small but statistically highly significant association (p= 0.001) was found between one-hour peak ozone concentrations recorded the previous day and respiratory hospital admissions during the summer months of May-August (Burnett et al. 1994). An independent increase of 5.0% of admissions was associated with an increase in ozone from 0 to 50 ppb, based on a model which included temperature and sulphates as covariates. The relationship was also significant, but somewhat weaker, for 1-h ozone concentrations recorded the same day, or lagged by two or three days, but was not significant for concentrations recorded four days previously. Sulphates (lagged one day) were also independently associated with hospital admissions, accounting for a further 1% (based on a 5.3 $\mu g/m^3$ level). There were no associations between a control group of non-respiratory hospital admissions and any of the three main variables, i.e. ozone, sulphate or temperature.

The data from the Southern Ontario study do not provide any evidence of a threshold for the effects of either ozone or sulphates (Burnett et al., 1994). The concentration-response relationship appeared to be linear at all concentrations. Figure 12.1 shows the hospitalizations observed in the Ontario study compared to ozone levels (lagged one day)(reproduced from Burnett et al. 1994). A similar graph for sulphates was also published.

In this study (Burnett et al., 1994), each hospital acted as its own control, and 91% of the independently calculated hospital-specific relative risks for increased admissions due to ozone were positive (Relative Risk range = 0.96-1.24 for a 50 ppb increase). The association with sulphates was positive for all 168 hospitals (RR=1.003-1.035 for a 5 $\mu g/m^3$ increase in sulphates). The associations were thus consistent across the entire study region, which included Canada's largest city and metropolitan area as well as large rural and forested areas, some of which were not affected by transboundary transport of air pollution.

Figure 12.1 Association of respiratory admissions in Ontario with ozone pollution (source: Burnett et al., 1994).



The association between ambient ozone levels and hospitalizations was manifested in spring, summer and fall, when ozone concentrations peaked, but was not the case for winter (Burnett et al., 1994). Ozone concentrations were generally low, with the average of 1-h peak concentrations less than 40 ppb for all months except the four months May–August. During summer (May-August), the overall average for the 22 monitoring districts was 52 ppb (range 32-70 ppb) and the 95th percentile was 92 ppb (range for the 22 districts 62 to 118 ppb). Other ozone metrics than the 1-h daily maximum was considered in this study, but the 1-hour maximum was chosen. This was because 1-hour maximum ozone were consistent with other previous studies in the same area (Bates & Sizto, 1987; Thurston et al., 1992, 1994a,b), and it was highly correlated with the 8-h daytime average and with the 24-h average (Pearson correlation coefficient 0.99 and 0.87, respectively).

Respiratory admissions were subcategorized (using ICD9 Codes) for asthma, COPD or chronic obstructive pulmonary diseases (bronchitis, emphysema, bronchiectasis, chronic airway obstruction) and infection (acute bronchitis, bronchiolitis, pneumonia). Upper airway respiratory admissions were not considered. All three categories of respiratory admissions were shown to be significantly increased by air pollution (ozone plus sulphates), at 7% for asthma, 6% for COPD and 4% for infections, the latter being significantly increased only for infants.

Of the three categories, asthma was the most significantly affected ($p<0.001$). Interestingly, although the 2-34 years age group is often most affected by asthma without a concomitant high prevalence of COPD, only 5.5% ($p<0.05$) of asthma in this age group could be associated with air pollution (ozone plus sulphates). The association with asthma was strongest in the 35-64 years age group (10%, $p<0.001$), and was also significant in infants aged 0-1year at 13% of respiratory admissions for asthma ($p<0.05$), but was not significant for the elderly. Almost 6% of total COPD admissions could be associated with air pollution ($p<0.01$). As expected, COPD admissions were significantly associated in the elderly at 6% ($p<0.01$), but a 24% increase ($p<0.05$) was also observed for the 2-34 years age group. The COPD increase was not significant for the 35-64y age group, although it would be expected due to the development of chronic conditions (such as smoking-related diseases) as people age. This, coupled with the anomalies noted above in admissions for asthma in the same two age groups, raises the question of misclassification of the respiratory subcategories due to inaccurate discharge diagnosis.

Admissions were also categorized by age into four groups: <2 years (12% of admissions), 2-34 years (30%), 35-64 years (22%), and 65+ years (36% of admissions). Significant increases in overall respiratory admissions due to ozone were seen in all age groups, but were most marked in infants, with 15% of their admissions calculated to be due to ozone ($P<0.001$). This is most likely due to increases (19%, $p<0.001$) in infections, but partly also due to asthma (13.0% increase, $p<0.05$). The air pollutant effect was least marked in the elderly (4.3% ascribed to ozone plus sulphate), due to a significant increase (6.0%, $p<0.01$) in COPD diseases, as expected for this age group. The calculated increases due to air pollution in the other two age

groups (5.5% and 7.2% for ages 2-34y and 35-64y respectively) were close to the overall average of 5.8% (5.0% for a 50 ppb increase in ozone and 0.8% for a 5.3 $\mu g/m^3$ increase in sulphate).

Multiple regression and a rigorous but conservative statistical treatment for random non-Gaussian (non-normal) effects were used to investigate the relative risk of increased hospitalizations due to ozone and sulphates, taking temperature into account. Long-term cyclic seasonal variations in the data for both hospitalizations and independent variables were detrended by using a 19-day weighted moving average, leaving only short-term variations to be examined. Terms were included for differences in admissions between days of the week, and for inter-hospital differences due to factors such as different admission rates for small community hospitals versus large teaching hospitals. Serial correlations were examined but were not found.

Exposure to ozone was estimated by 22 ambient monitors over the entire area (approximately 800 km east to west, 5^o of latitude, 42^o to 47^o or 550 km south to north), and the area was divided so that each monitor was representative of its own area. Pairwise correlations among the 22 monitoring stations showed a high degree of correlation (>0.68) between ozone values from stations 100 km or less apart. This is likely due to the nature of the circumstances producing ozone in southern Ontario, most of which is due to long-range transport from distant regions (Burnett et al., 1994). Therefore, ambient concentrations within each region were considered to be quite homogeneous spatially, and each regional monitoring station to represent quite accurately the ambient concentrations to which people entering all hospitals in the region were exposed. Exposure misclassification due to placement of the ambient monitors was not therefore very likely, and any misclassification would have arisen because of differences in activity patterns and indoor exposure. Concentrations from ambient monitors must correlate with concentrations from personal exposure monitors, if there is to be confidence that ozone concentrations measured at ambient monitors can be considered representative of population exposures. However, they do not need to be (and are not) the same. This correlation has been demonstrated in several Canadian and US cities (see Chapter 6 for detail). Indoor ozone levels tend to approximate outdoor levels most closely during summer when windows are open. In addition, many people tend to spend more time outdoors in summer.

Potential confounding factors were well handled in the study by including them into the regression analysis where possible, and by providing semi-quantitative estimates of their importance if they could not be included. Daily temperature was known to be independently predictive of hospitalizations, and was also moderately correlated with ozone (r=0.55, range 0.41 to 0.67). It was therefore a potential confounder, and was included in all regressions as the daily mean [which was correlated to the daily maximum temperature (r=0.95)]. Average relative humidity was weakly correlated with ozone (r=-0.17) and with sulphate (r=0.12), while average barometric pressure was not (r=0.03 for ozone and r=0.00 for sulphate). They were therefore dropped from the analysis.

The analysis of other covariates and potential confounders focused on particles since previous work had consistently shown them to be related to hospital admissions. The sulphate fraction of fine particles is even more homogeneous over southern Ontario than ozone, due also to long range transport, and 9 monitors therefore adequately characterized exposure. Daily estimates of exposure to particulate matter or particulate acid levels (as H^+) were not available for most of the province and could therefore not be included in the analysis. However, analyses of the relationship between inhalable particulate matter (as PM_{10}), fine particulate matter (as $PM_{2.5}$), excess H^+, and sulphates in northeastern North America showed them to be highly correlated with each other in the summer (>0.80) (Dann, 1994). Personal monitoring for sulphates have also been shown to be highly correlated with monitoring results from fixed site central monitors (R^2=0.9, Stieb et al., 1998), and more highly correlated than PM_{10} (Clayton et al., 1993). In addition, sulphates, being in the small size fraction of particulate matter, readily infiltrate indoors where the majority of time is spent for most people, thus ensuring that everyone is exposed. Indoor sources for sulphate are minimal. In a study on air pollutants and hospitalizations in Toronto, Thurston et al. (1994a,b) made several direct comparisons between different measures of particulate matter as covariates with ozone in associations with hospitalizations. Sulphate was a better predictor than fine mass, and much better than PM_{10}. The inclusion of sulphate in the Ontario analysis is therefore considered to be a good surrogate for exposure to particulate matter and acidity for southern Ontario in the 1980s (although it might not be so suitable in other locations or at other times, when the correlations might not be so strong). The effects of sulphate and ozone were additive, and sulphate reduced the association of hospitalizations with ozone only slightly (from 5.1%, reduced to 4.6%), while ozone halved the association with sulphate (from 2.2%, reduced to 1%) when each was regressed including the other.

Daily SO_2 and NO_2 readings were also obtained from 24 and 18 monitoring sites respectively, but correlations between sites were lower than 0.4 (SO_2) or 0.5 (NO_2), indicating that not enough monitoring stations were available to provide accurate exposure estimates for each of the 168 hospitals. Therefore, these two factors could not be included in the regression. Neither SO_2 nor NO_2 was considered to be a strong confounder for ozone or sulphate, since the correlations between ozone and daily maximum SO_2 (r=0.20) or NO_2 (r=0.29) were quite low, and the correlations for sulphate with SO_2 (r=0.16) and NO_2 (r=0.30) were also relatively low.

The second Canadian study (Burnett et al.1997a) involves an even more extensive area covering 16 cities in all populated regions across Canada, representing 12.6 million people, or about half the population of Canada in the years (1981 to 1991) of the survey. All cities with a population of over 100,000 for which monitoring data were available were included; from the Pacific coast to the Atlantic they were: Victoria and Vancouver (B.C), Edmonton and Calgary (Alta.), Regina and Saskatoon (Sask.), Winnipeg (Man.), Windsor, London, Hamilton, Toronto, and Ottawa (Ont.), Montreal and Quebec City (Que.), St. John (N.B.), and Halifax (N.S.). Respiratory admissions were not broken down into subcategories, nor were subclassifications by age examined, as they had been in the Ontario study. Multiple regression was carried out as in the previous Ontario

study (Burnett et al., 1994), using a 19-day weighted linear filter to detrend seasonal cyclic variations, dummy variables for hospital effects, day to day variations, location, and weather.

After simultaneous adjustment for CO and dew point temperature, RR of increased respiratory hospitalizations during spring, summer and fall for an increase in the daily 1-h maximum ozone (lagged 1 day) of 30 ppb (close to the mean) was 1.043 ($p<0.0001$) for all 16 cities. Only 11 cities had data of CoH (a PM index) available, and were used to adjust for PM effects. RR of respiratory hospitalizations for 30 ppb ozone was 1.024 ($p=0.026$) for these 11 cities with CoH, CO and dew point temperature in the model. There was no evidence of an association between ozone and a control group of non-respiratory hospital admissions for certain blood diseases and diseases of the nervous, digestive and genitourinary systems. This negative result suggests that the ozone association was not due to factors influencing admission to hospital in general.

The association between ozone and respiratory hospitalizations was similar for those patients older than 65 years of age (RR 1.040 for a 30 ppb increase, 95% CI: 1.010-1.072) representing one-third of admissions, and those patients younger than 65 years of age (RR 1.045, 95% CI: 1.021-1.068). This result suggests that the elderly are not the only people who are at risk for ozone episodes.

This increase in relative risks was seen for all cities except Montreal and Vancouver (RR=1.000 and 1.003 respectively, adjusted for dew point temperature and CO). Other city-specific relative risks varied from 1.021 (Calgary) to 1.069 (Regina). Several possible reasons for the lack of association in Montreal and Vancouver between admissions and ozone were explored. Adjustment for CoH made little difference. The Pearson correlation coefficients between ozone and dew point temperature were 0.29 for Montreal and 0.23 for Vancouver, similar to the study mean of 0.23, and therefore not high enough to suggest that this could be the cause of the non-significance. The unadjusted ozone relative risks were also low, but the reasons for such a weak ozone effect remain unclear. Other authors have found a similar lack of association for these two cities; Emergency Department visits for asthma in Vancouver were examined by Bates et al. (1990) and hospitalizations in Montreal were studied by Delfino et al. (1994).

The observations of lower risk of hospitalizations in Vancouver and Montreal (Burnett et al., 1997, delfino et al. 1994) than other Canadian cities are in line with the exposure data using the probabilistic National Exposure Model (pNEM, see Chapter 6.3.3). The pNEM study has demonstrated that when time-activity patterns and microenvironment ozone data were incorporated for population exposure estimates, Vancouver and Montreal had much lower population exposure levels of ozone than Toronto.

The effects of four sampling times were also considered, but the daily 1-hour maximum concentration of ozone was statistically the most significant factor explaining the excess hospitalization rate compared to the daily average, average 8am-8pm (daytime) concentration, or maximum 8-h running average. Also the 1 day lagged concentration was more predictive than the

concentration on the day of admission (day 0) or that of two days previously. Concentrations averaged over lagged days 0 and 1, days 0,1,and 2, and days 1 and 2 were also tested, but were also not as strongly associated as concentrations at lag day 1.

Ozone concentrations were low in all cities in comparison to the current objective of 82 ppb. For the spring-summer period when ozone levels are usually highest and a significant correlation with hospitalizations is most likely to be observed, the 16-city ozone mean and 95th percentile values based on the 1-hr daily maximum were 33 and 64 ppb, respectively. As observed previously, there was no increase in relative risk in winter when ozone levels were low (RR = 0.993), and the increase was highest in summer when ozone levels peak, (RR=1.043; 95% CI:1.021-1.066).

Daily maximum and minimum temperatures as well as dewpoint temperature, all of which were highly intercorrelated, were also examined, but the dew point temperature was selected for inclusion in the regressions as a potential confounder, since associations were judged to be strongest using this metric.

Four additional pollutants were considered as potential confounders. Although particulate matter had been shown in other studies to be an important covariate predictor of increased hospitalizations (for both respiratory and cardiovascular conditions), daily measures of particulate matter including sulphates, were not available for most of the cities in the study. Soiling Index (as CoH) is related to particles and was used as a substitute for 11 of the 16 cities. No CoH measurements were available for 5 cities, and they were not included in the analysis for particulate matter. The ozone RR for hospitalizations was reduced to 1.024 ($p=0.026$) for these 11 cities, adjusting for dew point, CO and CoH. CoH may be a less satisfactory surrogate for particulate matter than sulphate, based on results from several of the mortality studies. However, the weakness of the particle effect, as measured by sulphate in the Burnett et al. (1994) study in southern Ontario, and by sulphate, fine mass and PM_{10} in the Thurston et al. (1994a,b) study in Toronto, gives some assurance that the lack of a good particle surrogate in the national study was not an important source of confounding. There was little evidence of an association between respiratory hospitalizations and either NO_2 ($p=0.77$) or SO_2 ($p=0.13$) and they were dropped from the multiple regression analysis.

Two other Canadian studies conducted by Burnett et al. (1997b,c), though focusing on PM (1997b) or carbon monoxide (1997c) rather than on ozone, provided additional evidence for ozone effects on respiratory hospitalizations. In the study by Burnett et al. (1997b), the researchers investigated the effects of various PM metrics and ozone on respiratory and cardiac hospitalizations in Toronto between 1992-1994. The authors found that the adjustment for temperature did not affect the ozone-cardiorespiratory associations, RR for respiratory admissions was 1.064 ($p<0.05$), and for cardiac admissions was 1.074 ($p<0.05$), for a 11.5 ppb increase in ozone. No multi-pollutant regression was conducted for ozone, while for PM after the adjustment of gaseous pollutants, PM_{10}, $PM_{2.5}$, sulphate and H^+ still revealed a significant association with cardiac and respiratory admissions. The correlation coefficients of ozone with PM metrics were between 0.20 (coarse particles) and 0.53 (sulphates), and were minimal with other gaseous pollutants (r between 0.02-0.18). Thus the ozone-hospitalization associations

would have been more convincing if PM effects had been adjusted during the regression analyses.

In the study by Burnett (1997c), the study focused on CO effects on congestive heart failure in the elderly (>65 years of age). While the authors detected a significant association between CO and congestive heart failure even after adjusting for PM, and other gaseous pollutants, the effect of ozone was moderately significant. When controlled for temperature, log-RR coefficient was 0.0022 (t ratio=1.8); when controlled for temperature and all the other pollutants, log-RR coefficient=0.0021 (t ratio=2.0). This is not surprising, since other than in the study by Burnett et al. (1997b), ozone has not been documented to be associated with cardiac hospitalizations.

The results of the Ontario and the 16-Canadian city studies are quite consistent within each study, with each other and with the results of other time-series studies published in the past few years. Burnett et al. (1994,1997a) found virtually the same relative risk of 1.032 and 1.033 for respiratory hospitalizations due to ozone in the Ontario and in the national study. The Ontario study (Burnett et al., 1994) confirmed and extended the findings from a previous series of studies by Bates & Sizto (1987, 1989).

Following a request from the WGAQOG, Dr. R. Burnett revisited the above 2 Canadian studies, and performed a regression analysis using the data from 13 cities (Vancouver, Edmonton, Calgary, Winnipeg, Windsor, London, Hamilton, Toronto, Ottawa, Montreal, Quebec City, Saint John, and Halifax). The data were analyzed for both hospitalization and mortality endpoints using single-variate models. The actual methods and results of the analysis are provided in Appendix A (Burnett, 1998). The regression analysis showed that the ozone risk associated with hospitalization for respiratory diseases is 1.04% per 10 ppb increase in daily one hour maximum ozone (95%CI: 0.78-1.30%). The lowest observable adverse effect level (LOAEL) with statistical significance, derived from the data, is 25 ppb ($p<0.01$). Interestingly, the data show that the regression coefficient between ozone and hospitalization becomes negative between 15 and 20 ppb indicating a possible threshold for hospitalization based on the result of this new analysis.

An earlier study by Bates and Sizto (1987, 1989) covered a smaller area of southern Ontario than the 1994 study, and included 5.9 million people and data for nine years, 1974 and 1976-83. The analysis was confined to short two-month seasons, winter (January-February) and summer (July-August) in order to reduce cyclic seasonal variations in admissions. Longer term (multi-year) downward trends in some pollutant levels necessitated analysis of each year separately. Day-to-day variation in hospitalizations was shown to exist, and was handled by comparing only same-day (e.g., Tuesday) hospitalizations within the same 2 month period and same year to the pollution variable (lagged 0-4 days).

During summer (July and August), a significant association ($p<0.001$) was found between total respiratory hospital admissions and 1-h peak ozone levels (lagged 1 or 2 days). Ozone was also correlated with respiratory admissions minus asthma (lagged 2 days only) and with all-age asthma admissions, but not with asthma in children aged 0-14 years. Sulphate (SO_4) and sulphur dioxide (SO_2) were also correlated to the same three endpoints with about the same lag times for SO_4 and a lag of 2 days only for SO_2. Surprisingly, coefficient of haze (CoH) was not

correlated to any of the respiratory categories. There were no correlations of any air pollutant with a control group of non-respiratory diseases or conditions. In winter, correlation analysis between temperature, pollution factors, and hospitalizations showed that only temperature (lag 0,1,2 days) was correlated with total respiratory visits and asthma admissions for all ages including children aged 0-14 y (Bates & Sizto, 1987).

In summer, cross-correlation analysis indicated that all air pollutants plus temperature were highly correlated with ozone, with coefficients >0.6, except CoH at 0.49 and humidity at 0.003 (Bates & Sizto, 1987). Temperature was included in a multiple regression, which indicated that ozone, sulphate and temperature together, all lagged 0,1,2 days, accounted for 5.6% of variability in respiratory admissions. If temperature was forced into the regression first, it only accounted for 0.9% of the hospital admissions. Addition of SO_4 and ozone accounted for an additional 2.4% and 2.3% respectively (Bates & Sizto, 1989).

The Bates and Sizto (1987) study provided evidence that asthma is not the only condition that appears to be affected by ozone; the association remained significant for respiratory admission minus asthma, although the latter comprised about 50% of all summer respiratory admissions. The asthma admissions of children who have been suggested as a target group for toxicity of ozone, did not show a significant association with ozone. However, Burnett et al. (1994) compared the Bates & Sizto results to theirs in a separate analysis using their more extensive database and a more rigorous statistical method of analysis. They were able to show a positive association between ozone and hospital admissions for children aged 0-14 years, with an 8.2% increase in asthma admissions per 50 ppb ozone ($p=0.005$) (Burnett et al., 1994). The increased statistical power to detect this effect may have been due to the larger number of admissions (approximately 50% more admissions) in the study by Burnett et al. (1994) compared to that of Bates and Sizto (1987) and the method of statistical analysis.

Bates & Sizto (1989) pointed out several anomalies in the hypothesis that ozone is the agent responsible for the increased hospitalizations; in their data these included a lack of demonstrable effects on hospitalizations in June 1983 when ozone was consistently >82 ppb compared to the same period in 1982 when ozone was lower on average, and a lack of correlation for daily SO_4 at one central monitoring station when values for all monitors, collected every sixth day, were correlated with hospitalizations. They concluded that probably neither ozone nor SO_4 alone was responsible for the observed associations with acute respiratory admissions, and suggested that acidity (H^+ ion) was a good candidate as a potentiator of the ozone/sulphate effect.

It is noteworthy that the earlier Southern Ontario studies (Bates & Sizto, 1987) treated the whole area as one entity from the point of view of exposure. If ozone concentrations were not homogeneous in this area, then this may cause misrepresentation of exposure. This generalization of exposure also gave significant Pearson coefficients for ozone and SO_4, which might artificially weaken the potential effect of ozone. Burnett et al. (1994) refined the exposure data by using the ozone monitor closest to the hospital in which the admissions were being

recorded, which reduced the chance of misclassification of exposure. This resulted in an increase in the significance of the association between ozone and admissions. Zidek's recent calculations (1996) of individual exposure of people admitted to hospital for respiratory conditions based on the census code of the admitted individual and a system of "kriging" to compute probable ozone ambient exposure has added another order of magnitude to the level of data accuracy and significance found. The demonstrated increase in significance of the association as the exposure calculation is refined and improved, constitutes a powerful argument for causality.

Thurston et al. (1994a,b) examined the relationship of total respiratory and asthma hospital admissions in Toronto, Ontario, with ozone and fine particles, represented by sulphate and acidity as H^+ ion, during July and August 1986-88. After detrending the hospitalization, pollutant and temperature data, as well as controlling for day-of-the week effects, bivariate correlation analyses were carried out. Ozone was highly correlated ($r>0.6$) with SO_4, NO_2, and maximum temperature, while correlations with H^+ and SO_2 were moderate (0.51 and 0.41 respectively). As expected, the measures of fine particles H^+ and SO_4 were highly correlated with a coefficient of 0.81. The correlations between total respiratory or asthma-related admissions and ozone, SO_4 or H^+ were relatively weak, and all in the same range, 0.21-0.28, while correlations with SO_2, NO_2 and maximum temperature were all low, 0.2 or less. SO_2 and NO_2 were therefore dropped from the regression analysis, and simultaneous regression of temperature with each of ozone, SO_4 and H^+ in turn yielded independent relative risk (RR) estimates for respiratory and asthma-related hospitalizations.

Results from Thurston et al. (1994a,b) reveal strong associations between summer haze pollution (i.e., ozone, H^+ and SO_4) and total respiratory or asthma hospital admissions on the same or following days. For ozone, the RR was calculated to be 1.36 (95% CI 1.13-1.59) per 100 ppb ozone. For SO_4, the RR was 1.30 (95% CI 1.07-1.53) and for H^+, the RR was 1.25 (95% CI 1.06-1.44). Paired regressions were carried out between ozone, SO_4 and H^+ as well as fine particles (FP), PM_{10}, TSP, and the fraction of TSP above PM_{10} in size. Ozone remained highly significant as a predictor of respiratory hospitalizations with either SO_4 or H^+ in the model ($p=0.008$ in each case). The regression coefficients for ozone remained almost the same, while the coefficients for H^+ and SO_4 were reduced by one fourth to one third, and, in the case of SO_4, was only marginally significant. The coefficients dropped for all the ozone-PM metrics, but that for ozone remained significant with FP, and marginal with TSP and TSP-PM_{10}. Because of the high correlation coefficients of ozone ($r=0.64$-0.75) with all the particle metrics, their effects on hospitalizations could not be separated from each other. The correlation coefficients for O_3-H^+ was relatively moderate ($r=0.51$), thus allowing the authors to conclude that the adverse effects of H^+ on respiratory hospital admissions are real. The authors calculated the overall pollutant mean effect to be about 9% for the summertime haze combination of ozone, SO_4 and H^+, by averaging the individual pollutant mean effects of 19.9% for ozone, 5.6% for sulphate and 2% for acid H^+. Thurston and colleagues concluded that there was no clear discrimination of a single pollutant as the responsible agent, but the regression results suggest that ozone was the

summertime haze constituent of greatest relevance to hospital admissions. The authors also postulated a potentiating role for high H^+ concentrations in combination with ozone.

Concentration-response relationships were examined by categorizing data into quartiles for temperature, ozone and acid H^+ and plotting against total respiratory admissions (Thurston et al., 1994a,b). In the case of ozone, admissions were equally increased for the two highest quartiles at 60 and 90+ ppb, while there was no increase in the two lower quartiles, in both filtered and unfiltered data. For aerosol acidity H^+, the mean admissions were increased only for the upper quartile, >80 nmole/m^3. The filtered 1-h maximum temperature was the only one of the three to display a linear relationship with admissions, for the range 22-37^{0}C. The slope of the regression curve was also examined by means of a sensitivity analysis for evidence of changes in slope with concentration. The slope for total respiratory admissions for all 117 days was 0.051 admissions/ppb ozone. It decreased slightly to 0.048 when the two days >120 ppb were removed, and to 0.045 when all days above 80 ppb (N=22) were removed. The monotonically increasing linear dose-response with ozone seen in the Burnett et al. (1994) study in southern Ontario was thus not observed here. However, the Thurston study encompassed only metro Toronto, with a population of 2.4 million versus 8.7 million for the southern Ontario study (Burnett et al., 1994), and included only three 2-month periods compared to 9 years, with 4 months each year.

Thurston and colleagues presented an interesting comparison of lag effects, both negative and positive, between their Toronto data and Buffalo data (Thurston et al., 1992), concentrating on 1988, when hot hazy weather conditions were especially prevalent. Buffalo is 60 miles south west of Toronto and has a similar climate. It is reasonable that some time might elapse between the time of highest ambient pollutant level and the time that affected individuals are admitted to hospital. In both studies, and in others as well, this lag is observed. Admissions were also tested against a negative lag, i.e., pollutant levels 1-4 days after the hospitalization events. The lag effects were always in the expected direction for both respiratory and asthma visits correlated with ozone, SO_4, H^+ or temperature, but were randomly distributed for the control group of non-respiratory diseases. The proper temporality of the association was thus strongly evidenced. Lag times were 0-2 days for Toronto, with the lag of 1 day most highly correlated in the cases of ozone, H^+ and SO4, and 2 days for temperature. Lag times were slightly longer for Buffalo, 0-3 days with lag 2 days most highly correlated with ozone. These minor differences are likely due to differences in social or medical practices between the two cities.

Delfino et al. (1994) examined the relationship between the number of daily urgent hospital admissions for respiratory illnesses (31 hosptials) and ambient air pollution in Montreal, Quebec, during warm seasons between 1984 and 1988. A High-pass filter (19-d moving average) was used to eliminate yearly seasonal trends in the data. Day-of week trends were controlled by prefiltering the outcome variables prior to analysis. The authors used ordinary least-squares to regress single air pollutants on the outcome. They also tried to adjust for PM_{10}, sulphate and temperature by co-regressions with ozone. In summer (July and August), the results showed a statistically significant univariate association of all respiratory admissions to 8-hour average ozone. The association was substantially reduced when co-regressed with temperature. When

adjusted for PM_{10} or sulphate, the associations of ozone (1-hour maximum) with asthma and with non-asthma respiratory admissions were nonsignificant. The correlations of ozone with PM_{10}, sulphate and temperature were high (r=0.68, 0.66 and 0.72, respectively), which may have contributed to the weakened associations between ozone and respiratory hospitalizations. These strong correlations also made it difficult to separate the effect of ozone from other environmental factors. These findings are consistent with those reported by Burnett et al. (1997a) who also found that the associations of ozone with respiratory hospitalizations in Montreal were weak when compared with other Canadian cities.

12.3.2 Studies in other areas

Thurston et al (1992) found the relative risk for total respiratory admissions in Buffalo, NY and New York City (based on the 1988 high-pollution summer) were 1.22 and 1.19 for ozone. However, the high inter-correlation between SO_4, H^+ and ozone prevented the authors from performing multi-variate analysis, and from singling out the specific contribution of ozone to the relative risk of hospitalization due to pollution episodes.

Schwartz has examined Birmingham, AL (1994a), Detroit, MI (1994b), Minneapolis, MN (1994c), New Haven, CT and Tacoma, WA (1995), and Spokane, WA (1996) with respect to possible association of hospital admissions in the elderly (>65 years) with ozone and PM_{10}. In Birmingham, AL (Schwartz, 1994a), although the relative risk for respiratory hospitalizations increased, it was not statistically significant (RR=1.14 for 50 ppb increase in ozone, 95% CI: 0.94-1.38). Several methodological deficiencies exist in this study, including no correction for day of the week effects and no adjustment for other atmospheric pollutants (SO_2, NO_2, PM_{10}) when compared with studies from other cities (Schwartz, 1994b,c, 1995), which may have precluded detection of a significant effect from ozone.

The correlation was significant for ozone and hospital admissions for pneumonia and chronic obstructive pulmonary disease (COPD) in elderly people in Detroit and for pneumonia only in Minneapolis (Schwartz, 1994 b,c). In these two studies, temperature and PM_{10}, two most marked confounders, were simultaneously adjusted in the analyses. In Detroit, ozone was estimated to be responsible for 11.3% of excess admissions for pneumonia and 12.2% for COPD (Schwartz, 1994b). In Minneapolis, after adjustment for PM and temperature, the RR was 1.22 (95% CI 1.02-1.47, for 50 ppb increase in ozone) for pneumonia (Schwartz, 1994c). The effect of PM_{10} was about half the ozone effect for pneumonia. There was no significant association of either PM_{10} or ozone with asthma. This is not inconsistent with the Burnett et al (1994, 1997a) studies, since asthma is expected to occur more frequently in younger people, and the number of daily admissions for asthma may have been too low for the elderly to provide meaningful results.

Moolgavkar et al. (1997) conducted a re-examination of the data from Minneapolis-St. Paul and Birmingham AL, with the addition of two more years of data. Semiparametric Poisson regression models were used for analyses of the data. Temperature and day of study, the latter to adjust for temporal trends and variations in hospital admissions not attributable to pollution or weather,

were adjusted by nonparametric smoothers. PM_{10}, NO_2, SO_2 and CO were concurrently adjusted using multi-variate regression models. The reanalysis (Moolgavkar et al., 1997) confirmed Schwartz's results (1994a and 1994c), and concluded that a 15 ppb increase in ozone on the day before was associated with a 5% increase in respiratory admissions in the elderly (65+ years) in Minneapolis-St. Paul, but not in Birmingham. One explanation for the lack of associations in Birmingham is that the ozone data in winter were unavailable which limited the data size. An alternative explanation is that the results are sensitive to the form in which these covariates are entered into the model.

For New Haven and Tacoma (Schwartz 1995), respiratory hospital admissions were associated with SO_2, PM_{10}, and ozone, with ozone associated independently of the other pollutants. However, in New Haven, the association was marginal, with a relative risk of 1.07 (CI 1.00-1.15) when PM_{10} effect was adjusted. In Tacoma, the association of ozone with respiratory hospitalization was statistically significant both taken alone and after adjustment for PM_{10} ($p<0.005$ and $p<0.01$). The relative risk was higher than for New Haven, and was 1.20 (CI 1.06-1.37) for a 50 ug/m^3 (26 ppb) in mean 24-h ozone levels. The statistical analysis undertaken for the New Haven and Tacoma study was more comprehensive than the earlier analyses, and included use of a 19-day averaging period as a seasonal filter, and specific terms for each day of the week.

In Spokane (Schwartz, 1996), both PM_{10} and ozone were associated with an increased risk of respiratory hospital admissions in single-pollutant models. No multi-variate analysis was conducted because of too few days during which both measurements were taken (Schwartz, 1996). The RR for ozone (lagged 2 days) was 1.244 (95% CI 1.002-1.544) for a 26 ppb increase in ozone. This association remained significant when a two-dimensional smooth function of temperature and humidity was included, or when a smooth function of same-day and 4 preceding days' temperatures were included, but reduced to insignificance if the 5% of the days with the highest or lowest temperatures were removed prior to the analysis. This association is much higher than found by other authors, or by Schwartz in other studies, possibly because of the inability to control for particulate matter.

Anderson et al. (1997) investigated the data of ozone and hospital admissions for all age COPD from six European cities including Amsterdam, Barcelona, London, Milan, Paris and Rotterdam in the APHEA study. The authors found that both 1-hour maximum ozone and 8-hour average ozone, from both whole year and summer data, either one day before the hospitalization or 5 cumulative days, were significantly associated with all age COPD hospitalizations. Ozone in the cool season was not associated with COPD hospitalization. No multi-variate analysis was carried out in this study.

A separate analysis of respiratory hospital admissions in Amsterdam and Rotterdam found a significant association with 8-hr maximum ozone in Rotterdam but not in Amsterdam (Schouten et al., 1996). The reason for this was not explained. The results with 1-hr maximum ozone were

almost identical to the 8-hr maximum ozone results. This study did not examine the confounding effects of other pollutants.

Within the same European project (APHEA) using the same methodolgy, in London (Ponce de Leon et al., 1996), the association of ozone (both 1-hour maximum and 8-hour average, summer and whole year) with all respiratory hospitalizations was significant in all age groups except in children aged 0-14 years. The authors also conducted multi-variate analyses and adjusted the effects of PM (BS), SO_2, and NO_2. After the adjustment for other pollutants, ozone remained significantly associated with all age respiratory hospitalizations.

Two authors, Thurston (1995) and Schwartz (1995) have attempted to present a summary of the magnitude of the effects on morbidity seen in these different studies (the unpublished Canadian study was not included in either). The information in the two summaries is not entirely compatible due to inclusion of slightly different sets of results, choice of different units of ozone measurement, and different ways of presenting the risk in the various studies. In Table 12.2b, we include all the available studies as of April 1997, including the latest Ontario (Burnett et al., 1994) and the 16-Canadian city study (Burnett et al. 1997a). Relative risks were standardized from the original units to a percentage increase in hospitalizations for a 10 ppb increase in ozone. The Table illustrates the results from single-pollutant or multi-pollutant models. These estimates encompassed southern Ontario, 16 cities across Canada, and 7 U.S. cities including one on the west coast. The lower end of the range was about 1.1, and this value is most likely to represent the “true” value since it is close to the values observed in the studies reviewing the largest and most diverse population database from different geographic areas in Canada.

12.3.3 Summary of ozone effects on hospitalizations (Table 12.2b)

Among the eighteen hospitalization studies reviewed in this document, sixteen of them have demonstrated statistically significant associations between ozone and respiratory hospitalizations in one or more aspects, using single-pollutant or multi-variate models. The aggregate results from time-series studies provide good evidence that environmental exposure to ozone at levels commonly encountered in Canada, the USA and European countries, perhaps in concert with other pollutants, is associated with adverse respiratory effects that are sufficiently severe to require hospitalization. This association has now been consistently observed in studies conducted in cities geographically spread across North America and Europe, differing in pollutant levels, components, population characteristics, and differing also in the statistical methods employed to take into account confounders, covariates and short- or long-term seasonal cycles in hospital admissions. The specificity of ozone has been shown in some studies where particle levels were low (Schwartz, 1995). In most of the studies that adjusted for the effects of temperature and other co-pollutants such as PM, ozone effects remained significant (8 out of 9 studies). It has been found that, if temperature is not included in the regression but rather prefiltered out, then some of the ozone effect is removed. The most common pollutant variables showing an inter-correlation with ozone were particulate matter, sulphate and acid haze (H^+ ion).

It is possible that hospitalizations due to the primary irritant action of ozone on the lung and respiratory system are exacerbated by one or more of these other environmental components, as proposed by Thurston (1994a,b) for acid haze (H^+).

Four studies compared the effects of ozone on different age groups. Two of these studies (Ponce de Leon et al., 1996, Burnett et al., 1997a) did not find that elderly people (>65 years) were more at risk than younger populations (<65 years), whereas one study (Schouten et al., 1996) found that only elderly people had a significant increase in respiratory hospitalizations following an ozone episode. One study examined the effects in 0-1 age group and found that infants appear to be most sensitive to the effects of air pollutants compared with other age groups. Therefore, very young people and the elderly are identified as the subpopulations potentially most at risk. This may include a substantial segment of the total population, estimated to be about 5% for diagnosed asthma, up to 20% if atopic individuals are included.

For hospitalizations, given the very diversified health endpoints and age groups in these studies, it is difficult to group the studies and conduct a meta-analysis for a weighted mean ozone effect. Thurston and Ito (1999)[4] in their latest publication presented a synthesis of ozone hospital admission studies. They grouped the estimates into four groups, and used the random effects model to obtain a combined weighted RR (95% CI) for each 100 ppb ozone (1-hour maximum) increase, for each group. The results are all from single-pollutant models:

(1) Canada/New York major respiratory admissions for all ages (Thurston et al., 1992,1994a,b; Delfino et al., 1994; Burnett et al., 1994,1997a,b), RR=1.18 (95%CI 1.10-1.26);

(2) Canada/New York asthma admissions for all ages (Thurston et al., 1992,1994; Delfino et al., 1994) RR=1.18 (95% CI 1.07-1.30);

(3) US Medicare studies of pneumonia, COPD and total respiratory illnesses for elderly (>65 years) (Schwartz 1994a,b,c,1995,1996; Moolgavkar et al., 1997), RR=1.19 (95% CI 1.12-1.26);

(4) APHEA European studies (Anderson et al., 1997), RR=1.114 (95% CI 1.043-1.184).

For ozone effects from multi-pollutant models, a meta-analysis was conducted for this report by pooling all available data, using a random effect model. The criteria for study selection were the same as for the mortality studies, except that some populations involved the elderly only. Eight studies were included in the analysis, and the reasons for inclusion or exclusion for individual studies are indicated in Table 12.2.b. Data include all respiratory admissions, and separate disease categories (asthma, pneumonia and COPD). The weighted mean RR for respiratory hospitalizations per 100 ppb ozone (1-hour maximum) is 1.1118 (95% CI 1.073-1.151) (or 1.12% increase per 10 ppb ozone), within the same range as those obtained from single-pollutant models.

[4] This 1999 paper by Thurston & Ito is not an original research paper, rather a review paper, presenting meta-analyses conclusions (pooled RR estimates). It is included because the majority of the studies reviewed are also reviewed in this document (including the Canadian studies) thus the meta-analysis was not repeated independently for this document. Also, Thurston & Ito, 1999 did meta-analyses from single-pollutant models, which provide a useful comparison to the multi-pollutant meta-analysis performed here.

Table 12.2b Summary of relative risk estimates for respiratory hospital admissions due to a 10 ppb increase in ozone concentrations, in univariate and multi-variate models

Location and reference	Ozone mean ppb (range)(1-h max., unless indicated)	Outcome	Percent increase (95% CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Ozone only models	% increase (95%CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Multi-pollutant models	Inclusion / exclusion in quantitative analysis S: Significant NS: Non-sig
Southern Ontario Bates & Sizto, '87, '89	Winter 23.34 ppb Summer 56.07 ppb	all respiratory, asthma	Significant increase in risk. Value not given.	-	**Results S** Excluded, no data from multi-variate models
NYC Buffalo Thurston et al. '92	1988 -Buffalo: 75-164 -NYC: 69-206 1989: -Buffalo: 65-128 -NYC: 53-111	all respiratory, asthma	Respiratory: NYC: 1.40% (0.60-2.20%) Buffalo: 2.50% (0.40-4.60%) Asthma: NYC: 1.67% (0.95-2.41%) Buffalo: 3.26% (1.91-4.61%)	-	**Results S** Excluded, no data from multi-variate models
Montreal, Quebec Delfino et al., 1994.	1-h max.: May-Oct. 36 (90^{th}: 59.2); July-Aug.: 41 (90^{th}: 65.8). Ozone 8-h max.: May-Oct. 30.4 (90^{th}: 51.5); July-Aug.: 35 (90^{th}: 57.3)	all respiratory admissions Asthma admissions	1-h max. ozone: not given. 8-h avg. ozone, all respiratory: 0.41% (0.073-0.737%) + temperature. 0.676% (0.416-0.936%), no temperature.	Asthma: 1-h max. ozone: 0.175% (-0.02% to 0.37%), + PM_{10} Non-asthma respiratory: 1.65% (-22.0% to 25.3%), +sulphate.	**Results S** Included
Toronto Thurston et al. '94a,b	Mean 57.5 ppb (3 years) 2 days > 120 ppb 22 days > 80 ppb	all respiratory	3.83% (2.40-5.26%)	3.64% (2.16-5.12%), + H^+ 3.68% (2.18-5.18%), +sulphate 2.93% (1.24-4.62%) ,+fine particles 2.81% (1.06-4.56%), +PM_{10} 2.61% (0.96-4.26%), +TSP	**Results S** Included, used data from ozone + fine particles
Minneapolis Schwartz '94c	24-h avg.: 26 ppb (10-90% 11-41 ppb)	Pneumonia in elderly	24-h ozone: 3.8% (0.4-8.0%)	24-h avg. ozone: 4.4% (0.4-9.4%), +temperatury, PM_{10}	**Results S** Included
Detroit Schwartz '94b	24-h avg.: 21 ppb (10-90% 7-36 ppb) 1-h max.: 53 ppb	Pneumonia and COPD in elderly	-	24-h avg. ozone: Pneumonia: 5.2% (2.6-8.0%), +PM_{10}. COPD: 5.6% (1.8-9.8%), + PM_{10} No data for 1-h. max. ozone	**Results S** Included

Table 12.2b Summary of relative risk estimates for respiratory hospital admissions due to a 10 ppb increase in ozone concentrations, in univariate and multi-variate models

Location and reference	Ozone mean ppb (range)(1-h max., unless indicated)	Outcome	Percent increase (95% CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Ozone only models	% increase (95%CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Multi-pollutant models	Inclusion / exclusion in quantitative analysis S: Significant NS: Non-sig
Birmingham, AL Schwartz '94a	O_3 24-h avg.: 25 ppb (10-90% 14-25 ppb).	Pneumonia and COPD in elderly	24-h average ozone: Pneumonia: 2.8% (-1.2% to 7.6%) COPD: 3.4% (-2.8% to 12.0%) 1-h max. ozone: pneumonia: 0.8% (-0.6% to 2.4%) COPD: 1.4% (-0.8% to 4.0%)	-	**Results NS** Excluded, no data from multi-variate models
Southern Ontario Burnett et al., 1994	May-Aug: 52 ppb (62-118) Other months: <40 ppb.	All respiratory	May to Aug.: 0.93% (0.75-1.11%)	May to Aug.: 0.92% ($p<0.0001$), + sulphate + temperature	**Results S** Excluded, no data on variances or confidence intervals.
New Haven, Conn. Tacoma, Wa. Schwartz '95	April to Oct. 24-h avg.: New Haven : 28.6 ppb (10-90%, 15.8-45.4 ppb). Tacoma: 24.5 ppb (10-90% 13.3-35.7 ppb).	all respiratory elderly (>65 y)	24-h average ozone: New Haven: 2.35% (-0.39 to 5.10%) Tacoma: 8.23% (2.35-14.9%)	24-h avg. ozone: New Haven: 2.74% (0-5.88%), +PM_{10}, 1.96% (-0.78% to 5.1%), + SO_2. Tacoma: 7.84% (2.35-14.5%) +PM_{10} 8.24% (2.35-14.5%), + SO_2.	**Results S** Included for both cities
London UK Ponce de Leon et al. '96	O_3 8-h mean: Whole year: 15.6 ppb (10-90% 3-29 ppb); summer 7-36 ppb. O_3 1-h max: 20.6 ppb (5-95% 2-46 ppb)	All respiratory	8-h average ozone, summer: 1.66% (0.85-2.50%), all age 1.01% (-0.24 to 2.32%), 0-14 y 2.59% (1.22-4.01%), 15-64 y 2.12% (0.84-3.45%), >65 y 8-h avg., whole year: 1.13% (1.43-1.83%), all age 1.03% (-0.02% to 2.12%), 0-14 y 2.06% (0.89-3.26%), 15-64 y 1.75% (0.66-2.87%), >65 y 1-h max. ozone: 0.84% (0.56-1.12%)	Whole year ozone (8-h avg.): 1.12% (0.77-1.47%), +NO_2 1.12% (0.77-1.44%), + BS 1.10% (0.75-1.45%), +SO_2	**Results S** Included

Table 12.2b Summary of relative risk estimates for respiratory hospital admissions due to a 10 ppb increase in ozone concentrations, in univariate and multi-variate models

Location and reference	Ozone mean ppb (range)(1-h max., unless indicated)	Outcome	Percent increase (95% CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Ozone only models	% increase (95%CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Multi-pollutant models	Inclusion / exclusion in quantitative analysis S: Significant NS: Non-sig
Amsterdam, Rotterdam, the Netherland. Schouten et al. '96	O_3 8-h avg.: May-Oct. (5-95%): A: 44.1 ppb (14.3-77.6); R: 42 ppb (12.8-81.1) whole year: A: 35.2 ppb (2.55-68.4 ppb); R: 32.6 ppb (3.1-71.4). O_3 1-h max.: May-Oct.: A: 49.7 ppb (21.4-88.3); R: 49.2 ppb (18.4-94.9). Whole year: A: 40.3 ppb (5.1-77.0); R: 38.8 ppb (5.6- 83.7)	All respiratory	1-h max. ozone, summer: A: 2.14% (-0.25% to 4.84%), >65 y -12.2% (-2.4% to 1.7%), 15-64 y R: 6.78% (2.6-11.7%), >65 y 0.51% (-1.2% to 2.4%), 15-64 y 1-h max., ozone, whole year: A: 1.39% (-0.45% to 3.4%), >65 y -0.02% (-1.8% to 1.9%), 15-64 y R:5.3% (1.7-9.5%), >65 y 0.86% (-1.0% to 2.96%), 15-64 y. 8-h avg. ozone, whole year: A: 1.18% (-0.8% to 3.4%), >65 y 0.02% (-1.9% to 2.18%), 15-64y R: 4.9% (0.76-9.9%), >65 y 0.04% (-2.2% to 2.4%), 15-64 y	-	**Results S** Excluded, no data from multi-variate models
Spokane, WA. Schwartz, 1996	1-h max.: 40.3 ppb (10-90% 29.6-55.6 ppb). 24-h avg.: 28.6 ppb (10-90% 20.4-37.2 ppb)	All respiratory admissions, pneumonia, and COPD, Elderly (>65 y)	all respiratory admissions: -1-h max. ozone: 9.8% (0.8-21.8%) -1-h max. ozone + tem.: 14.9% (3.5-29.4%) -24-h avg. ozone: 11.4% (-2.9% to 31.1%) Pneumonia: -1-h max. ozone: 11.6% (-2.1% to 29.1%) COPD: -1-h max. ozone: 4.9% (-9.2% to 25.7%)	-	**Results S** Excluded, no data from multi-variate models

Table 12.2b Summary of relative risk estimates for respiratory hospital admissions due to a 10 ppb increase in ozone concentrations, in univariate and multi-variate models

Location and reference	Ozone mean ppb (range)(1-h max., unless indicated)	Outcome	Percent increase (95% CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Ozone only models	% increase (95%CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Multi-pollutant models	Inclusion / exclusion in quantitative analysis S: Significant NS: Non-sig
Minneapolis-St. Paul, MN Birmingham, AL. 1986-1991 Moolgavkar et al. (1997)	24-h ozone: mean (10th to 90th percentile): Minn: 26.2 ppb (13.5-40.1 ppb) Birm: 25.1 (13.5-37.6 ppb)	All respiratory Pneumonia COPD Elderly (≥65 y)	Total respiratory admission: Minn: 4% (2.2-5.8%). Birm: 0.18% (–0.13% to 0.49%)	Total respiratory admission: Minn: 3.43% (1.57-5.29%) Birm: 0.18% (–0.13% to 0.49%) Pneumonia: Minn: 4.4% (2.3-6.5%) COPD: Minn: 3.0% (-0.33% to 6.3%)	**Results S** Included for both cities
Six European cities Anderson et al. 1997	O_3 1-h mean all year: A: 39.5 ppb B: 32.8 ppb L: 19.5 ppb M: - P: 18.5 ppb R: 36.4 ppb 8-h avg. all year: A: 35.2 ppb B: 28.6 ppb L: 14.3 ppb M: - P: 10.2 ppb Rotterdam: 31.1 ppb	COPD, all age	8-h avg. ozone, whole year: lag 1 d: 1.69% (0.86-2.55%) 5 cumulative days: 2.2% (1.06-3.37%) 1-h max. ozone, whole year: lag 1 d: 1.14% (0.43-1.84%) 5 cumulative days: 1.92% (0.94-2.94%) 8-h avg. ozone: cool: 1.18% (0-2.74%) warm: 1.57% (0.78-2.74%) 1-h max. ozone: cool: 0.39% (-0.78% to 1.96%) Warm: 1.18% (0.39-1.96%)	-	**Results S** Excluded, no data from multi-variate models
16 Canadian cities Burnett et al. 1997a	Spring 40 ppb Summer 38 ppb Fall 21 ppb Winter 26 ppb Whole year 31 ppb (95th percentile 60 ppb)	All respiratory	All age: Winter: -0.2% (-1.2% to 0.83%); Spring: 1.4% (0.4-2.4%); Summer: 1.7% (0.87-2.47%); Fall: 0.93% (-0.07% to 1.97%) April - Dec.: 1.40% (1.14-1.66%) <65y, 1.5% (0.7-2.3%), April-Dec. >65y, 1.3% (0.33-2.4%), April-Dec.	April - Dec.: 1.43% (1.12-1.75%), +CO 1.03% (0.70-1.40%), +CO, dew point temperature 0.80% (p=0.0258), +CO, dew point temperature, PM (soiling index), in 11 cities w ith available PM data.	**Results S** Included
Toronto, Ont. Burnett et al., 1997b	Daily 1-h max. 41.2 ppb (5th-95th percentile 22-69 ppb) used 3 day average for regressions	Total respiratory Cardiac admissions	3-d avg. ozone: non temperature: respiratory: 5.9% (4.0-7.8%) cardiac: 5.0% (2.2-7.8%) + temperature and dew point temperature: respiratory:5.6% (3.5-7.7%) cardiac: 6.4% (3.1-9.6%)	-	**Results S** Excluded, no data from multi-variate models

Table 12.2b Summary of relative risk estimates for respiratory hospital admissions due to a 10 ppb increase in ozone concentrations, in univariate and multi-variate models

Location and reference	Ozone mean ppb (range)(1-h max., unless indicated)	Outcome	Percent increase (95% CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Ozone only models	% increase (95%CI) per 10 ppb ozone (1-h max., unless indicated otherwise). Multi-pollutant models	Inclusion / exclusion in quantitative analysis S: Significant NS: Non-sig
10 Canadian cities Burnett et al., 1997c	Daily 1-h max.: 32 ppb (5^{th} –95^{th} percentile: 10-64 ppb) 24-h avg.: 16 ppb (5^{th}-95^{th} percentile 3-35 ppb)	Congestive heart failure in elderly (>65 y)	24-h avg. ozone: not controlled for temperature 0.30% (0.03-0.57%) + temperature and dew point temperature: 0.32% (-0.025% to 0.66%)	+ temperature, DP temperature, CoH, NO_2, SO_2, and CO: 0.30% (0.006-0.594%)	Excluded, no respiratory data
Canada Burnett, 1998	O_3 1-h max: 31 ppb Range: (25-38 ppb)	All respiratory	1.04% (0.78-1.30%)	-	Excluded, no data from multi-variate models
Meta-analysis	Meta-analysis of multi-pollutant analyses, weighted mean increase (%) in respiratory hospitalizations +/- SD = 1.12% +/- 0.20% (n=8) per 10 ppb increase in ozone (1-hr max), 95% CI: 1.073 - 1.51%, p<0.05. Meta-analysis of single-pollutant analyses (Thurston and Ito, 1999), weighted mean increase (%) in respiratory hospitalizations +/- SD = 1.8% +/- 0.41% (n = 6) per 10 ppb increase in ozone (1-hr max), 95% CI: 1.0 - 2.6%, p<0.05.				

12.4 MORBIDITY—ACUTE EFFECTS: EMERGENCY DEPARTMENT VISITS

As with hospitalizations, emergency department (ED) visits provide a relatively objective and measurable indicator of the impact of ambient ozone concentrations on public health, by making use of administrative data records. A greater element of subjectivity than with hospitalizations is included in emergency department visits, since a visit is usually the result of an individual's (or family's) own decision that health has been seriously impaired, and that medical attention should be sought immediately. Partly because of this element of individual choice and partly because the health impact is not as severe, on average, as with individuals who have been hospitalized (by doctor's orders), the ED visit rates should be (and are) much higher than the hospitalization rates, thus demonstrating the applicability of the 'pyramid of effects' as set out by the American Thoracic Society (1985). Some idea of the relationship between hospitalizations and ED visits can be obtained from the study by Stieb et al. (1995a), who administered a questionnaire to a sample of 52 asthmatic volunteers in Winnipeg. One-quarter had visited an emergency department in the previous year for respiratory illnesses, while five percent (not necessarily the same individuals) had been hospitalized in the same period, a ratio of one hospitalization to every five ED visits. A similar set of results (a mean of 0.6 hospitalizations versus 2.7 ED visits in the past 12 months) was observed in Saint John, N.B. for ED patients discharged with asthma, in response to a questionnaire (Stieb et al., 1995b).

Ten studies utilizing emergency department visits as the outcome, were reviewed as an extension to the hospitalization series of studies, using the same criteria against which to judge the scientific merits and the reliability of the information on associations with ozone which they provided. These studies are presented in Table 12.3. Three of these studies were included in the combined analysis of hospitalizations and ED visits in the recent U.S. EPA Criteria Document on Ozone (1993). Two studies included in the EPA analysis were not included here (Tseng et al., 1992; Sunyer et al., 1991), since their methodology was judged (by the EPA reviewer) to be inappropriate and/or inadequate for detection of an ozone effect.

12.4.1 Studies reporting significant positive associations between ozone and Emergency Department visits

Six of the ten studies reviewed in this document found statistically significant associations between ozone levels and ED visits for asthma or for all respiratory causes (Cody et al., 1992; Weisel et al., 1995; White et al., 1994; Romieu et al., 1995; Delfino et al., 1997; Jones et al., 1995). The authors of the studies used various analytical techniques to detrend the ED visits and ozone data, and were successful in adjusting for the effect of temperature, a known confounder with ozone, by inclusion into the regression equation. Table 12.3a gives an overview of methodology and results of the individual studies, and Table 12.3b presents a summary of ozone risks associated with increased ED visits for respiratory diseases.

Risk of increased ED visits

The percent increase in ED visits from these studies varies from 6% to 8.6% per 10 ppb of 1-hour maximum ozone (Romieu et al., 1995; Delfino et al., 1997), or 5.6% to 14.2% per 10 ppb of 5-hour or 8-hour average ozone (Cody et al., 1992; Weisel et al., 1995, Delfino et al., 1997), or 11% per 10 ppb of 24-hour average ozone (Jones et al., 1995). Most studies controlled for seasonal and temperature variations. Three studies controlled for SO_2 (Cody et al., 1992, Weisel et al., 1995, Romieu et al., 1995), and three studies controlled for PM (Weisel et al., 1995, White et al., 1994, Delfino et al., 1997). The adjustment for environmental factors did not substantially reduce the risk of ozone-associated respiratory ED visits. As expected, the impact of ozone on respiratory ED visits is higher than on mortality (0.4% increase per 10 ppb) and hospitalizations (1.12% per 10 ppb). The results are considered consistent for the ED studies, given that two studies looked at children, two were for all ages in general, and two for 3 or 4 individual age groups.

Concentrations at which adverse outcomes were observed

The ED results were obtained from four cities or areas (Montreal, Quebec; central New Jersey adjacent to New York City; Atlanta, Georgia; and Mexico City), in three countries, representing a wide range of average ozone concentrations, between 30 and 90 ppb for the high summer season. Montreal had the lowest ozone concentrations at 33.2 and 36.2 ppb (mean of 1-h daily maximum) for 1992 and 1993 respectively, and the ozone value never exceeded 79 ppb (82 ppb is the Canadian objective). In Montreal, in line with the low ozone levels, the association with ED visits was not significant for ozone in 1992, but was significant in 1993. Mexico City had the highest average ozone levels, at a mean (1-h max.) of 90 ± 40 ppb, with 28% of days above 110 ppb (the Mexican objective).

Age of respondents

In Montreal (Delfino et al., 1997), only the elderly were significantly impacted by ozone, of the four age groups examined (< 2 years, 2-34 years, 35-64 years, 65+ years). This is not necessarily inconsistent with other studies in which children were found to be affected by ozone, because in the Delfino study, all respiratory diagnoses were included rather than asthma alone, due to a lack of diagnostic specificity in the database to separate out asthma. In Jones et al., (1995) the ozone effect on the elderly respiratory ED visits was marginal ($p<0.11$) compared with people aged 18-60 years ($p<0.04$). The elderly are more likely than younger age groups to have COPD or other conditions that compromise lung function, and are less likely to suffer from asthma. Two studies examined asthma visits in children (<16 years) (White et al., 1994; Romieu et al., 1995). Both studies found a significant association between ozone (1-hour maximum or 5-hour average) and children's asthma ED visits, after adjusting for temperature, and/or SO_2.

Concentration-response relationships.

Three of the studies reporting statistically significant results looked at the dose-response relationships by dichotomizing or categorizing their data on ozone levels, in addition to the regression analysis on continuous data. Weisel et al. (1995) found that for days with ozone > 60

ppb (average of 5 h from 10 am - 3 pm), there were 25.5% more visits by all age groups for asthma-related conditions than for days with ozone <60 ppb (p=0.0029).

For children in Atlanta GA (White et al., 1994), 43% more ED visits (95% CI 4-97%) were recorded for days when ozone (1-h maximum) was higher than 110 ppb compared to the days with ozone below 110 ppb. White et al. (1994) also examined the concentration-response relationship at ozone levels from 80 ppb to 110 ppb. RR for ozone-associated asthma visits increased monotonically from 1.01 (at 80 ppb) to 1.5 (110 ppb), although the RR was statistically significant at 110 ppb only.

In the study of Mexico City children (Romieu et al., 1995), 68% more asthma-related ED visits (95% CI 30-171%) were recorded on occasions when preceding and concurrent two days were above 110 ppb (mean of daily 1-h maximum). When ozone levels (1-hour maximum) during two preceding days were above 110 ppb, asthma-related ED visits increased 133% (95% CI 83-196%) (Romieu et al., 1995).

Table 12.3a Ambient ozone and emergency department visits

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Cody et al. 1992 central New Jersey 9 hospitals May –Aug. 1988-89 (2 summers)	ED visits, asthma and bronchitis, all ages; mean 28.7 y (1988), 29.9 y (1989) mean visits 3.6/d- asthma, 4.0/d- bronchitis, 18.0/d – wounds Total: : asthma 814; bronchitis 912; wounds 4066	O_3 -10 am-3pm (5 h means): 0.55 ppm (1988) 0.043 pp (1989) 34 days >120 ppb (1988) 8 days > 120 ppb (1989) 5 monitoring sites ((R=0.58-0.88 between sites)	SO_2- 9 ppb mean PM_2 (every 6th day) (no values given) visibility as surrogate for SO_4 also monitored temperature, pressure, relative humidity, 5 monitoring sites (3 near hospitals)	OLS multiple regression -Temp highly correlated with ozone, (r=0.64) therefore included in regression -lag days 0, 1, 2 checked -anal. Incl. SO_2, RH, visibility, -PM_{10} incl., separate model. -autocorrelation check	-Bivariate models: ED visits for asthma correlated with temperature (r^2=0.052, p=0.0006), and with ozone (r^2= 0.025, p=0.0147). indicating confounding effects of temperature. -Multivariate analysis of all environmental variables (SO_2, temperature, RH, visibility) and asthma visits, only ozone and temperature showed contribution: O_3 (5-h avg.), coefficient with asthma (SE, p), (% increase per 10 ppb, SE): 1988-1989 (lag 1d): 20.3 (7.17, p=0.005), (5.6%, 2.0%) 1988 (lag 1d):24.6 (8.28, p=0.0041), (7.4%, 2.5%) 1989 (lag 0d): 37.2 (13.5, p=0.0067), (9.7%, 3.3%); (lag 1d) 27.7 (11.8, p=0.0206), (7.3%, 3.0%). -Concluded 7%-9% increase in asthma visits was contributed to ozone (48 ppb mean); then for each 10 ppb, it was 1.4% to 1.9%. -No environmental associations seen with bronchitis or control cases (finger cuts). -correlation not significant for PM_{10} -1 day in 6 for particles, + visibility as surrogate for SO_4 may be inadequate, Therefore part of effect ascribed to ozone could have been from these -Checked for day of week effects, but not found important -did not control for seasonality, but used ozone season data only. -did not consider NO_2, SO_4, H^+
Weisel et al. 1995 central New Jersey May- Aug. 1986-90 (5 summers)	ED visits, asthma mean visits 5.36/day, range 4.49-6.05 (5 years)	O_3 52.8 ppb (5-y mean, 10 am-3 pm) range 46 - 57 ppb (5 years) Monitoring as in Cody et al. 1992	SO_4 , NO_2 , SO_2, visibility monitored but values not given -temp., relative humidity, rate of temp. change also recorded -PM_{10} not mentioned, but monitored in previous study, and possibly in this. Monitoring as in Cody et	-daily ED visits for asthma, all ages -looked at different lag times, considered visits from 3pm to 9 am, same day and lag 1 day -OLS multiple regression -Temperature, rate of temperature change, and relative humidity considered in prelim. Anal, but only ozone and temp. incorporated into	-Multiple regressions, controlled temperature, RH, sulphate, NO_2, SO_2, visibility, ED visits correlated with O_3 significantly. % increase asthma ED visits (SE) per 10 ppb: 1986: 7.1% (3.6%) 1987: 7.7% (3.0%) 1988: 7.0% (3.0%) 1989: 14.2% (3.2%) 1990: 6.9% (2.5%) -temperature explained 7.6% to 34% of variability (1988 lowest, 1990 highest)

Table 12.3a Ambient ozone and emergency department visits					
REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
			al. 1992	regression. -Ozone values were lagged 24, 48 hours for regression, each year regressed separately -covariance anal. For 60 ppb cutoff point, adj. For temp. -autocorrelation considered	-Low (<60 ppb) vs. high ozone (≥60 ppb), 5-year data: 25.5% increase in asthma visits due to ozone, P<0.0001. -When adjusted for temperature, ozone mean effect 3% per 10 ppb. -Daily SO_4, NO_2 visibility, and every 6th day SO_2 not correlated to ED visits. -analysis successfully decoupled temperature (most important potential confounder) from effects of ozone on ED visits.
White et al. 1994 Atlanta, GA (2 counties, 1 hospital in low soc.-econom. status area, 55,000 mostly black children, within 6 mi. of 1 hospital, 3 mo., , June-Aug 1990	ED visits, asthma in children, ages 1-16 (infants excluded) 609 visits in 92 days, (6.6± 3.06 visits/day) average age 6y	O_3 1-h max: 78ppb (range 15-163 ppb) 8-h mean: range 13-125 ppb (mean not given) O_3 > 110 ppb for 6 of 92 days 2 monitors, 1 and 7 miles from hospital correl. High(R=0.87)	SO_2 17-139 ppb PM_{10} 39.4 ug/m^3 (24-h mean) 67 ug/m^3 (mean of 1-h max.) dewpoint , temperature. and pollen counts also measured PM_{10} monitors in state network, + 1 of 2 O_3 monitoring locs, for 6 weeks (1/2 of time)	-daily ED visits for asthma, mostly black children, from low SES area -excl. bronchiolitis, pneumonia, + repeat visitors Poisson regression; included temp., day of week, PM_{10} (lag1); checked various time lags, autoregression 2nd Poisson regr. with generalized estimating equation for serial correlation	-Single pollutant model, not control of temperature, for asthma visits: 1-h max. ozone: >110 ppb RR=1.33, 95% CI 0.94-1.71 8-h avg. ozone, number of asthma visits: <80 ppb, 6.53 (5.83-7.23); >80 ppb, 6.61 (5.14-8.08); <90 ppb, 6.43 (5.79-7.07); >90 ppb, 8.00 (4.89-11.1). -RR (95% CI) for 110 ppb or high ozone (1-h max.) for other causes of visits: Total visits: 1.37 (1.02-1.73) Non-upper respiratory infection: 1.53 (1.14-1.92). -Multivariate analysis: • controlled for temperature, PM_{10}, day of the week: RR for asthma visits at ozone >110 ppb (1-h max.): 1.42 (0.99-2.0, p=0.057). • also corrected for autocorrelation + above factors, RR=1.43 (1.04-1.97) • controlled for temperature, PM_{10}, day of the week, pollen: RR=1.33 (0.91-1.92). • controlled for temperature, PM_{10}, day of the week, dose-response relations: 80-90 ppb, RR=1.01 (0.75-1.36); 90-99 ppb, RR=1.24 (0.93-1.65); 100-109 ppb; RR=1.29 (0.86-1.93); 110 ppb, RR=1.50 (1.02-2.21). - PM_{10} RR=1.02 for a 10 ug/m^3 incr. (CI 0.96-1.13; n.s.) -Seasonality was reduced by the study period selection, but within the season cycles not addressed.

Table 12.3a Ambient ozone and emergency department visits

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
Romieu et al. 1995 Mexico City, north- central area, low SES, 1 pediatric hospital (serves approx. 450,000 children) Jan-June 1990, (dry season Nov.-May, with highest air pollution)	ED visits, asthma (ICD-9 code 493), other respiratory diseases (IDC-9 codes 460-464, 466, 480-486), and non-respiratory diseases Children<16 y, 1 pediatric hospital serving approx 450,000 children Asthma visits 2.14/day (total 395) Respiratory visits 7.58/d (total 1365) Total visits, incl. non-respiratory, 15,698	mean O_3 1-h max 90 ±40 ppb (range 10-250) O_3 >110 ppb on 28% f days (49 d) Also O_3 8-h moving average Air monitoring station located in residential catchment area of hospital	Mean SO_2 70 ppb Mean NO_2 30 ppb Mean TSP 474 ug/m^3 (range 238-672) Measurements included daily min. temp., NO_2 and SO_2 24-h mean, SO_2 daily 1-h max., O_3 daily 1-h max and 8-h moving average. - TSP (by hi-vol sampler) was measured only every 6 days, total 44 days during the study period. -Air monitoring station located in residential catchment area of hospital	Poisson regression model. Terms for day-of-week effects, seasonal effects (Jan-Mar vs. Apr.-Jun) included. Three different lag times included (lag 0-lag 2). Two age categories examined (< 5 years, ≥ 5 years) -children < 5 y suggested as sl. more susceptible to effects of ozone	-50 ppb incr. in 1-h max. O_3 (lag 1d) assoc. with 43% incr. in asthma visits (RR=1.43; 95% CI 1.24-1.66, after accounted for potential confounding of day of the week, period, SO_2, temperauture). 50 ppb incr. in 1-h max. O_3 (lag 1d) assoc. with 43% incr. in asthma visits (RR=1.43; 95% CI 1.23-1.65, after accounted for potential confounding of day of the week, period, SO_2, temperauture, sex, age). -2 consecutive days (preceding and concurrent days) with O_3 >110 ppb gave 68% incr. in ED asthma visits (RR1.68, 95%CI 1.30-2.71). -RR=2.33 (95% CI 1.83-2.96), 133% increase, after high ozone levels on the 2 preceding days before the asthma-related ED visits. -O_3 also correl., (but weaker) with other resp. visits (P=0.02, 0.06 for lags 0,1) - SO_2, a 50 ppb increase in same day 1-h max., was marginally assoc. with a 5% increase in ED visits for asthma (RR 1.05; CI 0.99-1.11), and was strongly associated with other respiratory visits (p=0.002) - Exposure to particulate matter was not a significant predictor of asthma-related visits (but only 44 days available for analysis (authors noted inability to assess PM accurately) Analysis carefully done, but basic no. of visits very small.
Castellsague et al. 1995 Barcelona, Spain 5 years, 1985-1989 (4 years for O_3, excl. 1986)	ED visits for asthma, as recorded in asthma registry (validated for reliability) Residents >14 y old, to age 65 4 hospitals, incl. 80% of asthma visits Mean asthma visits -	Ozone 1-h max, ppb (converted from ug/m^3) Summer/winter mean 43/29 75th 53/35 95th 71/53	Pollutant mean (ppb) Summer winter NO_2 54 52 95th 96 80 SO_2 15 19 95th 31 35 BS (black smoke, ug/m^3) mean 48.2 68	-Poisson regression anal. -stratified by season, winter- Jan-Mar. summer- July-Sept -time trends tested with linear and quadratic terms for long trends, indicator variables for study year, month, and day of week -weather variables included	-No associations were found between ED visits for asthma and either O_3 or SO_2 -After adjusted for temperature and RH, month, day of the week, and soybean unloading, RR= 0.991 (summer, 95%CI 0.939-1.045) and 1.055 (winter, 95% CI 0.998-1.116) for 12.8 ppb O_3, p=0.1. -SO_2 , NO_2 and BS were associated with asthma visits in summer and in winter; the association was higher for a 1-day lag. -No multi-pollutant regression were done.

Table 12.3a Ambient ozone and emergency department visits

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
	2.7/day in summer, 3.9/day in winter (Total 912 visits)			temperature (min., max, mean), RH, dew point. (not clear if considered before or in the regression) lags 0-5 days tested, also tested cumulative exposure	-No correlation coefficient between ozone and co-pollutants was given. -Ozone levels were lower in Barcelona than in other cities where positive associations have been observed. This, combined with very low asthma visits/day and higher than average NO_2 may have accounted for the nonsignificant findings.
Rennick & Jarman 1992 Melbourne, Australia 1 year, 1989	ED visits, asthma All children > 2 years old -excl. repeat attendance < 3 days apart -1 hospital	for ozone days, average 2.7 (range 1-6) stations recorded ozone levels >120 ppb (1-h) and >50 ppb (8-h avg.).	Aiboorne particulate index, 5 stations (range 2-6) had API breach.	Pearson correlation analysis done on ozone and other pollutants. ANOVA used to control for confounding variables. Stepwise multiple regression analysis used for associations.	-Smog alert days not significantly related to asthma ED visits. -Ozone days not significantly related to asthma visits. Results not given. -Seasonality controlled by examining during summer and during ozone days. -No temperature controlled. -multiple stepwise regression did not reveal ozone effect. Results not given. -Significant association between asthma ED visits and API, $p<0.005$.
Delfino et al., 1997 Montreal, Canada (pop. 3,000,000) June-September 1992-1993 (2 summers) 25 hospitals	ER visits for all respiratory illness, asthma All ages separated into ages <2y, 2-18y, 19-34y, 35-64y, 65+y Mean of respiratory visits: 1923 visits; 98/d	O_3 1-h max (mean): 1992 1993 28.8ppb 30.7ppb O_3 8-h mean: 1992 1993 33.2ppb 36.2ppb 10 monitoring stations correl high: r=.80 (except for one station for which r=0.70)	Measured as a 24-h period: 1992 PM_{10}: 30.1 µg/m^3 $PM_{2.5}$: 18.5 µg/m^3 SO_4: 51.7 nmole/m^3 H^+: 11.3 nmole/m^3 1993 PM_{10}: 21.7 µg/m^3 $PM_{2.5}$: 12.2 µg/m^3 SO_4: 34.8 nmole/m^3 H^+: 4.0 nmole/m^3 Also monitored temperature and relative	-OLS multiple regression, using a 19-weighted linear filter to remove temporal trends and weather variables -Same day and lag days 1,2 checked -Autocorrelation check	-No significant association with ER visits were found for 1992 (33% of the particulate data were missing), data not reported. For 1993 results: -No ozone effects on age 2-64y, data not shown. -For age <2y, no ozone effect reported, presumably not significant. -For age >64 y, respiratory ED visits: - single-pollutant model: 1-h max. lag 1d ozone 10 ppb assoc. with 5.9% increase of visits (SE 1.78%); 8-h max. lag 1d ozone 10 ppb assoc. with 7.2% (SE 2.2%) increase in visits. - 8-h max. Ozone+PM2.5, 10 ppb assoc. with 5.7% (SE 2.8%) increase in visits. - When controlled for weather, single-pollutant model, ozone effect did not change

Table 12.3a Ambient ozone and emergency department visits					
REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
			temperature and relative humidity		effect did not change. -H^+ was significant for infants under age two (5% increase in ER visits) but was no significant for the elderly -O_3 and PM_{10} never exceeded 67 ppb and 51 $\mu g/m^3$ respectively (1993). -PM_{10} and $PM_{2.5}$ along with SO_4 were significant predictors of 16% and 12% respectively, of increases in ER visits (total respiratory) for the elderly (65+y). -1-h max. and 8-h avg. ozone were highly correlated (r=0.97). -Ozone correlated with PM_{10} (r=0.63), $PM_{2.5}$ (r=0.63), SO_4 (r=0.58), H^+ (r=0.46), and temperature (r=0.70).
Jones et al., 1995 Baton Rouge, Louisiana June 1, 1990 to August 31 1990 (92 days) 3 hospitals	Respiratory-related ED visits: (pneumonia, sinusitis, COPD, bronchitis, croup, asthma, shortness of breath and upper respiratory tract infection) 3 age categories: -pediatric (0-17y) -adults (18-60y) -geriatric (61+y)	Daily average O_3 28.2 ± 11.7 ppb (range 9.3-57.9 ppb) O_3 1-h max (mean): 69.1 ± 28.7 ppb (range 25.3-165 ppb) 4 days > 120 ppb 3 monitoring stations (r=0.95)	No other pollutants were measured Also monitored daily temperature and hourly relative humidity at 2 monitoring sites -Total respiratory-related ED: 1265 visits -Pediatric: 369/d -Adult: 629/d -Geriatric: 267/d	-Multiple regression analysis -Terms of temperature, humidity, mold, pollen counts, days of the week effects were examined -Autocorrelation check -Lag 2 days tested	-Respiratory-related ED visits in summer (June to Aug.) were significantly associated with 24-h ozone in adult (18-60 y), not assoc. with elderly (60+ y) and children (0-17y). -Single pollutant models: correlations between 24-h avg. ozone and daily respiratory ED visits were seen only in adults. Slopes (SE, t): Children: -0.028, (0.017, -1.63) (-7.0% increase per 10 ppb, 95% CI –15.4% to 1.4%) Adult: 0.076 (0.025, 2.99)(11.1% increase per 10 ppb, 95% CI 3.8-18.4%). Elderly: 0.013 (0.019, 0.70) (4.5% increase per 10 ppb, 95% CI –1.9% to 10.9%). -Multiple regressions with ozone, temperature, RH, mold and pollen, respiratory ED visits slope (t): - Children: -0.026 (t= –1.18), p<0.24, (-6.5% increase per 10 ppb, SE 5.5%, 95% CI –17.3% to 4.3%) - Adults: 0.068 (t=2.12), p<0.04, (9.9% increase per 10 ppb, SE 4.7%, 95% CI 0.71% to 19.1%) - Elderly: 0.039 (t= 1.59), p<0.11, (13.4% increase per 10 ppb, SE 8.4%, 95% CI –3.2% to 30.0%). -Day of the week do not appear for a factor in determining the respiratory-related ED visits (tested by One-way ANOVA) -44% of the adults and 43% of pediatric respiratory-related ED

Table 12.3a Ambient ozone and emergency department visits

REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
					visits were due to asthma -For geriatric respiratory-related ED visits, the predominant diagnosis were COPD (28%)
Bates et al., 1990 Vancouver, Canada (pop. approx.: 1,000,000) July 1, 1984 to October 31, 1986 (3 summers) 9 hospitals	ED visits, asthma (ICD-9 code 493), other respiratory diseases (ICD-9 code 466, 480-486, 491-492 and 496) and non-respiratory diseases All ages separated into ages 0-14y, 15-60y, 61+y 25 500 visits/months where 2.7% for respiratory conditions and of these, 41.3% for asthma	O_3 mean of the daily hourly maximum for all stations: Mean for a week in summer: 30.4 ppb and in winter: 18.8 ppb 11 monitoring stations	Mean of maximal hourly values for: SO_2, NO_2 and CoH (values not given) Also monitored: daily temperature SO_4 were collected between October 84 and December 86 at 2 monitoring sites: Winter (Nov.-April): 3.15 µg/m^3 Summer (May-Oct.): 3.54 µg/m^3	-Intercorrelations between environmental variables and emergency visits (Pearson correlation) -Stratified by season: Winter: November to April Summer: May- October (coefficients were calculated on the same day and lagged 24 and 48 hr)	-1-h max. ozone moderately correlated with SO_2, NO_2, SO_4 and CoH in summer (r ranging from 0.125 with sulphate to 0.35 with NO2), and in winter (r ranging from 0.308 with NO2 to 0.56 with CoH). -O_3 is strongly related to temperature, r=0.64 in summer, r=0.57 in winter. -Simple Pearson correlation shows: - In summer ozone was associated significant with total ED visits in all age groups (1-14 y, 15-60 y, 61+), and not significantly assoc. with asthma or respiratory visits. - In winter, ozone was assoc. with total ED visits only in adult group (15-60y). - The analysis did not take into account temperature, day of the week, within the season other cyclic variations, other pollutants, etc. -No risk estimates were given. -Total ED visits also significantly positively correlated with temperature in both summer and winter. -There was a day of the week effect on respiratory visits. -Respiratory visits are not related to temperature, O_3 or , NO_2 -Asthma and respiratory visits (group 15-60y) are correlated in summer with SO_2 and SO_4 ($p<0.001$) -In the 61+y group only, respiratory visits in the winter are related to NO_2 levels on the same day, and lagged 24 and 48 hr; asthma visits were related to SO_2
Kesten et al., 1995 Toronto July 1, 1991 to June 30, 1992 (1 year)	ED visits, asthma Total ER visits for asthma: 854 visits; 2.38 visits/d (highest number of	O_3: average of hourly measurements over a 24-h period (data not given)	Measured as an 24-h basis (data not given): SO_2 NO_2 Air pollution index	-Daily, weekly and monthly averages of the number of emergency room visits for asthma -Autoregressive technique; the number of visits, which is the dependent variable, was	-No association between emergency room visits for asthma and outdoor levels of SO_2, NO_2, O_3 and overall air quality index (on a daily, weekly or monthly basis). -Visits staggered by 1 and 7 days: relationship between emergency room visits and air pollution index and air quality index -Visits staggered by 7 days: associations were found between

Table 12.3a Ambient ozone and emergency department visits					
REFERENCE	ENDPOINT	MEAN O3, PPB	OTHER POLLUTANTS	STUDY DESIGN	RESULTS AND COMMENTS
one hospital (Toronto hospital)	visits is occurring in May and between September and December)		Air quality index Also monitored: daily temperature	the dependent variable, was fitted using the AUTOREG procedure from SAS, version 6.04	asthma ED visits and NO_2 (p=0.005), and O_3 (p=0.035). -Visits staggered by 1 day: no associations were found between asthma ED visits and NO_2 and O_3. -No detailed value of risk was given in the text. -Did not mention on the adjustments for season, weather, other pollutants, etc., likely did not control for these environmental factors.

Table 12.3b Summary of relative risk estimates for Emergency Department Visits due to a 10 ppb increase in ozone concentrations, in univariate and multi-variate models

Location and reference	Ozone mean oncentrations and range	Outcome (population included)	Percent increase (95% CI) per 10 ppb ozone. Ozone only models.	Percent increase (95% CI)_ per 10 ppb ozone. Multi-variate models.
New Jersey, USA Cody et al. 1992	49 ppb (mean of 5 h from 10am-3pm) 34 days >120 ppb (1988) 8 days >120 ppb (1989)	asthma, bronchitis (all ages)	-	5-h avg. ozone: +SO_2, temperature, RH, visibility: 1988-1989 (lag 1d): 5.6% (1.7-9.5%); 1988 (lag 1d): 7.4% (2.5-12.3%); 1989 (lag 0d): 9.7% (3.2-16.2%); 1989 (lag 1d): 7.3% (1.4-13.2%)
New Jersey, USA Weisel et al. 1995	53 ppb (mean of 5 h from 10am-3pm)	asthma (all ages)	-	5-h avg. ozone: +temperature, RH, sulphate, NO_2, SO_2, visibility: 1986: 7.1% (0.04-14.2%) 1987: 7.7% (1.8-13.6%) 1988: 7.0% (1.1-12.9%) 1989: 14.2% (7.9-20.5%) 1990: 6.9% (2-11.8%)
Atlanta, Ga., USA White et al. 1994	78 ppb (mean of 1-h daily max.) (range 10-163 ppb)	asthma (children, ages 1-16 yr., mostly black, low SES)	1-h max. ozone, when >110 ppb for asthma visits: 33% (-6% to 71%) for other causes of visits: Total: 37% (2-73%) Non-upper respiratory infection: 53% (14-92%).	1-h max. ozone: + temperature, PM_{10}, day of the week: asthma visits at ozone >110 ppb: 42% (-1% to 100%, p=0.057). also corrected for autocorrelation + above factors: 43% (4-97%) + temperature, PM_{10}, day of the week, pollen: 33% (-9% to 92%). +temperature, PM_{10}, day of the week, dose-response relations: 80-90 ppb, 1% (-25% to 36%); 90-99 ppb, 24% (-7% to 65%); 100-109 ppb; 29% (-14% to 93%); 110 ppb, 50% (2-121%).
Mexico City, Mex. Romieu et al. 1995	90 ±40 ppb (mean of 1-h daily max) (range 10-250 ppb) (28% of days >110 ppb)	asthma (children, <16 y)	-	1-h max. ozone: 8.60% (4.8-13.2%) +temperature, SO_2, day of the week; 8.6% (4.6-13.0%) +temperature, SO_2, day of the week, sex, age
Vancouver, BC Bates et al., 1990	1-h max., 30.4 ppb in summer; 18.8 in winter	Asthma, other respiratory and non-respiratory visits. All age, & 0-14 y, 15-60 y, 61+y	1-h max. ozone: Associated with total ED visits; not with respiratory visits. No values given.	-
Barcelona, Spain Castellsagne et al., 1995	1-h summer: 43 ppb, winter: 29 ppb	Asthma, 14-64 y.	1-h max. ozone: No association Value not given.	1-h max. ozone: +Temperature, RH, month, day of the week, soybean loading: Summer: -0.7% (-4.7% to 3.5%). Winter: 4.3% (-0.16% to 9.1%).
Melbourn,	For ozone days,	Asthma, >2 y	-Smog alert days not significantly	-

Table 12.3b Summary of relative risk estimates for Emergency Department Visits due to a 10 ppb increase in ozone concentrations, in univariate and multi-variate models

Location and reference	Ozone mean oncentrations and range	Outcome (population included)	Percent increase (95% CI) per 10 ppb ozone. Ozone only models.	Percent increase (95% CI)_ per 10 ppb ozone. Multi-variate models.
Australia Rennick & Jarman, 1992	average 2.7 (range 1-6) stations recorded ozone levels >120 ppb (1-h) and >50 ppb (8-h avg.).	children	related to asthma ED visits. -Ozone days not significantly related to asthma visits. Results not given.	
Toronto, ON Kesten et al., 1995	Data not shown	Asthma visits for all ages.	-Asthma visits not assoc. with ozone on daily, weekly or monthly basis; -associated with ozone with 7 day lag, but not 1 day lag. No value given	-
Montreal, Quebec Delfino et al. 1997	8-h: 1992: 33 ppb; 1993: 36 ppb; 1-h: 1992: 29 ppb; 1993: 31 ppb	all respiratory, asthma (all ages, separated into ages <2y, 2-34y, 35-64y, 65+y)	-No assoc. in 1992, no value given. -1993, no assoc. in <2y and 2-64y, no value given -1993, significant associations in >64y. 1-h max. ozone: 5.9% (2.4-9.4%); 8-h avg. ozone: 7.2% (2.9-11.5%).	1993 data, 8-h avg. ozone: the Elderly: 5.7% (0.21-11.2%) +PM2.5
Baton Rouge, Louisiana Jones et al., 1995	69.1 ppb (mean of 1-h max) (range 25.3-165 ppb) 4 days >120 ppb. 24-h average 28.2 (9.3-57.9).	all respiratory (all ages, separated into ages 0-17 y, 18-60y, 61+y	24-h avg. ozone: Children: -7.0% (–15.4% to 1.4%) Adult: 11.1% (3.8-18.4%). Elderly: 4.5% (–1.9% to 10.9%).	24-h avg. ozone, +temperature, RH, mold, pollen: Children: -6.5% (-17.3% to 4.3%) Adults: 9.9% (0.71-19.1%) Elderly: 13.4% (–3.2% to 30.0%).

Confounding effects of seasonal and weather variations

The variations in season and weather are known often to have close correlations with ozone and health outcomes, and may confound the results. All the studies reporting significant associations tried to control long wave seasonal variations of ozone and ED visits either by filtering techniques (Delfino et al., 1997), or by limiting studies to ozone season only (Cody et al., 1992, Weisel et al., 1995, White et al., 1994, Romieu et al., 1995, Jones et al., 1995). There is a limitation for the latter methodology, since using one-season data still cannot eliminate the within season cyclic variations.

All the studies attempted to adjust for the effects of temperature, many of which conducted co-regression with temperature as a co-variate. The adjustment for temperature did not substantially reduce the ozone effects, and ozone continued to be associated with respiratory ED visits.

Co-occurring pollutants

With respect to other air pollutant covariates, PM should also have been correlated with emergency department (ED) visits, based on other studies not examined in detail for this review. Direct measures of PM_{10} and $PM_{2.5}$ were available for the Montreal study (Delfino et al., 1997). Particles, along with sulphate, were significant predictors of increases in ED visits (total respiratory) for the elderly (> 64 years of age) 16% and 12% respectively (Delfino et al., 1997). By comparison, a stronger association was observed for ozone at 21% of increases in ED visits (for a 36 ppb increase in mean ozone). The predicted increase due to sulphate was only marginally significant at 6%. Particle strong acidity, as H^+, was also directly measured in this study, and was significant for infants under age two (5% increase in ED visits including a lag of 2 days and relative humidity in the model), but was not significant for the elderly or any other age groups (Delfino et al., 1997). Because of the potential confounding effects of PM on ozone-ED visit associations, PM_{10} was co-regressed with ozone in this study. After the adjustment of PM_{10}, ozone remained significantly associated with respiratory visits [6% increase in ED visits per 10 ppb ozone (8-hour average), SE 2.8%].

Although daily PM_{10} measurements were available for just under half the duration of the Atlanta children study (White et al., 1994), the authors conducted regressions with PM_{10} and ED visits. The association of PM_{10} with ED visits was positive, but was non-significant. Co-regression with PM_{10} did not reduce the effect of ozone on children's asthma ED visits (White et al., 1994).

Mean particulate levels (as TSP) were very high in Mexico City, at a mean of 474 $\mu g/m^3$, but did not show significant association with respiratory ED visits (Romieu et al., 1995). One explanation for the non-significance may have been related to the fact that only 44 days of measurements were available due to the 6-day monitoring schedule. The authors noted that the effect of particulate matter could not accurately be assessed from their data. TSP was not highly

correlated to ozone levels (r=0.25) (Romieu et al., 1995), and was not adjusted for during the analyses.

Cody et al. (1992) used visibility as a surrogate for PM. Results of co-regression of visibility with ozone showed that ozone was significantly associated with all-age asthma ED visits. Weisel et al. (1995) used sulphate to represent PM effects, and found no significant confounding effect on the ozone-asthma relationship. The association in this study was consistent in all five years examined (1986-1990). Sulphate was not found to be correlated with asthma-ED visits (Weisel et al., 1995).

Three studies investigated the potential effect of SO_2 (Cody et al., 1992, Weisel et al., Romieu et al., 1995), and one study examined the effect of NO_2 (Weisel et al., 1995). After the adjustment of SO_2 or NO_2, ozone maintained its significant association with respiratory ED visits. Pollen and mould also did not seem to confound the ozone effect on respiratory ED visits (Jones et al., 1995). Co-regressed with pollen, mould, temperature and relative humidity, ozone was still revealed to be significantly associated with respiratory ED visits (slope= 0.068/ppb, $p<0.04$, Jones et al., 1995).

12.4.2 Studies reporting non-significant associations between ozone and ED visits

Four studies found no significant association between ozone and respiratory ED visits (Bates et al., 1990, Castellsagne et al., 1995, Rennick and Jarman, 1992, Kesten et al., 1995).

In the Vancouver study (Bates et al., 1990), Pearson correlation analyses were carried out on the data, and a very good discussion of the results and their meaning was presented. However, more could have been accomplished with this extensive data set, had more rigorous and extensive statistical methods been used. The analysis considered two seasons, summer and winter (6 months each), which reduced seasonal variations in ozone concentrations and ED visits. But this category was too broad to eliminate within-season cyclic variations. SO_4 was measured as a surrogate for particulate matter. CoH was also measured. But the PM metrics evidently were not utilized in the analysis to correct for their potential confounding effects. A correlation between total ED visits and wintertime ozone plus minimum temperature was noted, but is probably spurious, since ozone levels are lowest in winter. The major interpretation for the failure of this study to find consistent associations with ED visits and ozone is considered to be the handling of the confounding by temperature. The authors noted a significant correlation between ozone and temperature (r=0.64 in summer and 0.57 in winter), and the likelihood of confounding by this factor. The authors did not make an attempt to separate the ozone effect from that of temperature. An additional reason may have been the lack of statistical methods to remove longer-term cyclic variations in ED visits that were not related to air pollution.

In Barcelona Spain (Castellsegue et al., 1995), neither ozone nor black smoke (BS) was associated with ED visits for asthma for adults aged 14 to 65 years. The statistical treatment was appropriate for the removal of short and seasonal long term cyclic variations, and

temperature was co-regressed with ozone. BS, SO_2 and NO_2 in single-pollutant models were shown to be related to asthma ED visits. Because no correlation coefficients between ozone and other co-pollutants were given, it is not clear whether these pollutants had confounding effects on ozone and asthma ED visits. No measure was taken to control these factors.

In the study by Rennick and Jarman (1992), the authors controlled the effect of seasonal variation on ozone and asthma visits by limiting the study period to ozone season and episode days. On the other hand, this limited ED visits and ozone days to a very small size. The data on the correlation between ozone and temperature as well as other co-pollutants were not reported, and no effort was mentioned on controlling these environmental factors. These limitations likely substantially reduced the statistical power for detecting a significant ozone effect.

In the Toronto study by Kesten et al. (1995), the authors regressed ozone levels against asthma ED visits, without considering an adjustment for the impact of seasonal cyclic variations, weather, day of the week, and co-pollutants, on ozone and ED visits. These environmental factors may have contributed to confounding the ozone effects.

12.4.3 Summary of ED visits

The data on emergency department visits suggest the same conclusion as the hospitalization studies. The results from ED visit studies demonstrate that ozone is correlated with ED visits when cyclic variables, weather (in particular temperature) and co-pollutants have been properly controlled. The studies that did not detect significant results can be explained on the basis of failure to accomplish one, or more, of these objectives. An increase of about 6% to 8.6% in ED visits for asthma is predicted per 10 ppb increase in ozone (1-h maximum), usually lagged one or two days. For a 10 ppb increase in 5-hour average ozone, the increase in respiratory ED visits is 5.6-14.2%, after adjusting for PM, temperature, and other gaseous pollutants. The predicted percentage increase in ED visits is dependent on ozone as cutoff levels rise, from > 60 ppb (26% in children) to > 110 ppb (43% in all ages). As the number of consecutive days in the pollution episode increases, up to about 2 or 3 days, 68% more visits have been observed at ozone concentrations higher than 110 ppb. In one study that examined concentration-response relationship at ozone levels from 80 to 110 ppb (1-h maximum), asthma ED visits were evidently dependent on ozone concentrations, though only at 110 ppb was the increase significant (White et al., 1994). The positive correlations for ozone and ED respiratory visits, principally for asthma, were observed in four different cities or metropolitan areas in three countries, including Canada.

12.5 FIELD (CAMP AND PANEL) STUDIES

A number of investigators have studied the effects of air pollution, including ozone, by conducting field studies on groups of people engaged in normal activities in the natural environment. Camp studies have the advantage that the subjects, usually children, are free ranging in an environment in which pollutant levels can be closely monitored. In panel studies, a group of subjects (who may be asthmatics) are selected and their medical history and activity patterns and episodes of

illness are closely followed. In such studies, pollution exposure can be more accurately gauged than in the general population, and exposures are usually to the ambient mix of pollutants. Endpoints studied were primarily changes in lung function and increased symptoms. This section is based largely on the review by Bates (1994, 1995). New studies published as of April 1997 have been added. A summary of results from field studies is presented in Table 12.4.

12.5.1 Camp Studies

Studies of FEV_1 in children at summer camps in Canada and the USA have indicated that the summer mix of pollutants, including ozone, is associated with measurable declines in function. Kinney et al. (1996) recently evaluated the data sets of six summer camp studies, two in New Jersey (Spektor et al., 1988a,1991), two in Ontario (Raizenne et al., 1989, Burnett et al., 1990), and two in California (Higgins et al., 1990, Avol et al., 1990). Average ozone concentrations (1-hour average at time when lung function measurement) were 53-123 ppb, and the maximum ozone concentrations were 95-245ppb. For each study, regression models were fit relating FEV_1 or Peak Expiratory Flow Rates (PEFR) to ozone.

The majority of the six studies showed significant decrements of FEV_1 in relation to ozone (-0.29 ml to -1.29 ml per ppb ozone, $p<0.05$) (see Table 12.4 for detailed information of each study). There was a wide variation in slopes from the individual studies, and a lack of correlation between the slopes and the means or maxima of ozone encountered in the environment, which may be explained by the different locations, various pollution combinations and gender differences among the camps. The combined six-study data set was used to estimate the mean slopes across all studies for FEV_1 regressed on ozone, with an adjustment for the time-trend in repeated lung function measurements. A pooled slope of -0.26 ml FEV_1 per ppb ozone (SE 0.07, $p=0.0003$) was obtained (temperature not included as a covariate). This was equivalent to a 2.7% drop in FEV_1 for 120 ppb ozone exposure, nearly identical to the 2.8% change observed previously in a controlled chamber study in children exercising for 2.5 hours at 120 ppb (McDonnell et al. 1985a,b). The conclusion was that, on balance, the FEV_1 decrements seen in the camp studies were about the same as demonstrated in the chamber studies.

Additionally, in one of these studies (Higgins et al., 1990), multi-variate regressions were conducted to adjust for temperature, relative humidity and PM_{10}. The multi-variate analyses show that these environmental factors did not substantially affect the slope of FEV_1 per ppb ozone (-0.38 ml/ppb in ozone-only model vs. -0.72 ml/ppb), and ozone remained significantly associated with FEV_1 decrement.

Thurston and his colleagues (1997) studied three groups of children attending a camp for asthmatic children in three consecutive years (1991-1993). The camp was located in the Connecticut River Valley which is frequently downwind of the New York City metropolitan area during the summer months. All medications were kept in a central tent minded by a nurse and a physician. There were 52, 58, and 56 children, respectively, in the groups each year. Average ozone concentration (1-hour maximum) was 83.6 ppb (range 20-160 ppb) for the three years.

Maximum temperature, relative humidity, sulphate and H+ were also measured and were found closely correlated with ozone (r=0.86, -0.52, 0.74, and 0.64, respectively). Health outcomes (medication use, PEFR, head and chest symptoms) were regressed on ozone, sulphate and H+.

Air pollution was found to be significantly and consistently correlated with acute asthma exacerbations, chest symptoms, and lung function decrements (Thurston et al., 1997). For ozone-only model, there was a 0.96 l/min decline (or a 0.3%) in PEFR for a 10 ppb increase in ozone. Chest symptom counts (0.031 symptoms/day/child/10 ppb) and medication use (0.02/day/child/10 ppb) were also significantly associated with daily 1-hour maximum ozone concentrations. When temperature was co-regressed with ozone, the changes in PEFR, medication use and chest symptoms in response to an increase in ozone concentration remained significant.

Exploratory regressions including multiple pollutants were also conducted to further investigate the relative roles of the pollutants (Thurston et al., 1997). In the case of PEFR, the ozone coefficient was virtually unchanged, whereas sulphate declined noticeably. For medication use, the ozone coefficient declined and became nonsignificant. For chest symptoms, the ozone coefficient remained unchanged and significant. In general, these various exploratory multipollutant analyses indicate that ozone is the air pollutant most strongly and consistently associated with adverse health effects in this population of children with asthma.

Spektor et al. (1991) concluded that camp studies generally yield higher effects of ozone than chamber exposures for four possible reasons:

- because the exposures in the field are longer;
- because there may be potentiation by other factors;
- because there may be persistence of effects from the prior day's exposure; and
- there may be persistence of a transient response associated with the daily peak exposure.

The authors cautioned: "It follows that projections of likely effects in the real world from controlled chamber studies should either have a large margin of safety, or the judgment of the extent of effects likely to occur among populations should be based directly on the effects observed in field studies".

Adults jogging in their lunch hour were studied by Spektor et al. (1988b) in Tuxedo, NU. Ozone concentrations (1-hour maximum) ranged 21-124 ppb. Many of these joggers were found to have ventilation levels in excess of 60 L/min (they had selected their own exercise level). Changes in FVC and FEV_1 were related to the ambient ozone on the day of their jogging. The mean slope of FEV_1 decrements across all subjects was -1.35 ml/ppb (SE 0.35). No symptoms were reported by subjects, and no persistence of effects were seen. The authors speculated that acid aerosols might have contributed to the decline of lung function, but no analytical data were reported.

12.5.2 Panel studies

In the early 1970s, Linn et al (1976) carried out an extensive series of studies in Los Angeles using a mobile van which contained an exposure chamber and pulmonary function testing equipment. After an initial finding that suggested that function decrements in the natural environment with photochemical pollutants was greater than that found in chamber exposures, they finally concluded that the observations of decreased function were explicable on the basis of the total ozone exposure. Later studies of competitive cyclists in the same mobile facility (Avol et al., 1984,1985) showed that FEV_1 declines occurred at ozone levels of 160 ppb (a result in accord with the controlled exposure data described above). They concluded that the decrement in lung function in the Los Angeles atmosphere was attributable to the ozone present.

Lebowitz et al. (1985) studied panels of asthmatics and others in Tucson, Arizona drawn from 117 white families from a symptom-stratified sample. Detailed measurements of air pollutants, pollen, bacilli, fungi and algae were made in and around a random cluster sample of 41 households. Thirty-five asthmatics provided daily peak flow measurements. The very complex resulting data showed that both ozone levels and temperature had effects on the peak flow data. The exact ozone data were not reported; instead the data were stratified into <38 ppb, 38-51 ppb, >51 ppb bins. Maximum temperature was also grouped into <61◦F, 61-80◦F, and 80-96◦F. PEFR was expressed as standard deviation scores to remove the effects of age and sex. In each temperature group, average PEFR was found to decrease in an ozone concentration-dependent fashion. The decrement of PEFR was statistically significant. After an adjustment for smoking, indoor TSP, relative humidity and gas stove usage using multi-factorial analysis of variance, outdoor ozone remained significantly associated with PEFR.

Javitz et al (1982) reanalyzed a previous study of 286 subjects with asthma, and chronic bronchitis (probably with and without accompanying emphysema) in Houston, Texas. Daily symptom diaries were kept, and home spirometry testing was done in about one third of the subjects. Respiratory symptoms and medication use increased as the daily ozone maxima increased. In the same city, Holguin et al. (1985) conducted an asthma panel study. They carefully defined an ‘asthmatic attack’, and followed the panel for six months. Ozone levels ranged up to 270 ppb. They showed that an increase in the 1-hour maximum ozone level of 100 ppb increased the attack probability from a baseline value of 10% to 16%. This 60% increase in risk was four times that observed by Whittemore & Korn (1980) for a panel study of asthmatics in Los Angeles. In Whittermore and Korn’s study (1980), they studied adult and child asthmatics living in six different communities in the Los Angeles area. Asthma symptoms were reported by the subjects. The ozone coefficient from the logistic model for daily high-hour ozone was 0.00166 (SE 0.00072). This value is equivalent to a RR of 1.0017 (SE 0.00072) per ppb ozone.

Gong (1987) studied 83 asthmatics in Los Angeles between February and December 1983. Ozone concentrations (1-hour maximum) were 10-110 ppb in 103 days, 350-380 ppb for 3 days. He reported that 39 of the subjects were “ozone responders” (top quartile of respiratory measures), with PEFR and symptoms significantly related to ozone levels. For the whole group, results had not shown a significant relationship. The cases were relatively mild, since 77% of the total group had peak flow measurements within the normal range.

Castillejos et al (1992) reported studies on a panel of normal children in Mexico City, where the daily maximum 1-h ozone level exceeded 120 ppb on 74% of days. This study showed that the FEV_1 and FEF_{25-75} decrements were strongly related to ozone levels averaged over 24 to 168 hours prior to spirometry. The relation of ozone in the previous hour to the lung function decrements was minimal. For example, FEV_1 slope was -0.592 (SE 0.109) ml/ppb for previous 48 hour ozone. For previous hour ozone, only FVC slope was significant, –0.059 (SE 0.23) ml/ppb ($p<0.05$). Temperature and RH reduced ozone effects. The authors suggested that the results might reflect an inflammatory response in the airways as opposed to an acute physiological response. One-hour average ozone levels in the hour preceding the tests had ranged up to 287 ppb, with a mean of 99 ppb.

Romieu et al. (1997) examined a panel of 67 children known to have asthma and registered at an allergy clinic southwest of the Mexico City. The panel was followed with daily diaries and twice daily peak flow measurements. Pollution levels were known from a monitoring station 200 m from the clinic. The 1-h maximum ozone level was between 40 and 390 ppb during the study, and PM_{10} was between 1.2 and 126 $\mu g/m^3$. The correlation between ozone and PM_{10} was high ($r=0.91$). When temperature was accounted for, a 50 ppb increase in ozone was significantly associated with an 8% increase in cough, a 24% increase in phlegm, an 11% increase in an index of lower respiratory symptoms, and 3% increase in medication use (all $p<0.05$). For PEFR, the decrement was most significant ($p<0.05$) on the second day, with a 2.32 L/min decrease per 50 ppb ozone. When PM_{10} and temperature were accounted for, ozone effects on symptoms (cough 10%, phlegm 29%, lower respiratory symptoms 12%) and PEFR (-2.75 L/min per 50 ppb) were almost the same as without the adjustment, $p<0.05$.

In a study in The Netherlands (Gielen et al., 1997), sixty one children aged 7-13, of whom 77% were taking asthma medication were followed. Peak expiratory flow rate (PEFR) was measured twice daily with miniWright flowmeters at home. Occurrence of acute respiratory symptoms and medication use was registered by the parents daily in a diary. Maximum 1 hour ozone never exceeded 130 $\mu g/m^3$ (65 ppb), 8-hour average ozone was 67.0 ppb (range 27.6-110.8 ppb), 24 hour Black Smoke was not higher than 41 $\mu g/m^3$ and PM_{10} was below 60 $\mu g/m^3$. Correlation between pollutants was moderate ($r<0.3$ between ozone and particles). Temperatures were moderate (8-22◦ C) during the study period, and did not seem to have significant influence on the outcomes. After adjusting for pollen, time trend, day of week, and particles, PEF index had the strongest association with ozone lagged 2 days, with a decrease of 1.86% (95% CI –3.58% to –0.14%) per 83.2 ppb in the morning and a decrease of 1.88% (-3.94% to 0.18%) per 83.2 ppb in the evening. Eight-hour average ozone was also associated with upper respiratory symptoms, with a RR of 1.23 (95% CI 1.03-1.43). Ozone was not significantly associated with bronchodilator use. The authors concluded that in this panel of children, most of whom had asthma, relatively low levels of particulate matter and ozone in ambient air were able to increase symptoms and medication use, and decrease lung function.

Brauer and Vedal and their colleagues have conducted several studies in the Fraser Valley, which is inland from Vancouver, B.C. They followed a cohort of 58 workers in the fields picking raspberries (Brauer et al., 1996a). These people were at work from dawn till dusk. Their spirometry was measured each morning before starting work, and each evening when they had

finished. There were local ambient monitors for ozone and particulate matter. The 1-hr daily maximum ozone had a mean of 40.3 ppb, with a single highest value of 84 ppb. Acid aerosol (3.1 nmol/m3), SO_2 (1-hour average <52 ppb) and NO_2 (1-hour average <28 ppb) were low during the study period, and were therefore not considered in the study. $PM_{2.5}$ mean was 11.4 $\mu g/m^3$. Ozone for the workshift time had a mean of 26 ppb, and a maximum of 54 ppb. Temperature and ozone were highly correlated (r=0.85). The mean FEV_1 fell -3.3 ml and the FVC fell -4.7 ml for each ppb increase in hourly maximum ozone. Deficits were still apparent on following morning. Over the 60 days of work, there was a steady fall in mean FEV_1 of the whole group, with an average 4 ml per day decline. Based on stepwise regression analyses to include sulphate, NO_3 and NH_4 in the models, ozone was still significantly associated with decreased lung function.

The following year, the study was repeated (Brauer et al., 1996b). There were 50 farm workers all of whom were of Punjab origin. Daily spirometry was conducted before and after work; 12-16 hour workdays; the study extended from July 1 - August 18, 1994. The mean of the daily 1-hour maximum of ozone was 39 ppb (range 10-89) and the mean daily maximum 8-hour ozone was 31 ppb (range 5-66). PM_{10} concentrations were low at a mean 24-hour average of 16 $\mu g/m^3$ (but were correlated with ozone r = 0.88). Observed decrements in FVC and FEV_1 were associated with ozone level. The associations were still apparent the following morning, suggesting a persistent air pollution effect. During both summer studies a marked seasonal decline in lung function was observed, but initial values had improved to their original level by the time the second study was done. In 12 subjects studied both years, there was no correlation in individual responses to ozone between the two periods. There was no significant aerosol acidity, but aerosol nitrates were present. Ozone meters were 5 km from farm 1, and 10 km from farm 2. Removing the period of the highest ozone episode did not alter the data. There were 5 possible asthmatics in the group of 50.

These studies are important in the context of standard setting. The Fraser Valley observations represent an exposure pattern that could hardly be replicated in a controlled chamber exposure, since a pattern of ten hours a day of controlled exposure, for 60 consecutive days, together with light exercise, would hardly be feasible. The results indicate that outside work in this atmosphere, in which particle levels were low, and hourly ozone maxima never exceeded 80 ppb during the second year of the study, is associated with an induced function decrement.

12.5.3 Summary of field studies

Field studies examine acute changes of lung function and symptoms of healthy or asthmatic children and adults. Twenty field studies were reviewed in this document, nineteen of which showed a significant association of ozone with lung function decrements and increased symptoms and/or asthma medication uses. Many studies used single pollutant models without adjusting for the potential confounding of co-pollutants. Five studies evaluated multi-pollutant

effects, and found ozone effects remained significant when adjusted for PM. Six studies adjusted for temperature and found that the ozone effect persisted.

Table 12.4 Summary of results from field studies

Location and references	Ozone concentration	Health endpoints	Results	Co-pollutants
New Jersey Spektor et al., 1988a	1-h avg. when conducting lung function tests: 53 ppb 1-h max.: 113 ppb.	Camp, 91 healthy children, lung function	Slope for afternoon FEV_1: -0.5 ml/ppb, SE 0.16, p=0.002	$PM_{2.5}$, PM_{15}, sulphate, H+ , temperature were measured too. No multi-variate analysis done.
New Jersy Spektor et al., 1991	1-h avg. when conducting lung function tests: 69 ppb 1-h max.: 137 ppb.	Camp, 46 healthy children, lung function	Slope for afternoon FEV_1: -1.29 ml/ppb, SE 0.27, p=0.0001	Temperature and H+ not correlated with lung function changes. No multi-variate analysis done.
Lake Couchiching, Ontario Burnett et al., 1990	1-h avg. when conducting lung function tests: 59 ppb 1-h max.: 95 ppb.	Camp, 29 healthy female children, lung function Asthmatic children, lung function	Slope for afternoon FEV_1: -0.19 ml/ppb, SE 0.44, p=0.66. FEV_1 decrements were significant on 2 episode days for methacholine-nonresponsive children.	-
CARES, Ontario Raizenne et al., 1989	1-h avg. when conducting lung function tests: 71 ppb 1-h max.: 143 ppb.	Camp, 112 healthy children, lung function	Slope for afternoon FEV_1: -0.29 ml/ppb, SE 0.10, p=0.003	Also see effect of H+, but no multi-variate analysis done.
San Bernardino, CA Higgins et al., 1990	1-h avg. when conducting lung function tests: 123 ppb 1-h max.: 245 ppb.	Camp, 43 healthy children, lung function	Slope for afternoon FEV_1: -0.84 ml/ppb, SE 0.20, p=0.0001 Slope of FEV_1 for previous hour ozone: -0.38 (SE 0.09) ml/ppb, p<0.01.	+Temperature, PM_{10}, RH in multi-regression: ozone slope FEV_1 decremen= -0.72 ml/ppb (SE 0.15), substantially larger than single pollutant models.
Pine Springs, CA Avol et al., 1990	1-h avg. when conducting lung function tests: 94 ppb 1-h max.: 161 ppb.	Camp, 295 healthy children, lung function	Slope for afternoon FEV_1: -0.32 ml/ppb, SE 0.13, p=0.013.	-
New York State Thurston et al., 1997	1-h max.: 83.6 ppb (range 20-160 ppb)	Camps, n=52, 58, & 56 for each year, asthmatic children, symptoms & medication use	PEFR: -0.96 l/min (or a -0.3%)/10 ppb, p<0.05. Medication use: 0.02/day/child/10 ppb, p<0.05. Chest symptom counts: 0.031 symptoms/day/child/10 ppb, p<0.05. + temperature: the changes in PEFR, medication use and chest symptoms in response to an increase in ozone concentration remained significant, values not reported.	+sulphate: PEFR: 0.96 l/min/10 ppb (t=-1.16), p>0.05. Medication use: RR=1.018 (t=0.97)/10 ppb, p>0.05. Chest symptoms: RR=1.053 (t=2.84)/10 ppb, p<0.01.

Table 12.4 Summary of results from field studies

Location and references	Ozone concentration	Health endpoints	Results	Co-pollutants
Tuxedo, NY Spektor et al., 1988b	1-h max.: 21-124 ppb	Jogging adults, n=30, lung function, symptoms	Slope of EEV_1 =-1.35 ml/ppb (SE 0.35). No symptoms reported.	-
Los Angeles, CA Avol et al, 1984	153±25 ppb	Panel of healthy adults (competitive bicyclists), n=50, mobile lab study. Symptoms and lung function	Mild increase in lower respiratory symptoms. FEV1 decrements: -5.3%, $p<0.05$, relative to control.	-
Los Angeles, CA Avol et al, 1985	144±43 ppb	Panel of healthy children (12-15 y), n=59, mobile lab study. lung function	Decrements ($p<0.05$) in FVC: -2.1%; FEV_1: -4.2%; $FEV_{0.75}$: -4.0%; PEFR: -4.4%, relative to control.	-
Tucson, Arizona Lebowitz et al., 1985	Micro-outdoor ozone, mean not given. stratified into <38 ppb, 38-51 ppb, >51 ppb	Panel of asthmatics, n=211, lung function	Maximum temperature grouped:<61°F, 61-80°F, and 80-96°F. Average PEF index decreased in an ozone concentration-dependent fashion, in each temperature group, $p<0.05$.	Adjusted for smoking, indoor TSP, RH and gas stove usage: outdoor ozone remained significantly associated with PEF index.
Houston, Texas Javitz et al., 1982	-	Panel of 286 asthmatics and chronic bronchitis. Lung function and symptoms	- Respiratory symptoms and medication use increased as the daily ozone maxima increased.	-
Houston, Texas Holguin et al., 1985	1-h max. Up to 270 ppb	Panel of asthmatics. Asthma attack probability	Asthma attach probablity increased 6.0%/10 ppb RR=1.062 (SE 0.023)/10 ppb	-
Los Angelus, CA Whittermore and Korn, 1980	-	Panel of asthmatics Symptoms	RR=1.017 (SE 0.0012)/10 ppb ozone, symptoms.	-
Los Angelus, CA Gong 1987	1-h max. 10-110 ppb (103 days), 350-380 ppb for 3 d.	Panel of mild asthmatics, n=83, symptoms, lung function, medication use	For whole group: 1-h max ozone not related to changes in lung function, symptoms and medication use For “responders” (top quartile of respiratory measures) : ozone related to PEFR and symptoms.	-
Mexico City Castillejos et al., 1992	daily maximum 1-h ozone level exceeded 120 ppb on 74% of days. In the hour preceding the tests ranged up to 287 ppb, with a mean of 99 ppb.	Panel of healthy children, n=148, lung function.	FVC slope =–0.059 (SE 0.23) ml/ppb, $p<0.05$, to previous hour ozone. For previous 24, 48, 168 h ozone, FEV_1 and $FEF_{25-75\%}$ decreased significantly. E.g. previous 48 h ozone, FEV_1 slope = 0.592 (SE 0.109) ml/ppb.	Temperature and RH reduced ozone effects. No adjustment for other pollutants.
Mexico City Remieu et al., 1997	1-h max.: 196 ppb (range 40-390 ppb)	Panel of asthmatic children, n=67, lung function and symptoms, medication use.	+temperature, PEFR mean (95%CI) L/min/50 ppb: lag 0: -1.81 (-3.6 to –0.01) lag 1d: -2.32 (-4.17 to –0.47) lag 2d: -0.21 (-2.44 to 2.02).	+temperature, PM_{10}: PEFR mean (95% CI): -2.75 l/min/50 ppb (-4.95 to –0.5).

Table 12.4 Summary of results from field studies

Location and references	Ozone concentration	Health endpoints	Results	Co-pollutants
			+temperature, symptoms odds ratio/50 ppb (95% CI), lag 0d: cough: 1.08 (1.02-1.15) phlegm: 1.24 (1.13-1.35) lower respiratory: 1.11 (1.05-1.19) in a concentration-dependent fashion (<120 ppb to >250 ppb). bronchodilator use: 1.03 (1.00-1.05)	Symptoms odd ratio/50 ppb (95% CI): Cough: 1.10 (1.00-1.20) Phlegm: 1.289 (1.17-1.43) Lower respiratory: 1.12 (1.01-1.23)
The Netherland Gieler et al., 1997	1-h max.: 77.3 ppb (33-130 ppb). 8-h avg.: 67.0 ppb (range 27.6-110.8 ppb)	Asthmatic children (61), lung function, symptoms and medication use.	-	1-h max. data not given. +PM_{10}, BS, 8-h avg. ozone: PEF index had strongest association with ozone, lag 2 d: Morning: -0.22% (95% CI –0.43% to –0.017%)/10 ppb. Evening: -0.226% (-0.474% to 0.022%)/10 ppb. RR (95% CI) for upper respiratory symptoms, lag 0: 1.23 (1.03-1.43) RR (95% CI) for bronchodilator use, lag 2 d: 1.16 (0.87-1.45)
Fraser Valley, BC Brauer and Vedal, 1996a	1-h max.: 40.3 ppb (13-84 ppb). Mean of workshift: 26 ppb (8-54 ppb).	Farmers, n=58, lung function	+temperature, day of study, 1-h max. ozone: FEV_1: -3.3 ml/ppb FVC: -4.7 ml/ppb	+sulphate, NO_3, NH_4: 1-h max. ozone was significantly associated with lung function decrements. Values not reported.
Fraser Valley, BC Brauer and Vedal, 1996b	1-h max.: 39 ppb (range 10-89 ppb). 8-h max.: 31 ppb (range 5-66).	Farmers, n=50, lung function	Observed decrements in FVC and FEV_1 were associated with ozone level. The associations were still apparent the following morning, suggesting a persistent air pollution effect.	PM_{10} concentrations were low (24-hour avg. 16 $\mu g/m^3$), and were correlated with ozone, r = 0.88.

12.6 CHRONIC EFFECTS

The acute effects of daily fluctuations in ozone on symptoms, lung function, and inflammation are generally considered to be relatively transient and reversible. Evidence that repeated exposures to very low concentrations over long time periods could result in chronic conditions would be viewed in a more serious light, from the perspective of standard-setting, than lung function decrements due to acute episodes of exposure to somewhat higher concentrations. The recent review by Bates (1994, 1995) of cross-sectional and longitudinal studies examining the evidence for the effects of chronic exposure to ozone serves as the basis for this section, with some additions of recently published studies. A summary of the results is presented in Table 12.5.

12.6.1 Cross-sectional comparisons

Cross-sectional studies examine and compare rates or prevalence of diseases or mortality across geographic locations. This type of study has often been applied to the examination of long-term or chronic effects and their relationship to air pollutants.

Hodgkin et al. (1984) found some evidence of more respiratory symptoms in non-smokers in higher oxidant regions, but the difference was not great. Linn et al. (1980) could not demonstrate consistent differences in either respiratory symptomatology or function between populations of office workers in areas with different levels of oxidant pollution.

An interesting comparison has been published of children in Austria living in relatively high and low ozone regions (Zwick et al., 1991). Two hundred and eighteen children (mean age 11.6 years) lived in the high ozone region in which ozone exceeded 100 ppb 9.68% of the time, and 281 children lived in a low ozone region where that value was never exceeded. The time metric of ozone was not given in the text. Other pollutants were similar between the regions, but no measurements of particle concentrations were taken. There were no specific exposure data for any of the children. There were no differences in allergic background, as judged by immunoglobulin (IgE) levels or asthma symptoms; no differences were detected in cough or breathlessness, nor in pulmonary function status, but there was a higher incidence of bronchial hyperresponsiveness to methacholine in the high ozone group (29% vs 21%; $p<0.02$), and differences in the ratios of types of lymphocytes. The 'high ozone' children showed a decrease in T-helper lymphocytes and an increase in T-suppressor cells compared to the children in the low ozone area. T_4/T_8 ratios were decrease by 17.7% ($p<0.001$) and natural killer cells by 12.6% ($p<0.001$), effects which have been linked to immunosuppressive function. Although the significance to the subjects of these hematological differences is unclear, the authors interpreted their overall findings to indicate that ozone had caused a significant difference in status.

Other epidemiological evidence of long-term adverse effects of ozone exposure has come from the analysis of the National Health and Nutrition Examination Survey (NHANES II) data in 44 cities in the US provided by Schwartz (1989). Youths (n=3,922) aged 6 to 24 years, were examined for lung function parameters. Average hourly values for the 365 days preceding spirometry were

used. Median average annual hourly ozone concentration was 33 ppb. However, only 25.6% of the subjects lived close enough to a monitor to have ozone exposure assigned to them. The author reported a decrement in FVC in children in relation to calculated long-term ozone exposures as low as 40 ppb annual average. The effect persisted after control for sex, race, age, family income, educational level, chronic respiratory symptoms, and smoking history. However only univariate analysis could be undertaken, and possible co-occurring pollutants could not be simultaneously evaluated.

Ostro & Rothschild (1989) used data from the Health Interview Survey in the US between 1976 and 1981, involving 50,000 households. The independent variables included ozone (1-hour maximum) and fine particles, age, sex, race, education, family income, quarter of the year when the individual was surveyed, marital status, existence of a chronic condition, and temperature. Correlation coefficients between ozone and these variables were low ($r<0.1$), with the exception of ozone and temperature ($r=0.5$ to 0.68 for 6 years). Health endpoints were respiratory-related restricted activity days (RRAD) and minor restricted activity days (MRAD). Using Poisson regression analysis, when RRAD was regressed on ozone alone, or on ozone and fine particles, ozone did not show a significant association with RRAD. For MRAD, when regressed with ozone alone, in 3 of the 6 years studied, MRAD showed a significant association with ozone. Co-regression with ozone and fine particles did not alter the results. Pooling data from 6 years demonstrated that an increase in 1 $\mu g/m^3$ (0.51 ppb) of ozone was associated with a 0.185% increase in MRAD (elasticity of 0.082). Since ozone displayed a significant seasonal pattern, additional analysis was conducted using only the second and third quarters of each year. The overall regression results did not change. This study confirmed earlier observations by Portney & Malloy (1986) who noted a relationship between ozone levels and reduced activity days by combining aerometric and survey data.

Stern et al. (1989) reported a cross-sectional study, conducted in 1983-1984, using second to sixth grade students who resided in Tillsonburg, Ontario (n=735), and Portage la Prairie, Manitoba (n=895). Tillsonburg had significantly higher concentrations of sulphate, SO_2 and particulate nitrate than Portage la Prairie, but NO_2 and PM_{10} differed little. Average annual maximum concentrations of ozone were similar in the two communities (136 ppb in Ontario, 130 ppb in Manitoba), but the elevated ozone levels above 80 ppb happened more frequently in Ontario (30 days) than in Manitoba (3 days). After adjusting for sex, length of residence, parental smoking and education, and gas cooking, small decrements in FVC (-2%) and FEV_1 (-1.7%) were found in the Ontario children compared to the Manitoba children, but the difference was significant. Because ozone and sulphate in Ontario were closed correlated, it was difficult to separate sulphate effects from ozone effects from this study.

Stern et al. (1994) conducted another cross-sectional study in 5 Ontario towns and 5 in Saskatchewan. Children (n=3,945), 7 to 11 years of age, were examined for respiratory symptoms and lung function. Annual mean 1-hour maximum ozone in Ontario was higher (46.3 ppb, 90^{th} percentile 80 ppb) than in Saskatchewan (34.1 ppb, 90^{th} percentile 47 ppb). PM_{10} and nitrate did not vary between the areas, but annual sulphate levels in Ontario were 3-4 times higher than in Saskatchewan. After adjusting for age, sex, weight, standing height, parental smoking and gas cooking, Ontario children had significantly larger decrements in FVC (-1.7%)

and FEV_1 (-1.3%) compared with Saskatchewan children. The adjusted prevalence of respiratory symptoms did not differ in 10 towns. Coincidence of increased ozone and sulphate precludes definite statements concerning ozone effects.

In the past year, a study by Kunzli et al. (1997) showed that long-term exposure to ozone is associated with declines in lung function, even after addressing potentially confounding pollutants. They investigated the feasibility of retrospective assessment of ozone exposure-relevant covariates and derived lifetime "effective exposure" to ozone. Mid- and end-expiratory flows ($FEF_{25-75\%,}$ $FEF_{75\%}$) were regressed against effective exposure and ecological lifetime exposure. A convenient sample of 130 University of California Berkeley freshmen, ages 17-21, participated twice in the same tests (residential history, questionnaire, pulmonary function were recorded), 5-7 days apart. Students had to be lifelong residents of Northern (San Francisco) or Southern (Los Angeles) California. Monthly ambient ozone concentrations were assigned based on the lifetime residential history. An "effective time" spent in ozone concentration environments was derived for each residence and age stratum (0-2 y, 3-5 y, 6-11 y, and 12+ y) with the use of questions about "total time spent outdoors" and time spent in "moderate" and/or "heavy" activity. Effective exposure was calculated over the lifetime (ozone concentration x effective time) of each subject. Ozone metrics used were 8-hr averages (10 AM - 6 PM) and "hours above 60 ppb." $FEF_{25-75\%}$ and $FEF_{75\%}$, which reflect small airway function, decreased with both effective exposure and ecologic assignment of ozone exposure. For a 20 ppb increase (interquartile range) in 8-hr ozone, $FEF_{75\%}$ decreased 14% (95% CI 1.0-28.3%) of the population mean $FEF_{75\%.}$ The corresponding effect on $FEF_{25-75\%}$ was 7.2% ($p = 0.08$) of the mean. Use of time-activity data to define exposure had no impact on estimates. Negative confounding factors were region (SF vs LA), gender, and ethnicity. Lifetime 8-hr average ozone concentrations ranged from 16 to 74 ppb with little overlap between regions. There was no evidence for different ozone effects across regions. Multi-variate linear regression was run to adjust for PM_{10}, NO_2, temperature and relative humidity. Effects were independent of lifetime mean PM_{10}, NO_2, temperature, or humidity. There was a trend of decrements in FEV_1, whereas those for FVC were inconsistent and small. The strong relationship of lifetime ambient ozone on mid- and end-expiratory flows of college freshmen and the lack of association with FEV_1 and FVC are consistent with biological models of chronic effects of ozone in the small airways. Since the present study was designed as a pilot study, these findings need to be confirmed in a larger sample that is representative of the target population.

12.6.2 Longitudinal studies

Abbey et al. (1991; 1993) have reported on a continuing study of Seventh Day Adventists over 25 years of age (AHSMOG)(non-smokers; n=7,261) resident in California, and who had resided 11 years or more in areas with different levels of oxidant air pollution. In the Abbey et al. study (1991), ozone exposures were corrected for time spent at work and time away from residence. Adjustments were made for the time spent indoors by individuals. The analysis focused on incident occurrence of obstructive airway disease (COPD). Incident symptoms of COPD were significantly associated with hours above several TSP thresholds, but not with hours above any ozone threshold. In the Abbey et al. study (1993), multiple, linear regression was used to

evaluate changes in respiratory symptom severity with the TSP and ozone thresholds. When ozone was considered alone, there was a trend toward an increased risk of asthma for each 1,000-hour average annual increment in the OZ10 criterion[5] (number of hours above 10 pphm ozone), RR 2.07, 95% CI 0.98-4.89). Multivariate analyses adjusted for past and passive smoking and occupational exposures. The multiple logistic regression model for OZ10 and asthma showed that RR for asthma was 1.40 (95% CI 0.99-2.34) for a 500-h average annual increment in OZ10 (1977-1987). Multiple linear regression models for ozone and change in severity score for each respiratory symptom complex showed that there was a statistically significant association of asthma severity score with mean concentration of ozone, and with average annual exceedance frequency for cutoffs of 10 pphm and 12 pphm (1977-1987). Stepwise multiple logistic regression for new cases of asthma was run to test the effects of ozone when TSP was adjusted. Both ozone and TSP were significantly associated with change in severity score for asthma. The correlation between the 1977-1987 average annual mean concentrations of ozone and TSP was 0.74, suggesting that it was not easy to separate TSP from ozone effects. Although this study did not take account of the possible confounding effect of fine particulate pollution, it provided significant evidence of worsening of asthma in those living in a cumulatively higher oxidant environment.

New results from the AHSMOG study indicate that long-term ozone exposure can induce new cases of asthma. In an abstract published in the Journal of Epidemiology (Nushino, et al, 1996), the authors reported that there was a statistically significant ($p<0.05$) association between ozone exposure and the development of asthma in men, but not women, with ozone being more important than any other pollutant. In this study, the gender differences may be the result of males spending more time outside in summer than females (males, 18.4 hrs/wk; females, 10.9 hrs/wk, $p<0.001$). These results are consistent with the results previously published by this group (Greer et al, 1993).

Greer et al. (1993) followed 3,914 nonsmoking California Seventh-Day Adventists, for 11 years. No ozone exposure data were reported. Cumulative ambient ozone exposure through 1987 was found to be significantly associated with definite asthma by reported symptoms or physician diagnosis, only in men (RR 3.12, 95% CI 1.61-5.85, per pphm ozone). The correlation coefficient between ozone and TSP was 0.74. Because no adjustment for TSP and other pollutants were mentioned in the text, the confounding effects of TSP cannot be ruled out.

Detels et al. (1987) reported a longitudinal study of non-smoking subjects in different regions of Los Angeles. Lancaster had lower 3 month mean daily peak hourly ozone (100 ppb) than Glendora (200 ppb). This study showed a faster rate of longitudinal decline of pulmonary function in more polluted regions when subjects were re-tested after an interval of five years. No difference in respiratory symptoms was found during follow-up for either community. There was a considerable loss of sample between the two observations, making interpretation difficult. Bresnitz & Rest (1988), in a review of oxidant epidemiologic data, noted difficulties in the interpretation of this longitudinal study. The question of whether the differences in rate of

[5] OZ10 is a measure of cumulative exposure, in hours above a value of 10 pphm (parts per hundred million).

longitudinal decline of lung function could be attributed to sample loss is a difficult one. Lippmann (1989) in his review of the effects of ozone felt that the preliminary evidence from this study could not be dismissed.

Tashkin et al. (1994) examined the relative impact of residential exposure to community air pollution. Current, former and never smokers, residing in three demographically similar communities that differed in air pollution levels, were followed for 5 – 6 years and evaluated for their annual lung function changes. The communities selected were: (1) Lancaster, with moderate levels of oxidants (70 ppb), and very low levels of other pollutants (sulphate 4.3 $\mu g/m^3$, TSP 85 $\mu g/m^3$, SO_2 10 ppb, NO_2 30 ppb); (2) Glendora, with very high levels of oxidants (120ppb), sulphate (11.0 $\mu g/m^3$), NO_2 (100 ppb), and TSP (133 $\mu g/m^3$); and (3) Long Beach, with high levels of sulphate (11.3 $\mu g/m^3$), NO_2 (110 ppb), TSP (101 $\mu g/m^3$), but low levels of oxidants (40 ppb). The authors reported significant decrements in FEV_1 related to residing in areas with high air pollution levels (Glendora and Long Beach). After the adjustment for baseline spirometry, age, height, history of allergy, the odds ratio for having a large decline ($\geq$90 ml/y for never-smoking men, and $\geq$72 ml/y for never-smoking women) in FEV_1, attributable to living in Long Beach and Glendora, was 1.63 (1.63-2.11) for Glendora, and 2.00 (1.53-2.61) for Long Beach, for both men and women. Smoking also had a significant impact on lung function decline. However, from the data of this study, the effects of ozone cannot be separated from those of co-pollutants.

It may be noted that on theoretical grounds, longitudinal studies should be more sensitive indicators of long-term adverse effects of oxidant pollutant exposure, but such studies are very difficult to organize, and it is difficult to avoid loss of a significant fraction of the surveyed population during follow-up. If this occurs, the interpretation of any result becomes open to question.

Kilburn et al. (1992) conducted spirometry on 556 Mexican-American children in Los Angeles in 1984. In 1987, they conducted spirometry on 251 Mexican-American children, including 106 of the children who had been measured in 1984. All pulmonary function test values were standardized for growth by expressing them as percentages of the predicted values based on sex and height. In 1987, the mean values for FEV_1 and FEF_{25-75} were lower by 4.5 % and 13.6 % of the predicted values respectively compared to 1984. Vital capacities were not statistically different than the predicted values (this is an important control for the test procedure). For the 106 children tested on both occasions, FEV_1 was 2.0 % lower than the predicted value and FEF_{25-75} was 7.0 % lower than the predicted value. There were no significant differences between the 1987 mean value for 145 children tested for the first time in 1987, and that of the 106 re-tested children. The authors concluded that the effects might be due to ambient air pollution, but the data in their paper are not easy to interpret, due to lack of reasonable exposure data.

12.6.3 Autopsy data

Some suggestion of effects on respiratory tissues of chronic exposure to high ozone is provided by the autopsy data of Sherwin and Richters (1991), who described changes of severe respiratory bronchiolitis in a high proportion (27%) of autopsy lungs from 107 young adults aged from 14-25 years, who died in the Los Angeles area from non-respiratory causes. Unfortunately nothing is known about the smoking status, other lifestyle factors or occupational history of these

subjects. Although this study has not yet been compared to a control region, and the degree of small airway disease has not been measured by quantitative morphometry, it seems likely that the lesion represents an aggravation of the respiratory bronchiolitis known to be a consequence of cigarette smoking. It may be significant that, as noted above, theoretical dosimetric calculations have indicated that ozone deposition in the human lung would be maximal in this region of the lung, and data on ozone-exposed non-human primates indicated that a respiratory bronchiolitis was the principal induced lesion (see chapter 10).

12.6.4 Summary for chronic effect studies

In general, chronic effect studies have not been able to give a satisfactory conclusion as to the long term effects of ozone. Among 6 cross-sectional studies reviewed, all found changes in lung function or symptoms that might be attributed to ozone pollution. Two of the cross-sectional studies examined the effect of other environmental factors and reported that ozone effects were independent of mean PM, NO_2, temperature and humidity. Three studies tried to adjust for the social-economic and life style differences among the communities studied. Since cross-sectional studies investigate the prevalence rather than the incidence of health effects, and several studies showed high correlation between ozone and PM, no definitive conclusion can be drawn from these studies in terms of ozone effects.

Among 5 longitudinal studies reviewed, all of the authors reported findings of a trend or a statistical significance of increased asthma symptoms or lung function decrements that were related to ozone pollution. However, loss of participants during follow-up and lack of control for other pollutants preclude drawing a conclusive relationship between ozone and long term health effects.

Table 12.5 Summary of results from Chronic effect studies

Location and references	Ozone concentration	Outcomes	Results	Co-pollutants
Austria Zwick et al., 1991	95 – 188 ppb, time metric not given	Cross sectional, children living in high ozone and low ozone areas. 281 children in each group. Hyperresponsiveness, symptoms, lung function, lymphocyte function	Between two groups: Symptoms: no differences in cough or breathlessness pulmonary function status: no difference. Hyperresponsiveness: a higher incidence of bronchial hyperresponsiveness to methacholine in the high ozone group (29% vs 21%; $p<0.02$) Lymphocyte function: The 'high ozone' children showed a decrease in T-helper lymphocytes and an increase in T-suppressor cells compared to the children in the low ozone area. T_4/T_8 ratios were decrease by 17.7% ($p<0.001$) and natural killer cells by 12.6% ($p<0.001$).	Other pollutants were similar between the regions, but no measurements of particle concentrations were taken
44 city National Health and Nutrition	Median of avg. annual hourly	Cross sectional. Age 6-24 y from 44	Nonlinear relationship between annual average ozone and lung function with	No control for other co-pollutants.

Table 12.5 Summary of results from Chronic effect studies

Location and references	Ozone concentration	Outcomes	Results	Co-pollutants
Examination Survey, USA Schwartz, 1989	ozone: 33 ppb	cities, 1976-1980. Lung function, demographic, smoking, and health co-variate data	threshold at 40 ppb,	The ozone effect persisted after control for sex, race, age, family income, educational level, chronic respiratory symptoms, and smoking history.
Health Interview Survey, USA Ostro and Rothschild, 1989	1-h max.: 41 to 48 ppb, 1976-1981	Cross sectional. 1976-1981, 50,000 households. Subjects aged 18-65 y. lung function.	An increase in 1 $\mu g/m^3$ (0.51 ppb) was associated with a 0.185% increase in minor restricted activity days (MRAD, elasticity of 0.082). Ozone was not associated with respiratory-related restricted activity days (RRAD).	Co-regression with fine particles: MRAD: 0.17%-0.54% increase per 1 $\mu g/m^3$ (0.51 ppb). RRAD: not significant.
San Francisco and Los Angeles, CA Kunzli et la., 1997	Effective ozone exposure, 8-h avg.: 123.1 ppb-hr (median 88, IQR 207).	130 university students, life-long residents in SF and LA. Lung function.	8-hr ozone: $FEF_{75\%}$: -14% (95% CI 1.0-28.3%)/20 ppb $FEF_{25-75\%}$: -7.2% (p = 0.08)/20 ppb	Effects were independent of lifetime mean PM_{10}, NO_2, temperature, or humidity. +PM, $FEF_{75\%}$: -0.237 L/sec/ppb (SE 0.117) +NO_2, $FEF_{75\%}$: -0.257 L/sec/ppb (SE 0.118) +all: $FEF_{75\%}$: -0.173 L/sec/ppb (SE 0.124).
Ontario and Manitoba Stern et al., 1989	Annual mean 1-h max.: 34 to 50 ppb 90th percentile	Cross sectional study, 1983-1984. Second to sixth grade students, n=735 in Ontario, n=895 in Manitoba. Respiratory health and lung function.	Ontario town had more ozone days >80 ppb, 30 days compared to Manitoba town, 3 days; small decrements in FVC (-2%) and FEV_1 (-1.7%) were found in the Ontario town compared to the Manitoba town, p<0.05; adjusted for age, sex, height, parental smoking.	High sulphate and ozone correlation, and ozone possible effects were completely confounded with sulphates.
Ontario and Saskatchewan Stern et al., 1994	Annual mean 1-h max.: Ontario: 46.3 ppb (90th, 80 ppb) Saskatchewan: 34.1 ppb (90th 47 ppb)	Cross sectional study, 1985-1986. 7-11 y children, n=3,945, 5 towns in Ontario, and 5 towns in Saskatchewan. Respiratory health and lung function.	Adjusted for age, sex, weight, standing height, parental smoking and gas cooking. Ontario: FVC –1.7% (p<0.05), FEV1 –1.3% (p<0.05) compared with Saskatchewan children. No effect for mid-volume flows, except for subjects with asthma. No effects for symptoms, odds ratios 0.77 (cough) -1.15 (bronchitis), p>0.05.	-Coincidence of increased ozone and sulphate precludes definite statements concerning ozone effects.
AHSMOG, CA Abbey 1991, 1993	Not reported	7,261 Seventh Day Adventists resident in CA over 25 years of age, who had resided 11 years or more in areas with different levels of oxidant air pollution.	a trend toward an increased risk of asthma for a 1,000-hour average annual increment in the OZ10 (number of hours above 10 pphm ozone) criterion: RR=2.07, 95% CI 0.98-4.89.	+smoking, occupational exposures asthma symptoms RR=1.40 (95% CI 0.99-2.34) for a 500-h average annual increment on OZ10 (1977-1987). asthma severity score: associated with mean concentration of ozone (1977-1987), and with

Table 12.5 Summary of results from Chronic effect studies				
Location and references	**Ozone concentration**	**Outcomes**	**Results**	**Co-pollutants**
				average annual exceedance frequency for cutoffs of 10 pphm and 12 pphm (1977-1987). +TSP: jointly was significantly associated with change in severity score for asthma. But ozone itself lost significance. No interaction between TSP and ozone was found.
AHSMOG, CA Greer et al., 1993	Not reported	3914 nonsmoking California Seventh-Day Adventists, followed for 11 years.	Cumulative ambient ozone exposure through 1987: RR (95% CI) for definite asthma by reported symptoms or physician diagnosis, per pphm: men: 3.12 (1.61-5.85),p<0.05 Women: 0.94 (0.68-1.34), not significant. Men+women: 1.31 (0.96-1.78).	Between ozone and TSP, r=0.74. Did not control for TSP.
Lancaster and Glendora, CA Detels et al., 1987	3 month mean daily peak hourly values: Lancaster: 100 ppb Glendora: 200 ppb	5-y follow-up study. Non smoking no Hispanic whites, 7-59 years of age.	No difference in respiratory symptoms over follow-up for either community Across all age groups, slope of Phase III of N2 washout deteriorated more rapidly in Glendora than in Lancaster.	-
Lancaster and Glendora, Long Beach Tashkin et al., 1994	Lancaster: oxidants 70 ppb, sulphate 4.3 µg/m^3, TSP 85 µg/m^3 Glendora: oxidants 120ppb, sulphate 11.0 µg/m^3, TSP 133 µg/m^3 Long Beach: oxidant 40 ppb, sulphate 11.3 µg/m^3, TSP 101 µg/m^3	Never (n=621-763), former (n=317-479) and smokers (n=472-691), 25-59 y, non Hispanic whites, followed 5 y in Lancaster and Glendora, and 6 y in Long Beach, annual lung function changes	Adjustment of baseline spirometry, age, height, history of allergy. A large decline in FEV1 is defined as ≥90 ml/y for never-smoking men, and as ≥72 ml/y for never-smoking women. Odds ratio (95% CI) for having a large decline in FEV1 attributable to living in Long Beach and Glendora was: Men: 1.84 (1.23-2.77) for Glendora, 2.58 (1.69-3.94) for Long Beach Women: 1.48 (1.05-2.09) for Glendora; 1.51 (1.06-2.17) for Long Beach Men + women: 1.63 (1.63-2.11) for Glendora; 2.00 (1.53-2.61) for Long Beach	-
Los Angeles, CA Kilburn et al., 199	Not reported	556 2nd and 5th grade students, Mexican-American. Lung function	Interpretation of results was difficult due to loss of participants during follow-up and lack of reasonable exposure data.	-

12.7 SUMMARY AND CONCLUSIONS

The major emphasis of this epidemiological review has been on the studies of mortality, hospitalizations and Emergency Department visits, because of the more complete information for these endpoints. All of these studies made use of administrative databases in time-series (longitudinal) studies. Environmental or field studies, including camp studies on children and adolescents, and panel or cohort studies on various ages and groups including asthmatics and the elderly, were also considered for qualitative information and coherence with the results obtained for the more serious health endpoints.

12.7.1 Mortality

On balance, the time-series studies examined in this analysis indicate that the association between ozone and mortality is positive, consistent, and independent of other co-occurring air pollutants including particulate matter. Seventeen of the 23 studies examined reported statistically significant positive associations using single pollutant models. Fourteen studies reported results using multi-pollutant models, eleven of which demonstrated statistically significant independent associations between ozone and mortality. These associations were found in cities across North America, in four U.S. and 13 Canadian locations, in Santiago Chile and three European cities, and in a meta-analysis including seven European cities, demonstrating consistency of results despite widely varying climatic conditions, pollutant mixtures, population compositions, and life styles. These associations were reported for cities with mean ozone concentrations (expressed as the one-hour maximum) between 20 and 75 ppb, i.e. below, and in most cases well below the current Canadian Air Quality Objective for ozone of 82 ppb (one-hour maximum).

A meta-analysis was conducted to obtain a pooled estimate of risk. Ten studies that provided suitable quantitative information were selected for meta-analysis based on a list of criteria (see section 12.1.3). Relative risks from these studies were weighted based on their variances, which reflect the size of standard deviations and sample sizes. Seasonal and weather variations and co-pollutants were adjusted in all the selected studies. The weighted mean of mortality risk per 10 ppb increase in ozone (1-hour maximum) was 0.4% (95% CI: 0.19-0.60%).

Using the data from 13 Canadian cities (Burnett, 1998 in Appendix A), the risk for non-accidental mortality is 0.79%/10 ppb increase in daily one-hour maximum ozone (95% CI: 0.59-0.99%). The LOAEL with statistical significance is 20 ppb ($p \leq 0.01$). These values were from single-pollutant models. For mortality, the data show a concentration-dependent relationship, with effects increasing monotonically as concentrations increase. Effects are observed even at very low O_3 levels (down to 10 ppb), although below 15 ppb, the positive associations are not statistically significant. There appears to be no threshold for mortality.

12.7.2 Hospitalizations

The weight of evidence is strong for an association between hospitalizations for respiratory conditions and exposure to ozone at the levels now commonly encountered in Canada. The weighted means of risk of hospitalization for respiratory illness per 10 ppb increase in ozone (1-hour maximum) vary, according to different locations and illness, between 1.8% (95% CI 1.0-

2.6%) for all age respiratory admissions from Canada/New York studies, 1.8% (0.7-3.0%) for all age asthma admissions in Canada/New York studies, 1.9% (1.2-2.6%) for elderly pneumonia, COPD and total respiratory illnesses from US Medicare studies, to 1.14% (0.43-1.84%) from APHEA European studies.[6] These data are from single-pollutant models. (Thurston and Ito, 1999).

For ozone effects from multi-pollutant models, a meta-analysis was conducted for this report by pooling all available data. The criteria for study selection were the same as for mortality studies, except that some populations involved the elderly only. Data include all respiratory admissions, and separate disease categories (asthma, pneumonia and COPD). The weighted mean for respiratory hospitalizations per 10 ppb increase in ozone (1-hour maximum) was 1.12% (95% CI 0.73-1.51%), within the same range as those obtained from single-pollutant models. These studies included all of Southern Ontario, 16 cities in a cross-Canada study, and several U.S. and European cities.

Using the results from 2 Canadian studies (Burnett et al., 1994,1997), a regression analysis was performed for hospitalizations (data from 13 cities, single-pollutant models) (Appendix A, Burnett, 1998). The regression analysis showed that the risk of hospitalization for respiratory diseases is 1.04% per 10 ppb increase in daily one hour maximum ozone (95%CI: 0.78-1.30%). The LOAEL derived from the data is 25 ppb ($p<0.01$). Interestingly, the data show that the regression coefficient between ozone and hospitalization becomes negative between 15 and 20 ppb indicating a possible threshold for hospitalization based on the result of this new analysis.

12.7.3 Emergency Department Visits

The data on hospital Emergency Department (ED) visits generally support the findings from the respiratory hospitalization studies, i.e., increases in ambient ozone concentrations, in the forms of 1-hour maximum, or 5 to 24 hour average, result in significantly increased visits to the Emergency Department due to respiratory illness. To give an example, the percent increase in respiratory ED visits was 6-8.6% per 10 ppb ozone (1-hour maximum), and was 5.6-14.2% per 10 ppb ozone (5-hour average) after adjusting for PM, temperature, and other gaseous pollutants. The association was seen in four cities/metro areas in three different countries (including Montreal), at mean summertime ozone levels (1-5 h metrics) that varied between 30 ppb and 90 ppb. One drawback of the ED visit studies involves the much smaller databases used, when compared with mortality and hospitalization studies. Most of the ED visit studies considered only 1-2 years of data from a few clinics. Many studies tried to control seasonality by limiting the analysis to only high ozone season. Most of the studies considered only asthma-related visits, either of all age groups, children, or the elderly. For studies in which an association could not be shown, the results could usually be attributed to the lack of adjustment for confounding factors, including seasonality, weather, and co-pollutants.

[6] The findings from Thurston and Ito (1999) were reported as Relative Risk (RR) values per 100 ppb increase in ozone in section 12.4 of this report. Here they are presented as % increase in incidence of the various endpoints, per 10 ppb increase in ozone.

12.7.4 Field (Camp and Panel) Studies

The field studies give convincing evidence that healthy and asthmatic children and adults are affected by ambient ozone pollution at mean levels from 40 ppb (Fraser Valley, BC) to 153 ppb (Los Angeles), reporting increased symptoms and medication use, and decreased FEV_1 or PEFR. Healthy individuals working or exercising outdoors have also been shown to be affected at ozone levels with mean hourly maxima at 40 ppb. Their decline in lung function was consistent with data from controlled exposure studies, but in addition showed a long term decline over the period of 60 days of observation (Brauer et al., 1996a,b). Greater declines in lung function demonstrated from camp studies when compared with controlled exposure studies can be explained on the basis that children in camps are exposed for long periods outdoors, to a pollutant mix, and may be exposed sequentially for several days with insufficient recovery time between daily peaks.

12.7.5 Chronic effects

Recent cross sectional and longitudinal studies demonstrate that there appears to be lung function decrements and the induction of new asthma cases that are associated with long-term exposure to ozone at annual mean 1-hour levels of 34 to 200 ppb. The drawbacks of these studies involve lack of control for co-pollutants and loss of participants during follow-up (in longitudinal studies). In the future, if better designed studies confirm the association between long-term ozone exposure and the development of asthma, this will be an important finding with significant implications for public health.

12.7.6 Effects occurring at low concentrations

The increases in respiratory-related adverse health effects associated with ozone occurred in cities where mean ambient concentrations are well below the current Canadian National Ambient Air Quality Objective for ozone of 82 ppb (one-hour maximum).

The concentration-response relationship analyses in mortality and hospitalization studies show a monotonic increase from ambient levels as low as 20 ppb up to 95 ppb. Increases in Emergency Department visits were also seen at quite low ambient ozone (36 ppb mean for 1-hour ozone in Montreal). The camp studies on children, and panel studies on asthmatics, normal, exercising individuals, and school children, all support this finding.

One interpretation for the substantial sensitivity to ambient ozone concentrations observed in epidemiological studies may be the high heterogeneity of human populations. It is conceivable that there is some small segment of the population at the tail end of the response distribution curve that will react to the stimulus at low concentrations.

12.7.7 Criteria for causality

All of the data considered thus far in this section are ecological in nature, that is, results are based on populations, not individuals, and the exposure of individuals to ozone is not known. It is therefore particularly important to examine these data critically if some idea of causality is to be

entertained. The criteria set out by Hill (1965) may give some useful guidance for drawing an inference of causality from association data:

Strength of Association. The associations seen in all the studies are quite weak, in the range of 0.4% (mortality) to 1.9% (hospitalization), to 8.6% (ED visits) for a 10 ppb increase in ozone (1-hour maximum)(a relative risk of less than 1.50, or 50% increase, is considered to be low). They are, however, highly statistically significant in many cases. Inexact exposure information might well have weakened the associations (it is unlikely to have strengthened them).

Consistency. Although the study designs of these time-series studies were similar, the association was seen by a number of investigators in various cities across North America and in several cities in central and South America, all of which differ in their pollutant mix, ozone levels, weather, and socioeconomic status. The 16 city Canadian study (Burnett et al., 1996) included cities from all five regions of Canada. Only two were found to have non-significant associations. The Ontario study by Burnett et al. (1994) was consistent with other studies that had taken place in the same geographic area (Bates & Sizto, 1987; Thurston et al., 1994a,b). Some studies for each endpoint were unable to find a positive association, but their negative results usually could be explained on the basis of the conduct of the analysis, such as lack of controlling for confounding factors, or small sample sizes.

Specificity A number of studies indicated that ozone was the most important of the several pollutants in the mixture, for hospitalizations (Burnett et al., 1994;1996; Schwartz, 1994b, 1995), Emergency Department visits (Weisel et al., 1995; White et al., 1994; Delfino, 1996), and asthma attacks (Javitz et al., 1982; Holguin et al., 1985; Whittemore & Korn, 1980). The hypothesis that H^+ was an important component of the pollutant mixture, possibly necessary for effects of ozone to be seen, was tested in the study by Delfino et al. on Emergency Department visits in Montreal; H^+ was not associated with ED visits for any age group, except for infections in infants (Delfino et al. 1996). Other studies are required to confirm this. Recent data from environments in which aerosol acidity is known to be absent, and in which aerosol sulphates are at very low concentrations, serve to confirm that the primary association is with ozone (Brauer et al., 1996a,b).

Temporality. Most authors investigated the possibility that pollutant levels one or more days before the admission or visit ('lag time') were more important predictors than current day concentrations. Lag times were generally 1 to 2 days for hospitalizations, and perhaps a little shorter for Emergency Department visits, especially if the hospital served as the only source of medical advice, as in areas of low socioeconomic status (White et al., 1994; Romieu et al., 1995). In wealthier areas the family physician might be the first call. Negative lag times were investigated for both control diseases and respiratory diseases by Thurston et al. (1994a,b), and Burnett et al. (1994), and were not found to be

associated for the respiratory conditions, but were occasionally associated with other conditions by chance.

Biological gradient. A concentration-response relationship was clearly shown in the Burnett et al. (1994) study in southern Ontario, and one was evident, but not quite so clear in the 16-city national study (Burnett et al., 1997a). Stratification by ozone level was performed in several other studies, but only high ambient exposures resulted in significant elevation of relative risk.

Biological Plausibility. Ozone has been shown in animal experiments and in human controlled exposure studies to result in inflammation, cell necrosis, lowered lung function, and increased airway reactivity. In addition, asthmatics and individuals with 'hyperreactive' bronchi have been shown to be sensitive to the effects of ozone, with pain on deep inspiration, lowered lung function, increased need for medication, and asthma attacks. The progression of these effects to the point where medical attention is sought is quite plausible in light of the above.

Coherence. The data from the three administrative databases on mortality, hospitalizations, and emergency department visits provide a quite coherent picture of progression of effects from high numbers of incidents recorded as ED visits, compared to those who were hospitalized. The slope of the concentration-response curve was steeper for ED visits than for hospitalizations, as would be expected on the basis that an element of choice is involved in the decision to seek medical attention at an Emergency Department or doctor's office, while hospitalizations represent only the most serious cases as determined by a physician. At first glance, there seems to be a lack of coherence when one moves from hospitalizations to mortality, for which the slope was so low as to cast some doubt on whether the effect was real (using the respiratory mortality data). This may be partly explainable on the basis that ozone is associated with respiratory mortality, which is a relatively small part of total mortality (approximately 8% according to a recent economic analysis of Canadian medical care costs). When non-accidental mortality data is selected, or cardiovascular mortality, then the slope is very similar to the one observed for hospitalization data. Farther down what has been referred to as the 'pyramid of effects' (American Thoracic Society 1985), two analyses of relationships of medical care required by asthmatics, one in Winnipeg and one in St. John N.B. (Stieb et al. 1995a,b), showed that asthmatic individuals attended Emergency Departments about five times more frequently than they were admitted to hospital for respiratory disease. Doctors' visits were also shown to be more elevated than emergency Department visits, and days with reduced activity (absences from work or school) were also more frequent. The field or environmental studies also confirm that asthmatic attacks, symptoms, and medication use are increased in a significant portion of the population when photochemical smog is high. An independent analysis has recently confirmed this 'pyramid of effects', and gives some indication of the magnitude of effect that pollution-related increases of only a very few percent, as calculated for ozone, would have on the health care system. In 1990 in

Canada, hospital-days for asthma (about 40% of all respiratory visits), were estimated to be 281,000, and Emergency Department visits were estimated at 182,000 to 697,000 (depending on source of the estimate), while estimates of physician services (based on two physician surveys) ranged from 2 million to 3.6 million, and days in bed and off work or school were estimated at 2.1 million (Krahn et al. 1996).

12.8 Research Needs

- Since most Emergency Department visit studies had limited databases, and investigated only asthma-related visits, future ED visit studies need to expand their databases, and include ED visits for other cardio-respiratory diseases.

- More longitudinal studies should be conducted to examine the long term effects of ozone exposure.

- Most field (camp and panel) studies have used pulmonary function as an indicator for adverse health effects. Clinical studies have shown that pulmonary function changes do not correlate with tissue injury such as pulmonary inflammation. More sensitive biological markers thus need to be developed to detect tissue injury rather than functional changes.

- In field studies personal exposure monitoring should be carried out, in order to determine exactly what levels of ozone susceptible populations are exposed to, and the relationship with health effects.

- It is not clear why ozone causes cardiac mortality - is it via the impact on the respiratory system with subsequent stress on the heart, or is there a direct link with heart disease. Field studies with more sensitive biological markers may be able to shed some light on this question.

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