

THE SEARCH FOR NON-LINEAR EXPOSURE-RESPONSE RELATIONSHIPS AT AMBIENT LEVELS IN ENVIRONMENTAL EPIDEMIOLOGY

Morton Lippmann □ New York University School of Medicine, Nelson Institute of Environmental Medicine, Tuxedo, NY

□ *Environmental exposures to ambient air particulate matter (PM), ozone (O₃), environmental tobacco smoke (ETS), and to dioxin and related compounds are of considerable public health concern, and risk assessments for them have generally been based on linear, non-threshold models derived from epidemiological study data. While the epidemiological databases for PM, O₃, and ETS have been sufficient to show that adverse health effects are occurring, the relative risks have been quite low, and it has not been possible, to date, to identify thresholds or non-linear relationships for them. For dioxin and related compounds, the evidence for excess cancer risks has been inadequate to establish causality, and there is suggestive evidence that hormesis may have occurred.*

Keywords. Particulate matter, Ozone, Environmental tobacco smoke, Dioxin, Threshold, Hormesis

INTRODUCTION

It is generally recognized that epidemiology is a blunt tool, and that searches for evidence of either linearity or non-linearity in dose-response relationships are seldom successful. On the other hand, the epidemiological data bases for the criteria air pollutants are relatively rich, and the procedures used for setting National Ambient Air Quality Standards (NAAQS) in the U.S. and establishing Air Quality Guidelines (AQGs) by the World Health Organization (WHO) give preference to data from epidemiological studies (Lippmann and Maynard, 1999). When standards or guidelines are set, or quantitative risk assessments are performed for complex mixtures such as ambient air particulate matter (PM), environmental tobacco smoke (ETS), or dioxin and related compounds (dioxins), definition of the shape of the dose-response relationship is inherently more difficult. For these mixtures, exposures are characterized in terms of one component, and responses among the general public are characterized by relative risks (RRs) that are typically below 1.5, and sometimes below 1.1. The at risk component of the population is largely composed of individuals with uncommon genetic or age-related susceptibilities, pre-existing disease, or greater than average exposures. With all of these variables, the “noise” associated with

Address correspondence to Morton Lippmann, New York University School of Medicine, Nelson Institute of Environmental Medicine, 57 Old Forge Road, Tuxedo, NY 10987. Phone: 845-731-3558. FAX: 845-351-5472. E-mail: lippmann@env.med.nyu.edu

them, and with the typically limited range of environmental exposures, it is generally assumed, in the absence of any mechanism based model, that there is a non-threshold linear dose-response relationship.

In this paper, I review the evidence for non-linear dose-response relationships in epidemiological databases for general populations for some complex mixtures, i.e., PM, ETS, and dioxin and related compounds. I also review the evidence for ozone (O_3), as an example of a criteria pollutant that is a clearly defined chemical.

PARTICULATE MATTER

PM in the ambient air is composed of primary particles, i.e., those that are emitted into the air and remained suspended for some appreciable time, and secondary particles, i.e., those that form in the air from gaseous precursors. Some primary particles, such as soot from Diesel engine exhaust, remain in the accumulation mode of the particle size range (See Figure 1), but most of the primary particles are either of biological origin, or are mineral particles. The mineral particles are mechanically dispersed, are greater than $1\ \mu\text{m}$ in aerodynamic diameter, have chemical compositions comparable to surface soils, are only slightly soluble in water, and are basic.

By contrast, secondary particles, formed initially in high number concentrations in sizes in the low nanometer range, rapidly agglomerate, form droplets or aggregates in the 0.2 to $0.8\ \mu\text{m}$ range, and remain suspended for many days in the absence of rain. Some are composed largely of semi-volatile organic compounds, while others are inorganic acids or hygroscopic salts of sulfuric and nitric acids.

Routine monitoring of ambient air PM has been done by optical transmittance or reflectance [Black Smoke (BS), Coefficient of Haze (CoH)], or by mass. The mass concentration measures used have been: total suspended particulate (TSP); thoracic particles, i.e., those less than $10\ \mu\text{m}$ in aerodynamic diameter that can penetrate the airways of the head (PM_{10}); and fine particles (those less than $2.5\ \mu\text{m}$ in aerodynamic diameter ($PM_{2.5}$)). All of these indices of PM concentration are chemically non-specific, although BS and CoH are most influenced by elemental and organic carbon in the particles. In arid regions, where windblown soil dominates the mass of measured PM_{10} , there is generally a poor correlation between PM_{10} and $PM_{2.5}$, and PM_{10} concentrations can vary widely. On the other hand, in the more humid eastern half of the U.S., where secondary aerosol dominates the mass of the PM, $PM_{2.5}$ and PM_{10} are usually highly correlated, and both have relatively homogenous regional concentrations.

When relying on concentrations measured at central monitoring sites for epidemiological studies, regionally uniform concentrations can provide an index of population exposures to PM with less measurement error than can measures having more spatial concentration variations. This is espe-

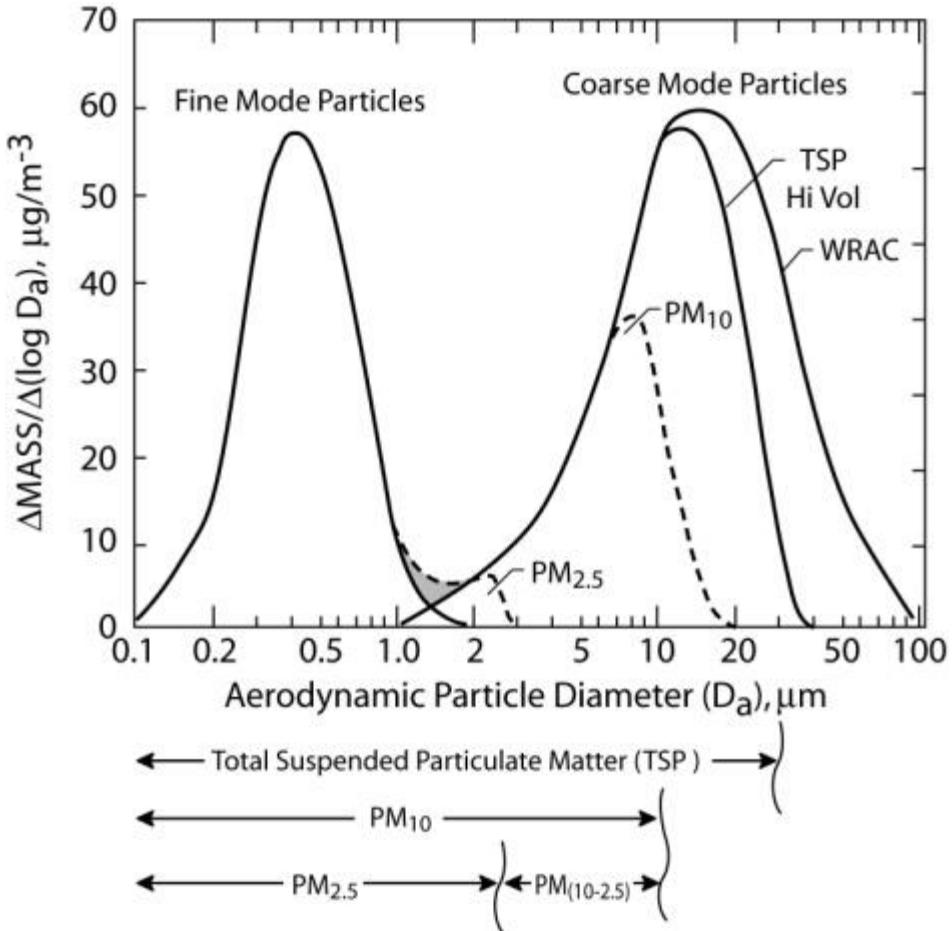


FIGURE 1 Representative biomodel mass distribution as a function of aerodynamic particle diameter for Phoenix, Arizona, showing effect of size-selective sampling inlet on mass collected for (a) wide-ranging aerosol classifier (WRAC), (b) standard total suspended particulate (TSP) high-volume sampler, (c) sampler following EPA's (PM₁₀) criteria for thoracic dust, and (d) sampler following EPA's criteria for fine particulate matter (PM_{2.5}).

cially true for PM_{2.5} of ambient air origin, for which indoor concentrations approach those measured out-of-doors.

Many different human health effects have been associated with ambient PM concentrations, including daily and annual mortality rates, hospital admissions for cardiopulmonary diseases, reduced pulmonary function and increased symptoms, and lost time from school and work. Some are most closely associated with PM_{2.5}, most notably mortality and especially mortality attributed to cardiac disease. Others, such as upper respiratory symptoms and hospitalizations are more closely associated with PM₁₀, or with the coarse particle component of PM₁₀, i.e., PM_{10-2.5}.

There is an enormous, and rapidly growing epidemiological literature on PM and mortality. EPA's latest Criteria Document draft for PM lists hundreds of time-series studies of daily mortality (EPA, 2003). Much of the recent focus on exposure-response for peak exposures to PM and daily mortality rates has centered on the National Mortality and Morbidity Air Pollution Study (NMMAPS) on the basis of its application of a uniform approach across many U.S. cities. For this study, Dominici *et al.* (2003) examined evidence for the presence of a threshold using the largest 20 U.S. cities for 1987–1994. Several analytic models were fit for each city separately. The best fit among the models, within each city and over all cities, were determined using the Akaike's Information Criterion (AIC). As shown in Figure 2, the results using the natural spline model showed that, for total and cardiorespiratory mortality, the spline curves were roughly linear, consistent with the lack of a threshold. For mortality from other causes, however, the curve did not increase until PM₁₀ concentrations exceeded 50 $\mu\text{g}/\text{m}^3$. The hypothesis of linearity was examined by comparing the AIC values across models. The results suggested that the linear model was preferred over the spline and the threshold models. Thus, these results suggest that linear models without a threshold may well be appropriate for estimating the effects of PM₁₀ on the types of mortality of main interest.

While there have been far fewer studies of annual mortality rates in relation to long-term PM exposure, the public health impact of such exposures is more quantifiable and considerably greater. Several large prospective cohort studies (Pope *et al.*, 1995, 2002; Dockery *et al.*, 1993, Laden *et al.*, 2001) have shown that long-term exposure to fine particulate air pollution (PM_{2.5}) is associated with increased risk of death from cardiopulmonary

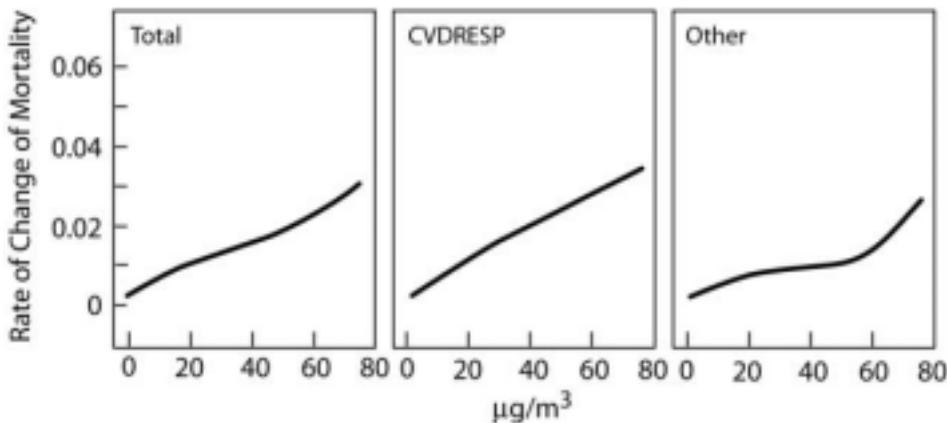


FIGURE 2 Particulate matter < 10 μm in aerodynamic diameter (PM₁₀)-total mortality concentration-response curves for total (TOTAL) mortality, cardiovascular and respiratory (CVDRESP) mortality, and other causes (OTHERS) mortality, 20 largest US cities, 1987–1994. Source: Dominici *et al.*, (2003).

diseases. These findings indicate that people who live in areas with elevated $PM_{2.5}$ experience cumulative adverse health effects in addition to acute transient effects. Since cardiovascular-related deaths account for the majority of cardiopulmonary deaths, these recent studies suggest that long-term exposure to $PM_{2.5}$ causes chronic irreversible effects on the cardiovascular system. Figure 3 illustrates the exposure-response relationships between $PM_{2.5}$ concentrations and mortality for the latest update on the American Cancer Society cohort study (Pope *et al.*, 2002). It demonstrates increasing rates of cardiopulmonary and lung cancer mortality with increasing average concentration, and no $PM_{2.5}$ influence on all other causes of mortality. It also shows no evidence for a threshold, but rather the steepest slopes at the lowest levels. A further analysis of these data, by Pope *et al.* (2004), illustrated in Figure 4, demonstrated that cardiac causes accounted for most of the excess deaths.

The plausibility of a linkage between $PM_{2.5}$ exposure and cardiac disease has been strengthened in recent years by laboratory exposures to concentrated ambient air PM (CAPs) in human volunteers (Ghio *et al.*, 2000;

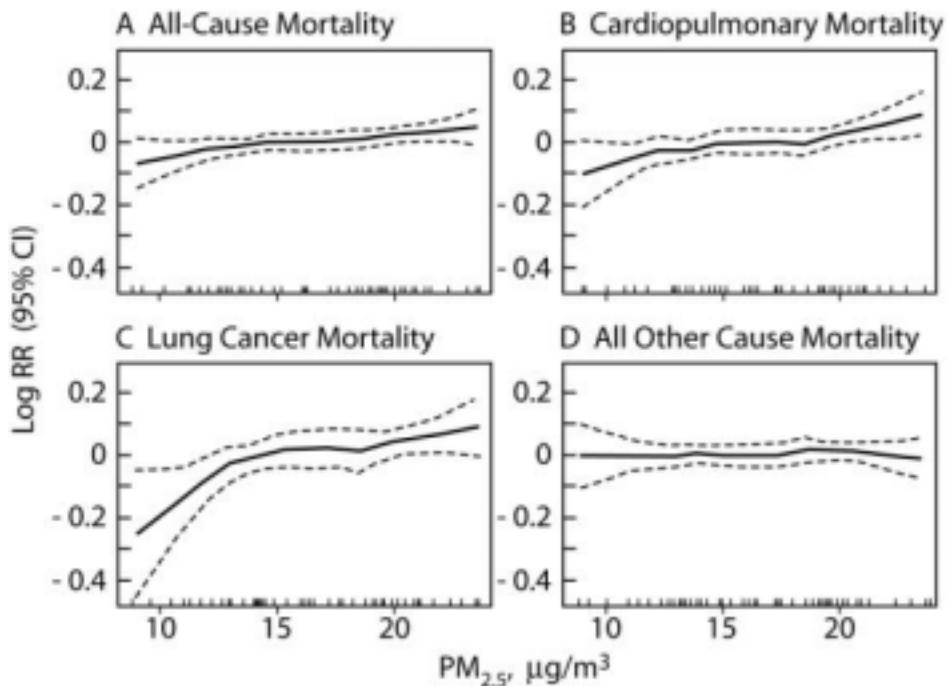


FIGURE 3 Nonparametric smoothed exposure response relationship for annual mortality. Vertical lines along x-axes indicate rug or frequency plot of mean fine particulate pollution; $PM_{2.5}$, mean fine particles measuring less than 2.5 μm in diameter; RR, relative risk; and CI, confidence interval. Source: Pope *et al.*, JAMA 287 (2002).

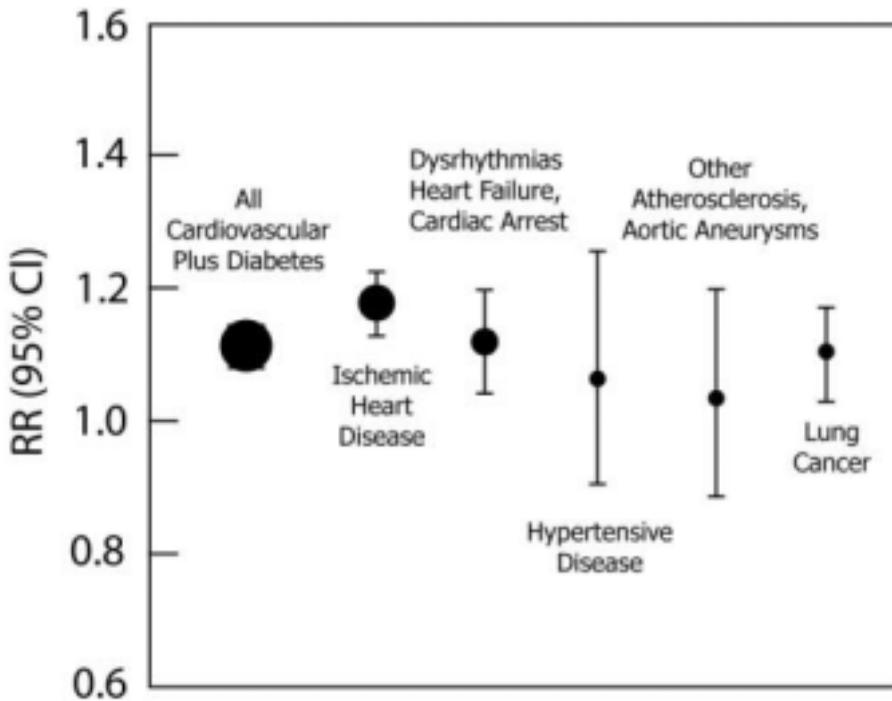


FIGURE 4 Cardiovascular mortality and lung cancer affected by long-term fine particulate matter. Relative risks and 95% CI's are shown for a $10 \mu\text{g}/\text{m}^3$ increase in annual average $\text{PM}_{2.5}$ mass concentration. The size of the dots corresponds to the relative number of deaths. Sources: Pope *et al.*, *Circulation* 109:71–77 (2004); Pope *et al.*, *JAMA* 287:1132–1142 (2002).

Harder *et al.*, 2001; Petrovic *et al.*, 1999; Gong *et al.*, 2000) and laboratory animals (Clark *et al.*, 2000; Saldiva *et al.*, 2002; Nadziejko *et al.*, 2001, 2002; Godleski *et al.*, 2000; Wellenius *et al.*, 2003; Zelikoff *et al.*, 2003; Gordon *et al.*, 1998, 2000), which have demonstrated changes in heart rate and heart rate variability. In a panel study in humans, discharges of implanted cardiac defibrillators have been associated with $\text{PM}_{2.5}$ concentrations (Peters *et al.*, 2001). Other studies in human populations have demonstrated $\text{PM}_{2.5}$ associated changes in heart rate and heart rate variability (Liao *et al.*, 1999; Pope *et al.*, 1999a,b, 2000; Gold *et al.*, 2000; Creason *et al.*, 2001). These studies showed that these markers of cardiac function varied in association with PM concentration.

Ambient PM concentrations have substantially declined in the U.S. since about 1960, when average TSP levels in large cities were several hundreds of $\mu\text{g}/\text{m}^3$. By 1970, levels were closer to $100 \mu\text{g}/\text{m}^3$, and subsequent enforcement of air quality standards has brought average PM_{10} levels below $50 \mu\text{g}/\text{m}^3$. The decline in cardiovascular mortality illustrated in Figure 5 may be due, at least in part, to the coincident fall in PM concentrations.

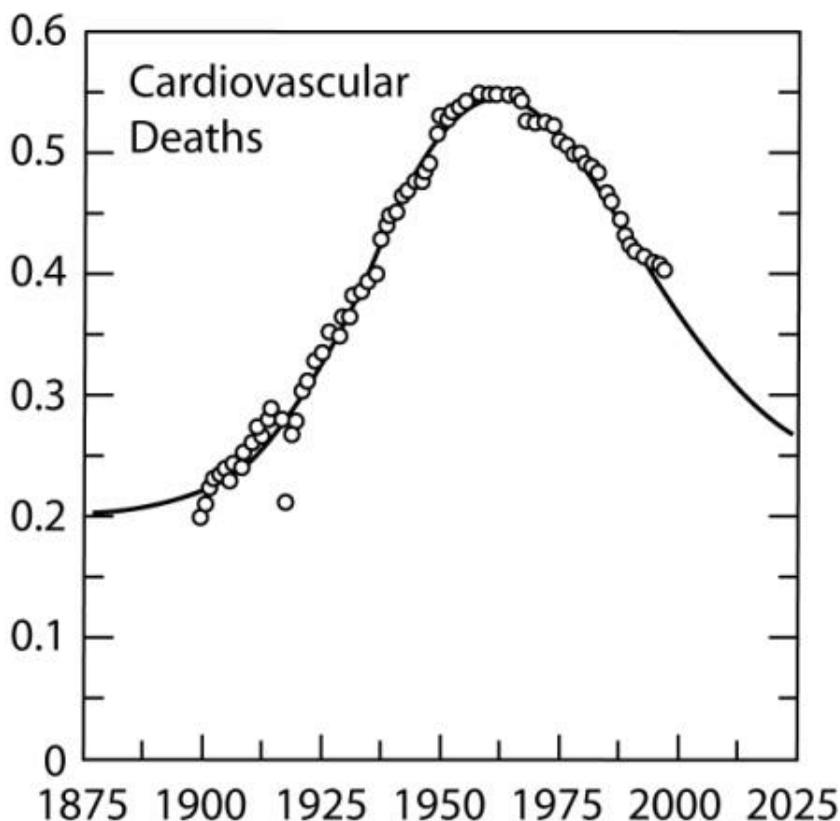


FIGURE 5 Cardiovascular causes as a fraction of all deaths: U.S. 1900–1997. Data source: Ausubel *et al.*, *Technol Soc* 23:131–146 (2001).

ENVIRONMENTAL TOBACCO SMOKE

Environmental tobacco smoke (ETS) is a mixture of side-stream smoke released from the burning end of a cigarette and exhaled mainstream smoke, both of which are complex mixtures whose concentrations vary with butt length, inhaled smoke volume, and interval between puffs. Further changes in particle size and chemical composition occur while the smoke particles remains suspended in the indoor microenvironment into which they are discharged as particles grow by coagulation and shrink as semivolatile components, such as nicotine, evaporate.

Crude, but generally adequate indices of exposure of nonsmokers for epidemiological studies are: 1) the number of cigarettes smoked in the environment per day for acute effects; and 2) the number of pack-years of smoking by other occupants of the home or work environment. A more individual index of short-term exposure is the concentration of cotinine, a metabolic product of nicotine, in samples of blood or saliva.

Most epidemiologic studies of the health effects of ETS have assumed linear exposure-response relationships. Summaries of many of the effects of ETS on human health are available in the recent review articles listed in Table 1. Data on exposure-response for lung cancer relative work in relation to cumulative exposure is presented in Figure 6. The regression lines in this figure suggest a linear relationship, but the data points that are plotted therein are also consistent with a J-shaped relationship.

DIOXIN AND RELATED COMPOUNDS

The issue of the shape of the exposure-response relationship for dioxin (2,3,7,8-Tetrachlorodibenzo-p-dioxin, aka TCDD) and related components was a controversial topic in the EPA Science Advisory Board (SAB) review (USEPA, 2001) of EPA's Risk Reassessment for dioxin. The related compounds include 17 dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs), as well as 13 planar polychlorinated biphenyls (PCBs) that all

TABLE 1 Summary of Significant Health Effects Associated with ETS Exposures

Effects	Review Paper
Cardiovascular Disease Endpoints	Jousilahti <i>et al.</i> (2002)
Stroke	
Myocardial Infarction	
Coronary Heart Disease	
Abnormal ECG	
Respiratory Disease Endpoints in Elderly	Jaakkola (2002)
Lung Cancer	
Chronic Symptoms	
Asthma	
COPD	
Respiratory Infections	
Lung Function Deficits	
Respiratory Disease Endpoints in Adults	Jaakkola and Jaakkola (2002a)
Acute and Chronic Symptoms	
Lung Function Deficits	
Asthma Induction and Exacerbation	
COPD	
Respiratory Infections	
Respiratory Disease Endpoints in Children	Jaakkola and Jaakkola (2002b)
Acute Symptoms	
Asthma Induction and Exacerbation	
Bronchial Hyperresponsiveness	
Lower Respiratory Illness	
Otitis Media	
Lung Function Deficits	
Respiratory Function Effects in Nonsmoking NHANES Adults	Eisner (2002)
Birthweight	Lindbohm <i>et al.</i> (2002)

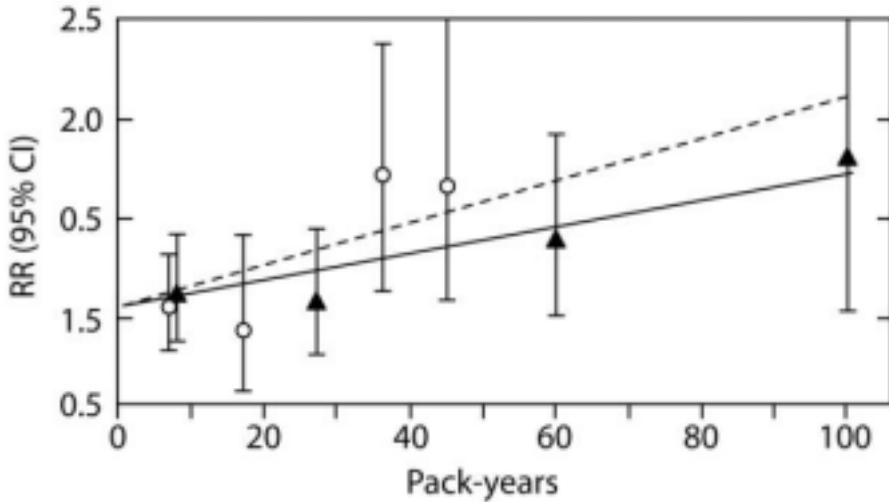


FIGURE 6 Relative risk of lung cancer by cumulative exposure to involuntary smoking. [Circles: Boffetta *et al.*, 1998, triangles: Fontham *et al.*, 1994]. Source: Boffetta. Scand J Work Environ Health 28(Suppl 2):30-40 (2002).

compete with TCDD for binding sites on the Ah receptor. Each compound has an assigned Toxicity Equivalence Factor (TEF). The Toxicity Equivalent Quotient for the mixture is the sum of the concentrations of dioxin-like compounds in the mixture multiplied by their corresponding TEFs.

In the SAB review (USEPA 2001), the Panel concluded that the actual shape of the low-dose exposure response relation could not be determined from the available data. Some Panel members believed that there may be evidence for anti-carcinogenicity of TCDD at low doses in the animal studies, and that EPA should have been more forthcoming about that evidence, i.e., the discussion should have been more complete, with consideration of what is known about the promoter-like characteristics of 2,3,7,8 TCDD. The Kociba (1978) study in rats actually showed a deficit for all tumors combined in all dose groups in comparison to the controls. That finding was statistically significant for the lowest two dose groups, and deficits in uterine, mammary, and pituitary tumors in female rats and pancreatic and adrenal tumors in male rats were statistically significant in the highest dose group. When the analysis was restricted to all malignant tumors, the data showed statistically significant deficits at the lower two doses and a statistically significant increase only at the highest dose (Kociba, 1982). The EPA risk reassessment document discounted most of the deficits as related to significant weight loss, but did not offer an explanation for the mammary tumor deficit. It also did not discuss the implications of significant weight loss on the evaluation of maximally tolerated dose. Without the highest dose, the Kociba experiment would have been judged negative. Kociba's

own conclusion was that the data “indicate that doses of TCDD sufficient to induce severe toxicity increased the incidence of some types of neoplasms in rats, while reducing the incidence of other types.”

Similarly, in the Pitot et al. (1987) study, the investigators examined the numbers and size of altered hepatic foci (AHF) in livers of adult female rats. The authors concluded in the abstract of the paper that “At several sub-threshold doses of PB and TCDD an inhibition of AHF formation and growth . . . was observed.” These findings from Kociba et al. (1978) and Pitot et al. (1987) suggested to some SAB Panel members that TCDD might be a net carcinogen at higher exposures but a net anticarcinogen at lower exposures, raising the possibility that TCDD would be an anti-carcinogen in the human population at current levels of exposure. The Panel concluded that EPA should acknowledge the possibility that reducing current body burdens of TCDD might lead to no change at all in cancer incidence, or even a net increase. Given the uncertainty in the data, the Panel agreed that choice of complex models cannot be justified.

The occupational epidemiological studies on the carcinogenesis of dioxin that EPA relied on in their risk reassessment were considered to be inconclusive by most members of the SAB Panel on the basis that most of them could not control for smoking or for exposures of the chemical plant workers to other toxic chemicals. Subsequent to the SAB Panel’s report, several papers have carefully reviewed the epidemiological studies of dioxin exposed workers.

Starr (2001) showed the all cancer standardized mortality ratios (SMRs) for the three largest occupational cohorts. As shown in Figure 7, the SMRs were above 1 for all but one of the cohorts, but were relatively independent on body burdens over a range extending over three orders of magnitude. I interpret these results as indicating that the SMRs were more likely elevated because of exposures to cigarette smoke and/or other workplace exposures than to dioxin exposure.

Crump et al. (2003) analyzed data from the same cohorts and fit a linear model to them. They concluded that there was a significant dose-related trend (See Figure 8). However, it is clear that this conclusion depends on the presence of the few very high doses on the right side of the plot.

Bodner et al. (2003) added 10 years of follow-up to the largest cohort (over 2,000 workers) within the NIOSH study, and “found no coherent evidence of increased cancer risk from dioxin exposure”.

Mackie et al. (2003) did an analysis of the NIOSH cohort and two non-occupational cohorts. They were a relatively large population exposed by a large accidental release in Seveso, Italy, and a relatively small population of military personnel exposed to Agent Orange in Vietnam (Ranch hand study). As shown in Figure 9, the data were fitted two ways. Giving equal weight to each study’s SMR showed a flat exposure-response relationship.

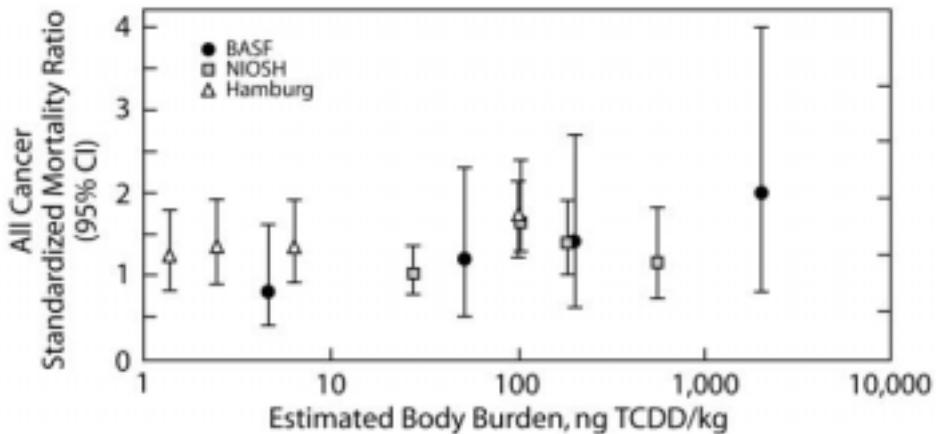


FIGURE 7 Standardized mortality ratios (SMRs) and 95% confidence intervals for all-cancer mortality versus estimated lifetime average TCDD body burden for twelve study/exposure subgroups in the initial dose-response analyses. Source: Starr. *Toxicol Sci* 64:7–13 (2001).

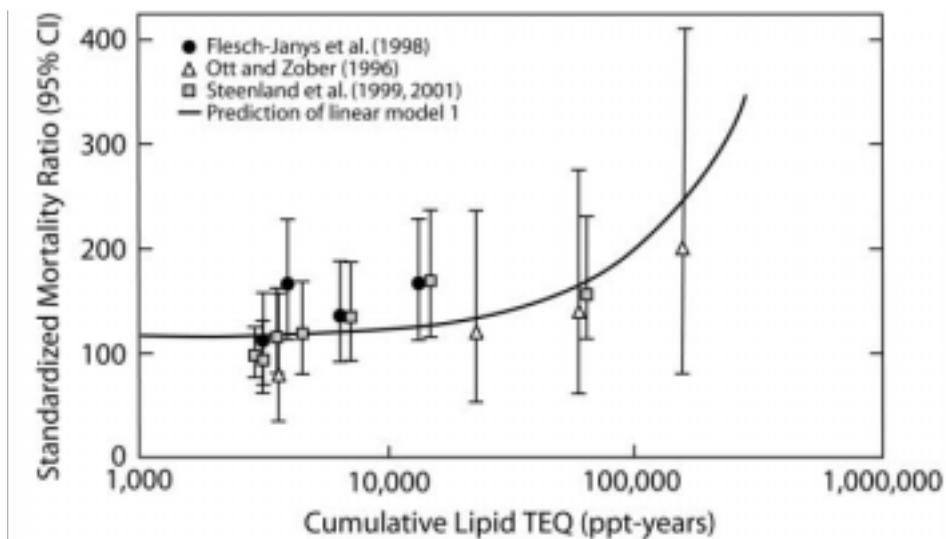


FIGURE 8 SMRs (with 95% confidence bounds) from three studies categorized by cumulative lipid concentration, adjusted to include background TEQ. Source: Crump *et al.*, *Environ Health Perspect* 111:681–687 (2003).

Weighting each study's SMRs according to population size suggests that lower dioxin exposures are protective against cancer.

In my view, these dioxin epidemiological data provide no convincing evidence that dioxin is carcinogenic to humans at exposures within several orders of magnitude of current general population exposures, and that hormesis may be consistent with these results.

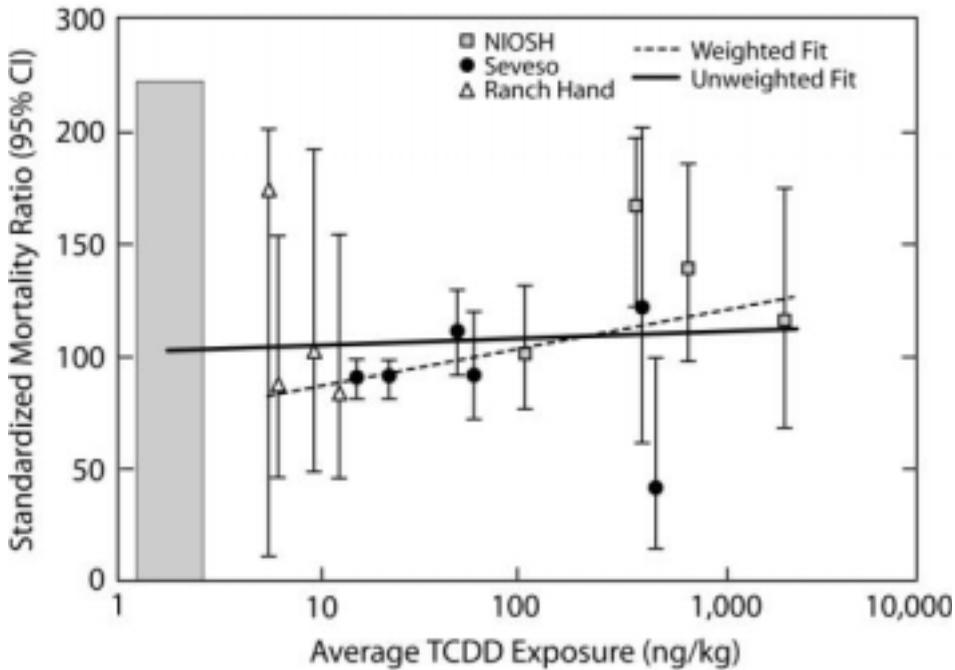


FIGURE 9 Population-weighted and unweighted linear-log regressions of SMR for all cancers versus TCDD exposure. The shaded area shows the range of general population TCDD exposures. Source: Mackie *et al.*, *Environ Health Perspect* 111:1145–1147 (2003).

OZONE

For a single toxicant like O_3 , it is possible to explore the nature of exposure-response for short-term exposures and acute responses in humans under controlled laboratory conditions and in field studies (Lippmann, 2000). Furthermore, O_3 is a very strong oxidant and has a limited range of reactions with lung cells and lung surface fluids. Despite these advantages, in comparison with the complex mixtures discussed previously, there are many variations in human responses to O_3 exposure that remain poorly understood. Well documented responses to short-term exposures include: deficits in pulmonary function; increased respiratory symptoms; increased hospital admissions for respiratory diseases such as asthma, influenza, pneumonia, and chronic obstructive pulmonary disease (COPD) (Lippmann, 2000). There are also increased rates of daily mortality as illustrated in Figure 10 from Thurston and Ito (2001). By contrast, chronic exposure to O_3 has less effect on lung function growth in children than other pollutants in ambient mixtures, such as nitrogen dioxide, acid vapors, and fine particles (Gauderman *et al.*, 2002), and no apparent effect on annual mortality rates (Pope *et al.*, 2002).

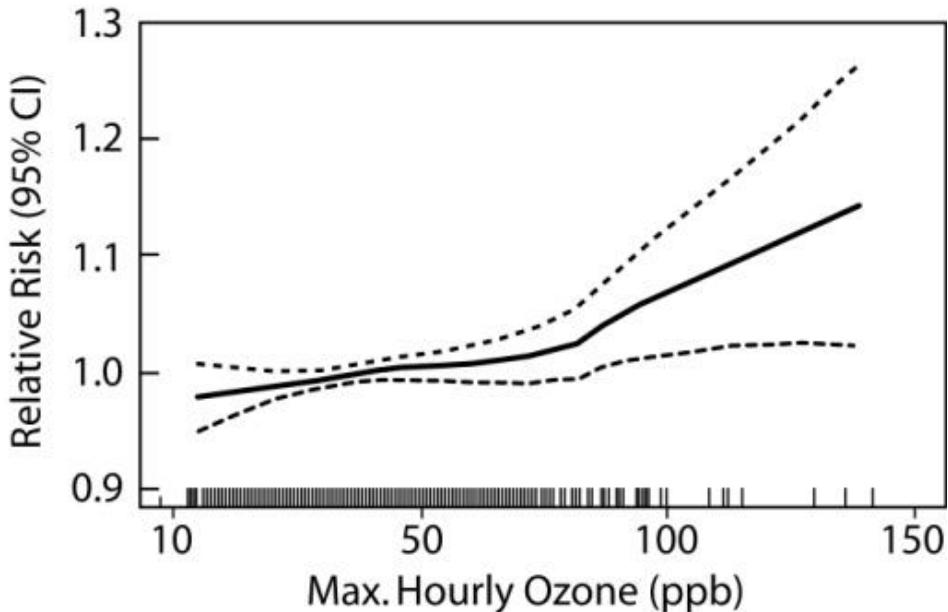


FIGURE 10 Total mortality RR versus O₃ concentration (adjusted for weather, season, day-of-week, and PM) in Detroit, MI. Source: Thurston and Ito. *Expos Anal Environ Epidemiol* 11:286–294 (2001).

In studies by Horstman et al. (1990) involving 6.6 hours of O₃ exposure in chambers at 80, 100 and 120 ppb with moderate exercise in young adult volunteers, the average deficit in forced expiratory volume in one second (FEV₁) grew steeper with each hour of exposure in a concentration related fashion (See Figure 11). However, when examining the variability of responses among those exposed in the same protocol (See Figure 12) it can be seen that some individuals exposed at 100 and 120 ppb had very little, if any, response, while others had FEV₁ reduced by half. It has also been shown that individuals have reproducible responses. Susceptibility factors that could account for such extreme variability have been sought, but not yet found, other than that the FEV₁ response varies with age (See Figure 13). It is also of interest that other health effects endpoints were measured in some of the volunteers who were exposed to O₃ in the series of 6.6 hr studies. Devlin et al. (1991) reported that a significant inflammatory response, as indicated by increased levels of neutrophils, was also observed in bronchoalveolar lavage fluid from subjects exposed to either 80 or 100 ppb O₃ for 6.6 hours. As illustrated in Figure 14, the 6.6 hours at 100 ppb O₃ produced a 3.8-fold increase in neutrophils at 18 hours after the exposure, whereas the 6.6 hours at 80 ppb produced a 2.1-fold increase. The amounts of O₃ inhaled in the 80 and 100 ppb protocols were about 2.0 and 2.5 μg, and about 3.6 μg in the 400 ppb protocol. Thus the effect of concentration was apparently somewhat greater than that of exposure dura-

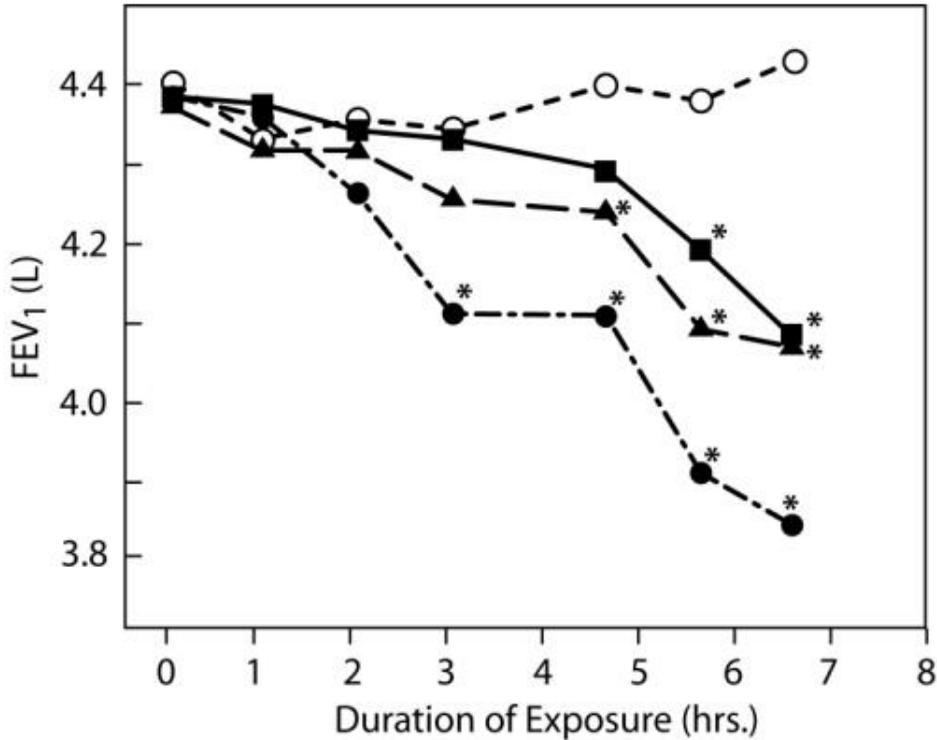


FIGURE 11 Mean FEV₁ after each 50 min of exercise during exposures to O₃ at 0 (open circles), 80 ppb (squares), 100 ppb (triangles), and 120 ppb (solid circles). Asterisks indicate significant reduction in FEV₁ from corresponding values at 0 ppb. From Horstman *et al.*, *Am Rev Resp Dis* 142:1158-1163 (1990).

tion. The significant increase in neutrophils at a concentration as low as 80 ppb suggests that lung inflammation from inhaled O₃ has no threshold down to ambient background O₃ levels.

Other studies indicate that the inflammatory process caused by O₃ exposure is promptly initiated (Seltzer *et al.*, 1986) and persists for at least 18 hours (Koren *et al.*, 1989). The time course of this inflammatory response and the O₃ exposures necessary to initiate it, however, have not yet been fully elucidated. Furthermore, these studies demonstrate that cells and enzymes capable of causing damage to pulmonary tissues were increased, and the proteins that play a role in the fibrotic and fibrinolytic processes were elevated as a result of O₃ exposure.

Of further interest is the fact that different individuals exhibit different kinds of responses to these controlled O₃ exposures. The levels of O₃-induced symptoms and respiratory tract injury and inflammation have not been closely correlated with the levels of decrements seen for FEV₁ or other functional parameters.

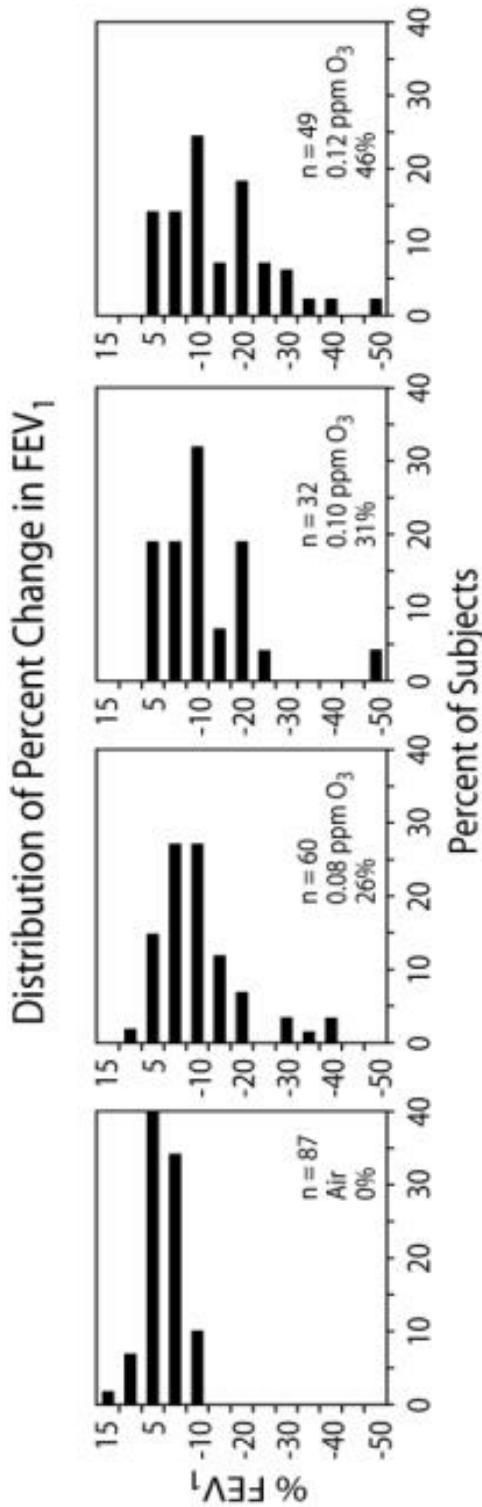


FIGURE 12 Percentage change in FEV₁ in healthy nonsmokers following 6.6 hours exposures to clean air and O₃ at 80, 100, and 120 ppb during exercise lasting 50 minutes of each hour for studies performed at EPA's Clinical Research Laboratory at Chapel Hill, North Carolina. Each box shows the number of subjects studied and the percentage of subjects with reductions in FEV₁ that were greater than 10%.

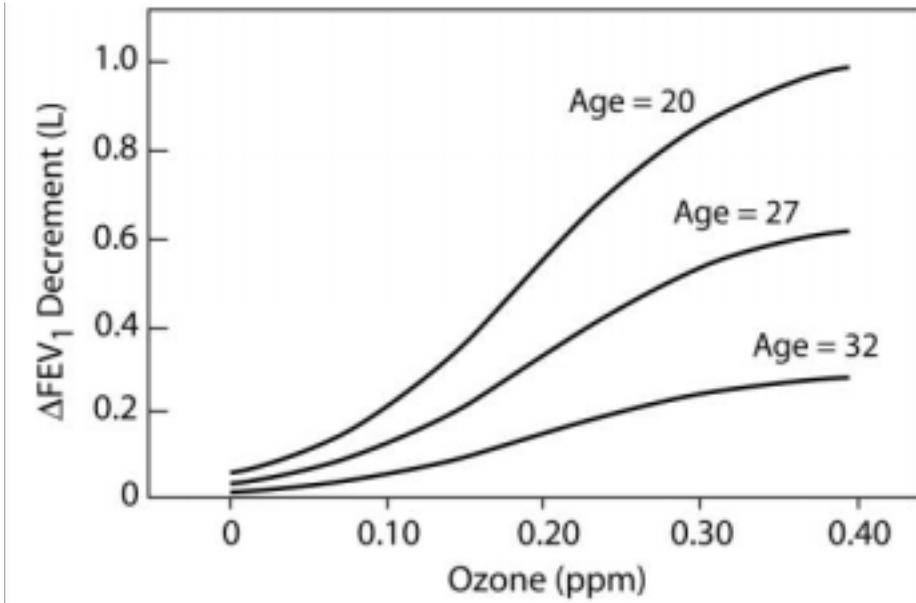


FIGURE 13 Predicted mean decrements in forced expiratory volume in L (ΔFEV_1) following 2 hours exposures to ozone while undergoing heavy intermittent exercise for three ages. (Note: To convert ΔFEV_1 to % ΔFEV_1 , multiply by 22.2%.) From: McDonnell *et al.*, *Am Rev Resp Dis* 147:818–825 (1993).

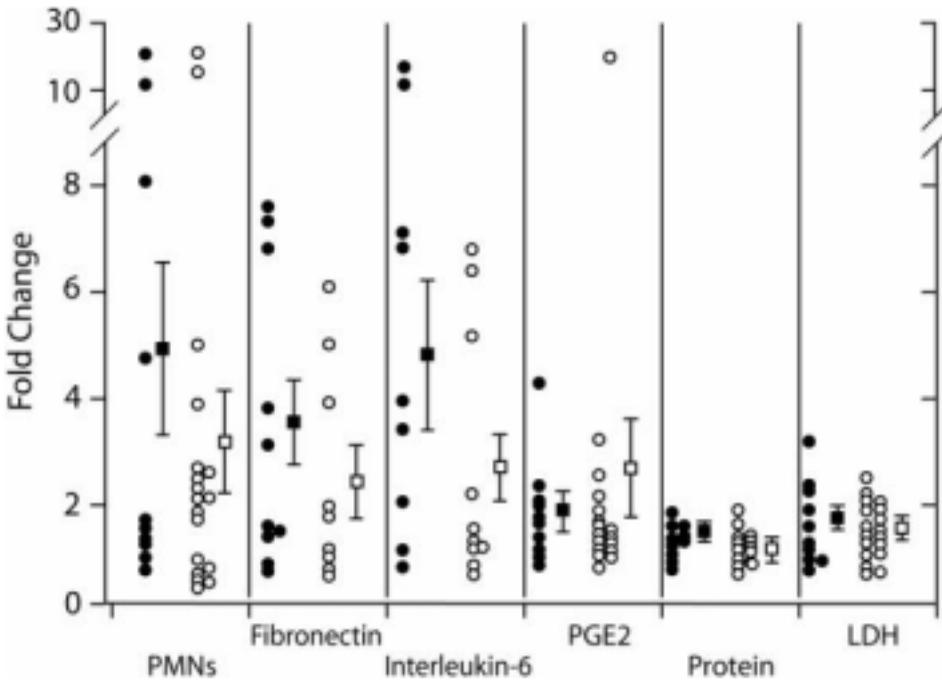


FIGURE 14 Range of subject response 18 hours after 6.6 hours of O_3 exposure at 100 ppb (closed circles) or 80 ppb (open circles). Squares indicate the mean changes ($\pm SE$). From: Devlin *et al.*, *Am J Resp Cell Mol Biol* 4:72–81 (1991).

In terms of epidemiological studies focussed on associations between community air concentrations to O_3 and health effects there is little evidence for non-linearity. Figure 15, from Burnett *et al.* (1984), illustrates an essentially linear relationship between daily O_3 1 hour peak levels and hospital admissions for respiratory diseases. Figure 16, from Yang *et al.* (2003), shows that effect size for respiratory hospital admissions varies with age, as noted earlier for controlled chamber exposure studies, with some differences for the elderly (age > 65 years) according to socioeconomic status.

In summary, even for a well-defined pollutant such as O_3 , which tends to be relatively uniform in outdoor concentration over broad geographic areas, it is difficult to determine if non-linear exposure-response relationships for general populations. Thus, the assumption of a linear, non-threshold relationship when establishing ambient air quality standards or issuing public health advisories appears to be reasonable and prudent.

ACKNOWLEDGMENTS

The research in this paper was supported, in part, by Center Grants ES 00260 from the National Institute of Environmental Health Sciences and R 827351 from the U.S. Environmental Protection Agency.

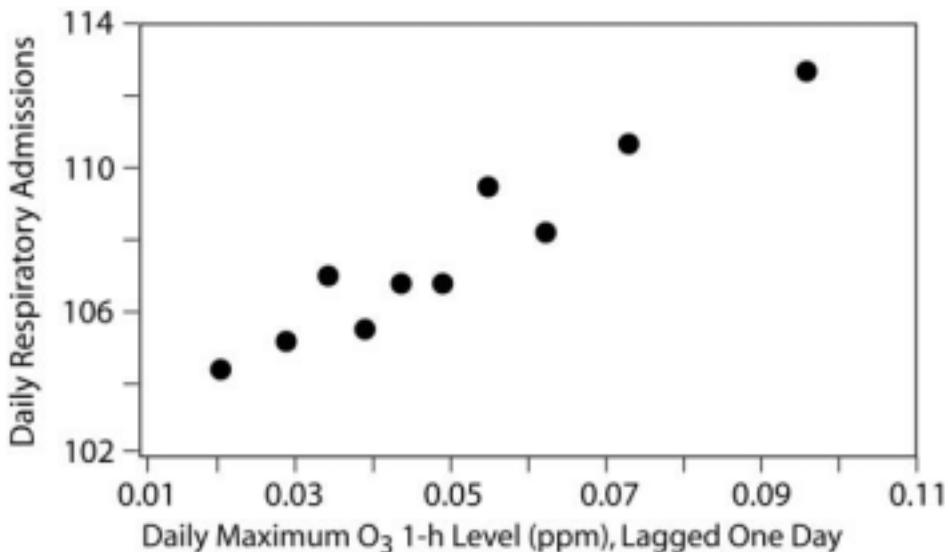


FIGURE 15 Average number of adjusted respiratory admissions among all 168 hospitals by decile of the daily 1 hour maximum ozone level (ppm), lagged 1 day. From: Burnett *et al.* (1984).

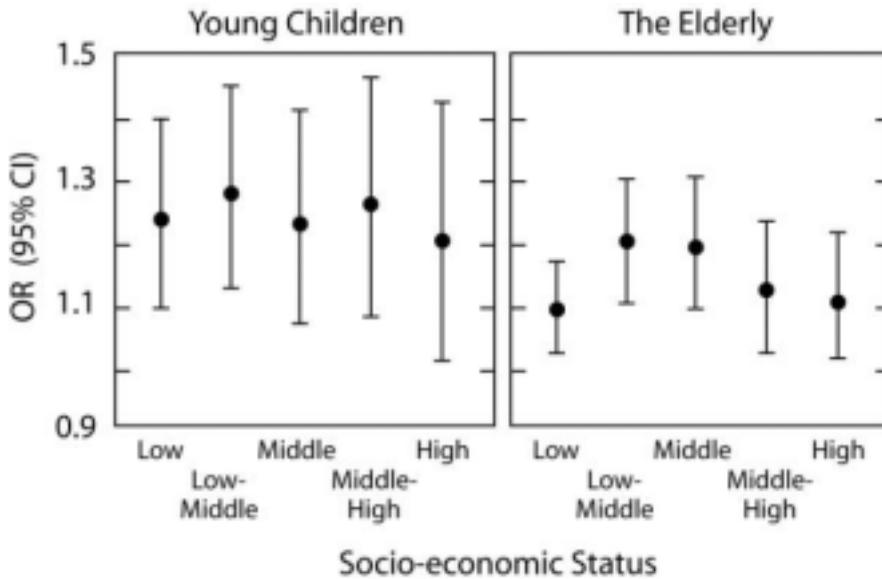


FIGURE 16 Adjusted odds ratios (95% confidence intervals) for respiratory admission associated with ozone adjusted for copollutants (carbon monoxide, nitrogen dioxide, sulfur dioxide, and CoH) exposures by socioeconomic status, Vancouver, Canada, 1986–1998. Source: Yang et al. *Inhal Toxicol* 15:1297–1308 (2003).

REFERENCES

- Bodner KM, Collins JJ, Bloemen LJ, and Carson ML. 2003. Cancer risk for chemical workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Occup Environ Med* 60:672–675
- Boffetta P. 2002. Involuntary smoking and lung cancer. *Scand J Work Environ Health* 28(Suppl 2):30–40
- Burnett RT, Dales RE, Raizenne ME, Krewski D, Summers PW, Roberts GR, Raad-Young M, Dann T, and Brook J. 1994. Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. *Environ Res* 65:172–194
- Clarke RW, Coull B, Reinisch U, Catalano P, Killingsworth CR, Koutrakis P, et al. 2000. Inhaled concentrated ambient particles are associated with hematological and bronchoalveolar lavage changes in canines. *Environ Health Perspect* 108:1179–1187
- Creason JJ, Neas L, Walsh D, Williams R, Sheldon L, Liao D, Shy C. 2001. Particulate matter and heart rate variability among elderly retirees in the Baltimore 1998 study. *J Expos Anal Environ Epidemiol* 11:116–122
- Crump KS, Canaday R, and Kogevinas M. 2003. Meta-analysis of dioxin cancer dose response for three occupational cohorts. *Environ Health Perspect* 111:681–687
- Devlin RB, McDonnell WF, Mann R, Becker S, House DE, Schreinemachers D, and Koren HS. 1991. Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. *Am J Respir Cell Mol Biol* 4:72–81
- Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, and Speizer FE. 1993. An association between air pollution and mortality in six U.S. cities. *N Engl J Med* 329:1753–1759
- Dominici F, Daniels M, McDermott A, Zeger SL, and Samet JM. 2003. Shape of the exposure-response relation and mortality displacement in the NMMAPS database. In: *Revised analyses of time-series studies of air pollution and health*. Special Report, pp 91–96. Available: <http://www.healtheffects.org/news.htm> [16 May 2003]

- Eisner MD. 2002. Environmental tobacco smoke exposure and pulmonary function among adults in NHANES III: Impacts on the general population and adults with current asthma. *Environ Health Perspect* 110:765–770
- EPA. 2003. Draft of Air Quality Criteria for Particulate Matter. Research Triangle Park, NC: National Center for Environmental Assessment-RTP Office, Report No. EPA/600-P-99/002 (Dec. 2003)
- Gauderman WJ, Gilliland GF, Vora H, Avol E, Stram D, McConnell R, Thomas D, Lurmann F, Margolis H, Rappaport EB, Berhane K, Peters JM. 2002. Association between air pollution and lung function growth in Southern California children. *Am J Respir Crit Care Med* 166:76–84
- Ghio AJ, Kim C, and Devlin RB. 2000a. Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. *Am J Respir Crit Care Med* 162:981–988
- Godleski JJ, Verrier RL, Koutrakis P, Catalano P, Coull BA, Reinisch U, et al. 2000. Mechanisms of morbidity and mortality from exposure to ambient air particulate. Research Report #91, Cambridge, MA: Health Effects Institute
- Gold DR, Litonjua A, Schwartz J, Lovett E, Larson, A, Nearing B, et al. 2000. Ambient pollution and heart rate variability. *Circulation* 101:1267–1273
- Gong H Jr, Sioutas C, Linn WS, Clark KW, Terrell SL, Terrell LL, Anderson KR, Kim S, and Chang M-C. 2000. Controlled human exposures to concentrated ambient fine particles in metropolitan Los Angeles: Methodology and preliminary health-effect findings. In: Phalen RF (ed), *Inhalation Toxicology: Proceedings of the third colloquium on particulate air pollution and human health (first special issue)*; June, 1999; Durham, NC. *Inhal Toxicol* 12(suppl. 1): 107–119
- Gordon T, Nadziejko C, Chen LC, and Schlesinger R. 2000. Effects of concentrated ambient particles in rats and hamsters: An exploratory study. Cambridge, MA: Health Effects Institute; research report no. 93
- Gordon T, Nadziejko C, Schlesinger R, and Chen LC. 1998. Pulmonary and cardiovascular effects of acute exposure to concentrated ambient particulate matter in rats. *Toxicol Lett* 96–97:285–288
- Harder SD, Soukup JM, Ghio AJ, Devlin RB, and Becker S. 2001. Inhalation of PM_{2.5} does not modulate host defense or immune parameters in blood or lung of normal human subjects. *Environ Health Perspect Suppl.* 109(4):599–604
- Jaakkola MS and Jaakkola JJK. 2002a. Effects of environmental tobacco smoke on the respiratory health of adults. *Scand J Work Environ Health* 28(Suppl 2):52–70
- Jaakkola JJK and Jaakkola MS. 2002b. Effects of environmental tobacco smoke on the respiratory health of children. *Scand J Work Environ Health* 28(Suppl 2):71–83
- Jaakkola MS. 2002. Environmental tobacco smoke and health in the elderly. *Eur Respir J* 19:172–181
- Jousilahti P, Patja K, and Salomaa V. 2002. Environmental tobacco smoke and the risk of cardiovascular disease. *Scand J Work Environ Health* 28(Suppl 2):41–51
- Kociba RJ and Schwetz BA. 1982. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *Drug Metab Rev* 13(3):387–406
- Kociba RJ, Keyes DG, Beyer JE, Carreon RM, Wade CE, Dittenber DA, Kalnins RP, Frauson LE, Park CN, Barnard SD, Hummel RA, and Humiston CG. 1978. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin study in rats. *Toxicol Appl Pharmacol* 46:279–303
- Koren HS, Devlin RB, Graham DE, Mann R, McGee MP, Horstman DE, Kozumbo WJ, Becker S, House DE, McDonnell WF, and Bromberg PA. 1989. Ozone-induced inflammation in the lower airways of human subjects. *Am Rev Respir Dis* 139:407–415
- Laden F, Schwartz J, Speizer FE, and Dockery DW. 2001. Air pollution and mortality: A continued follow-up in the Harvard Six Cities Study. *Epidemiology* 12:S81 (Abstract)
- Liao D, Creason J, Shy C, Williams R, Zweidinger R. 1999. Daily variation of particulate pollution and poor cardiac autonomic control in the elderly. *Environ Health Perspect* 107:521–525
- Lindbohm ML, Sallmen M, and Taskinen H. 2002. Effects of environmental tobacco smoke on reproductive health. *Scand J Work Environ Health* 28(Suppl 2):84–96
- Lippmann M and Maynard RL. 1999. Air quality guidelines. In: Holgate ST, Koren HS, Samet JM, and Maynard RL (eds), *Air Pollution and Health*, pp 983–1017, Academic Press, London
- Lippmann, M. 2000. Ozone. In: Lippmann M (ed), *Environmental Toxicants: Human Exposures and Their Health Effects*, 2nd edition, pp 655–723. Wiley-Interscience, New York, NY
- Mackie D, Liu J, Loh YS, and Thomas V. 2003. No evidence of dioxin cancer threshold. *Environ Health Perspect* 111:1145–1147

- Nadziejko C, Fang K, Chen LC, Cohen B, Karpatkin M, and Nadas A. 2002. Effect of concentrated ambient particulate matter on blood coagulation parameters in rats. Boston, MA: Health Effects Institute. Available: <http://www.healtheffects.org/Pubs/Nadziejko.pdf>
- Nadziejko C, Fang K, Gordon T, and Chen LC. 2001. Quantitative analysis of arrhythmias. Presented at the Workshop on Cardiovascular Effects Associated with Air Pollution, 7–8 March 2001, University of Rochester
- Peters A, Dockery DW, Muller JE, Mittleman MA. 2001. Increased particulate air pollution and the triggering of myocardial infarction. *Circulation* 103:2810–2815
- Petrovic S, Urch B, Brook J, Datema J, Purdham J, Liu L, Lukic Z, Zimmerman B, Toffler G, Downar E, Corey P, Tarlo S, Broder I, Dales R, and Silverman F. 1999. Cardiorespiratory effects of concentrated ambient PM_{2.5}: A pilot study using controlled human exposures. In: Phalen RF (ed), *Inhalation Toxicology: Proceedings of the third colloquium on particulate air pollution and human health (first special issue)*; June, 1999; Durham, NC. *Inhal Toxicol* 12(Suppl 1):173–188
- Pitot HC, Goldsworthy TL, Moran S, Kennan W, Glauert HP, Maronpot RR, and Campbell HH. 1987. A method to quantitate the relative initiating and promoting potencies of hepatocarcinogenic agents in their dose-reponse relationship to altered hepatic foci. *Carcinogenesis* 8:1491–1499
- Pope CA III, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, and Godleski JJ. 2004. Cardiovascular mortality and long-term exposure to particulate air pollution. *Circulation* 109:71–77
- Pope CA III, Verrier RI, Lovett EG, Larson AC, Raizenne M, Kanner ME, et al. 1999a. Heart rate variability associated with particulate air pollution. *Am Heart J* 138:890–899
- Pope CA III, Dockery DW, Kanner RE, Vollegas GM, Schwartz J. 1999b. Oxygen saturation, pulse rate, and particulate air pollution: A daily time-series panel study. *Am J Respir Crit Care Med* 159:365–372
- Pope CA, III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, and Thurston GD. 2002. Lung cancer, cardiopulmonary mortality and long-term exposure to fine particulate air pollution. *J Am Med Assoc* 287:1132–1147
- Saldiva PHN, Clarke RW, Coull BA, Stearns RC, Lawrence J, Krishna-Murthy GG, Diaz E, Koutrakis P, Suh H, Tsuda A, and Godleski JJ. 2002. Lung inflammation induced by concentrated ambient air particles is related to particle composition. *Am J Respir Crit Care Med* 165:1610–1617
- Seltzer J, Bigby BG, Stulbarg M, Holtzman MJ, and Nadel JA. 1986. O₃-induced changes in bronchial reactivity to methacholine and airway inflammation in humans. *J Appl Physiol* 60:1321–1326
- Starr TB. 2001. Significant shortcomings of the U.S. Environmental Protection Agency's latest draft risk characterization for dioxin-like compounds. *Toxicol Sciences* 64:7–13
- Thurston GD and Ito K. 2001. Epidemiological studies of acute ozone exposures and mortality. *J Expos Anal Environ Epidemiol* 11:286–294
- USEPA (U.S. Environmental Protection Agency). 2001. Dioxin Reassessment—An SAB Review of the Office of Research and Development's Reassessment of Dioxin. EPA-SAB-EC-01-006. Science Advisory Board, Washington, DC
- Wellenius GA, Coull BA, Godleski JJ, Koutrakis P, Okabe K, Savage ST, et al. 2003. Inhalation of concentrated ambient air particles exacerbates myocardial ischemia in conscious dogs. *Environ Health Perspect* 111:402–408
- Yang Q, Chen Y, Shi Y, Burnett RT, McGrail KM, and Krewski D. 2003. Association between ozone and respiratory admissions among children and the elderly in Vancouver, Canada. *Inhal Toxicol* 15:1297–1308
- Zelikoff JT, Chen LC, Cohen MD, Fang K, Gordon T, Li Y, Nadziejko C, and Schlesinger RB. 2003. Effects of inhaled ambient particulate matter on pulmonary antimicrobial immune defense. *Inhal Toxicol* 15:131–150
- Zelikoff JT, Nadziejko C, Fang K, Gordon T, Premdass C, and Cohen MD. 1999. Short-term, low-dose inhalation of ambient particulate matter exacerbates ongoing pneumococcal infections in *Streptococcus pneumoniae*-infected rats. In: Phalen R and Bell Y (eds), *Proc. of the Third Colloquium on Particulate Air Pollution and Human Health*, p 8–94