Responses to CASAC questions on the Ozone ISA from Consultant Dr. Frederick W. Lipfert

Introduction

Ozone differs from other pollutants in important ways. I begin my response with a discussion that illustrates some of them, including nonlinearities that affect the development and interpretation of C-R functions and thus presumption of causality. I also provide some C-R estimates from the literature and some epidemiological background. This information is pertinent to many of the CASAC questions and presenting it here avoids duplication. Appendices include abstracts of 2 papers that may be unfamiliar to CASAC and lists of pertinent references.

Background Discussion of Ozone

Ozone (O_3) is a gaseous pollutant not directly emitted from outdoor sources but created in the *troposphere* by reacting with NO_x and volatile organic compounds (VOCs) in the presence of ultraviolet (UV) light. This is why s*tratospheric* ozone protects against harmful UV radiation. Figure 1 shows the complex patterns of these reactions based on photochemical modeling.

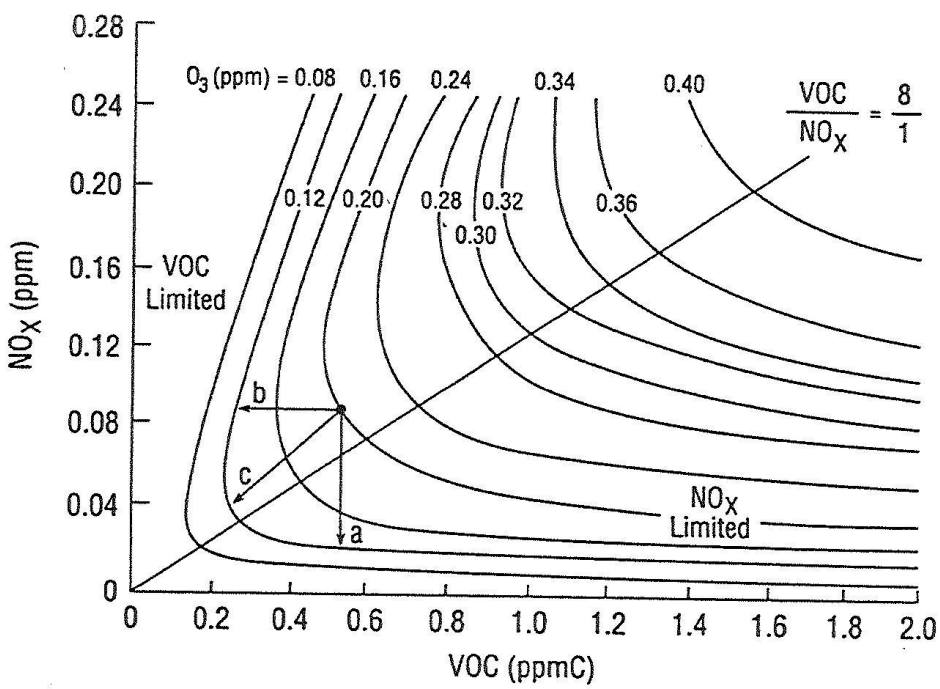

Figure 1. Dependence of ozone on NOx and VOCs (Kleinman and Lipfert, 2003). Current ozone levels (~70 ppb) are near the origin of this plot and the national average NO_x is about 0.02 ppm (Lipfert and Wyzga, 2018). O_3 photochemistry is greatly accelerated at ambient temperatures above 70^0F (Figures 2 and 3), leading to a nonlinear relationship. Above about 80^0F, peak urban O_3 increases by about 4 ppm per degree that would lead to an increase of about 80 ppb at 100^0F relative to about 60 ppb for temperatures around 70^0F. Figure 3 illustrate geographic differences among small cities and rural areas. Note that O_3 at Mammoth Cave, KY, is about 50 ppb higher on hot days than in North Dakota but that levels tend to be similar under more normal conditions. Time-series studies of acute ozone relationships usually control for temperature, which also has strong nonlinear health effects, especially

for the frail elderly. However, only a few long-term studies have attempted to do so, including the Veterans Cohort studies (Lipfert et al., 2000 et seq.)

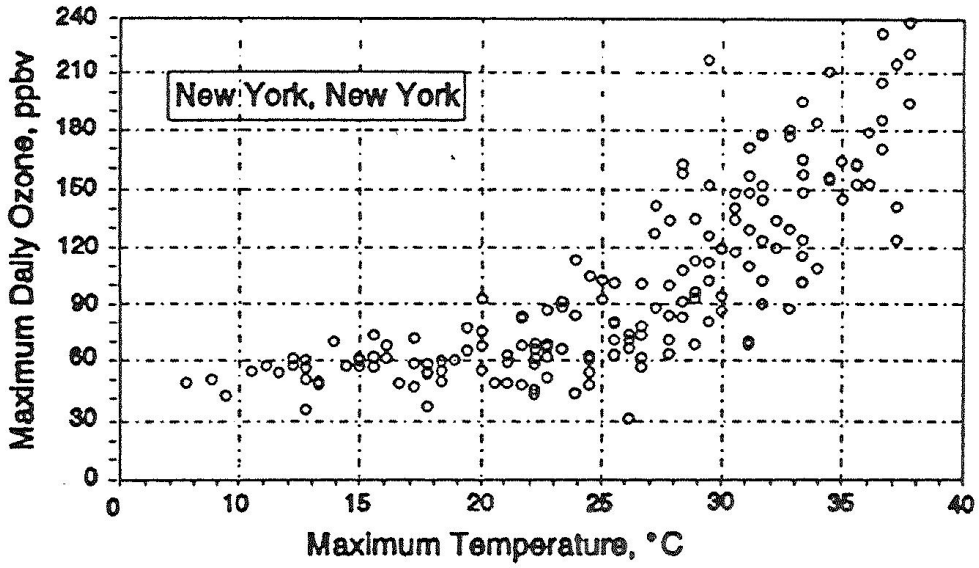

Figure 2. Temperature dependence ozone in New York City (Kleinman and Lipfert, 2003).

Ambient ozone has very different temporal and spatial relationships with respect to other air pollutants, with both diurnal and seasonal peaks (Figure 4). Outdoor workers would thus appear to be most at risk and persons remaining indoors during daylight less so. Urban ozone levels are often high because of high local levels of NO_x and VOCs; those photochemical reactions continue downwind in urban plumes, leading to episodic O_3 levels in suburban and rural areas up to ~100 mi downwind. As a result, exposure patterns based on ambient monitors may be difficult to interpret and gradients in annual. O_3 has no domestic indoor sources and tends to be adsorbed onto indoor surfaces (Kruza et al., 2017) such that indoor levels may be only 20-30% of outdoor. Foley et al. (2003) reported that EPA considered outdoor ambient air quality from fixed ambient monitoring sites to be a "surrogate for exposure".

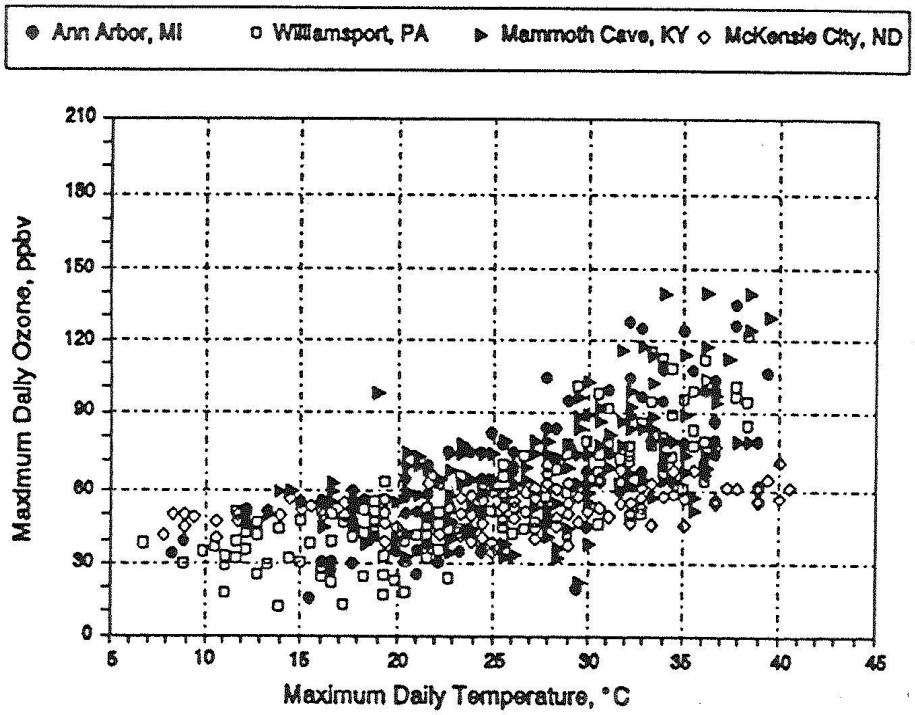

Figure 3. Temperature dependence of daily maximum ozone in 4 U.S. locations

Causality

Epidemiology is concerned with establishing cause and effect, often beginning with statistical associations, but some cautions are in order beyond statistical significance; we need to understand the entire system. The mere presence of a pollutant in the atmosphere does not constitute a "cause", for which personal exposures and translocation to a target organ are required. A long-term "effect" relates to damage to a target organ and implies specific mechanisms; excess mortality or admission to hospital may be a *consequence* of such clinical effects. However, there are exceptions. Acute heat wave mortality cannot always be ascribed to a specific mechanism may result from failure to maintain homeostasis which may also be the case for peak exposures to various air pollutants (Frank and Tankersley, 2002). Cigarette smoking may have different chronic health effects through various mechanisms but has been established as causal. Ammonia and formaldehyde are well-known respiratory irritants.

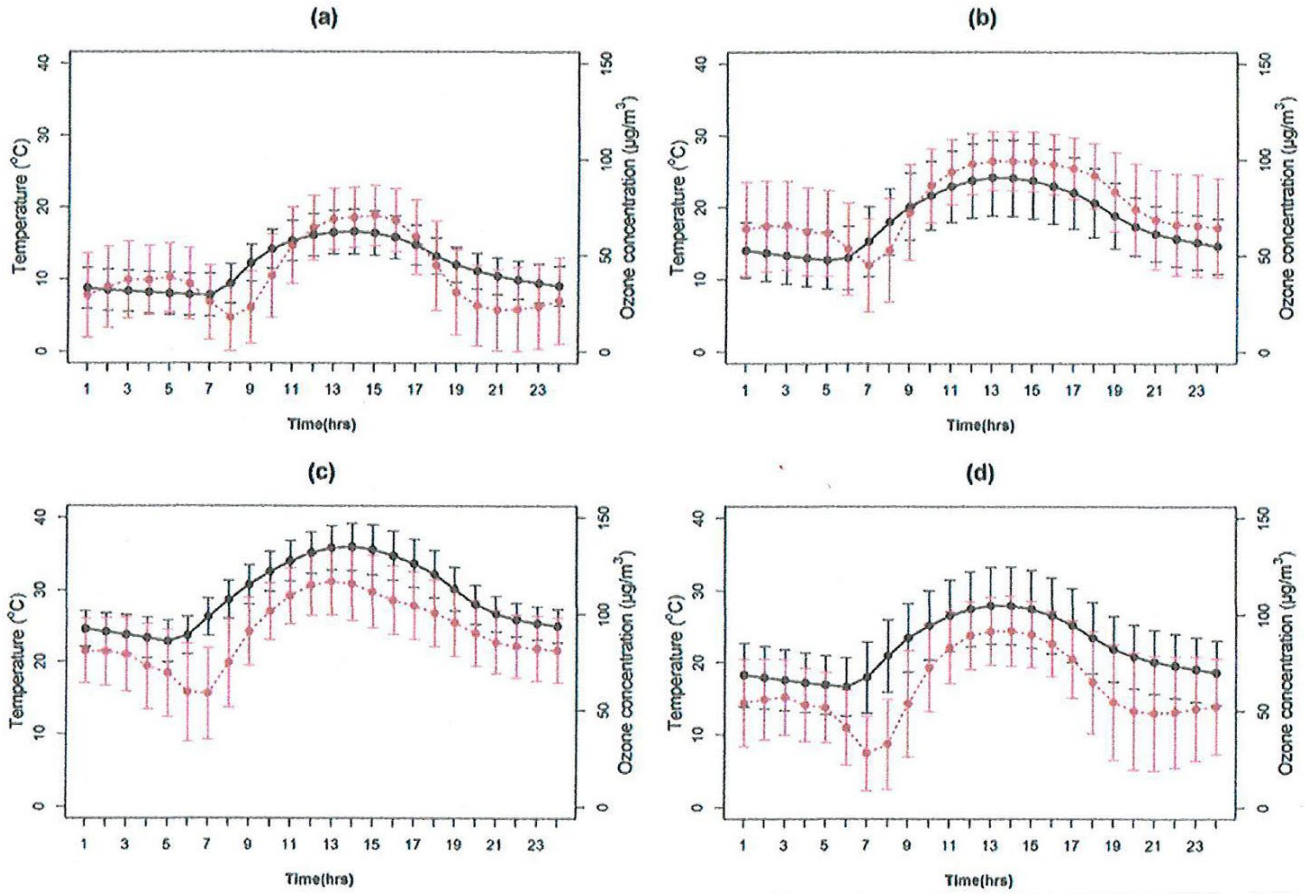

Figure 4. Diurnal variability in temperature (back) and ozone (red) by season. (a) winter. (b) spring. (c) summer (d) autumn. From Pyrgou et al., 2018

Validation of causality through experimental exposures

Comparing health indicators before and after a known exposure is perhaps the most definitive expression of causality and accountability. This was accomplished after the 1952 fog episode in London by autopsies. Time-series analyses in which an endpoint such as daily mortality or admission to hospital rises and falls synchronously with ambient air quality may also qualify after accounting for seasonal cycles, temperature, and co-pollutants. Controlled human exposures may be the most direct means of validation. Figure 5 shows an example for peak ozone.

These experiments were specific to pure ozone without complications arising from ambient co-pollutants such as other photochemical oxidants. They involve precisely determined exposures without measurement error, facilitating identification of thresholds (e.g.,~20 ppb in the above example). Individual test subjects are identified as they would be in a cohort. Lung function is the endpoint in this example and may be related to other endpoints through statistical analysis.

Figure 5 also illustrates potential pitfalls in the assumption of linearity. The data show diminishing benefits from O_3 abatement as the air gets cleaner, as might be expected. However, a linear relationship

based on O_3 > 60 ppb would have predicted a threshold around 35 ppb, while the nonlinear C-R clearly shows residual risk.

This experimental protocol is problematic for PM, in no small part because ambient PM is not a chemical but rather a mixture that varies in time and place. In previous decades, a device was developed that concentrated ambient particles (CAPS) centrifugally to as much 50 times the local ambient level. Various subjects including humans were tested for various endpoints. However, no pulmonary function impacts were ever found with CAPS experiments (A. Ghio, personal communication Oct. 21, 2019), Graff et al., 2009). It thus appears that health effects on healthy subjects have been validated experimentally for peak ozone but not PM.

However, experiments can provide evidence of health effects under controlled conditions and thus conditions and establish that ozone *may* be harmful to human health. Epidemiology is required to illustrate the conditions under which such health effects *have actually been observed* and the subpopulations most at risk.

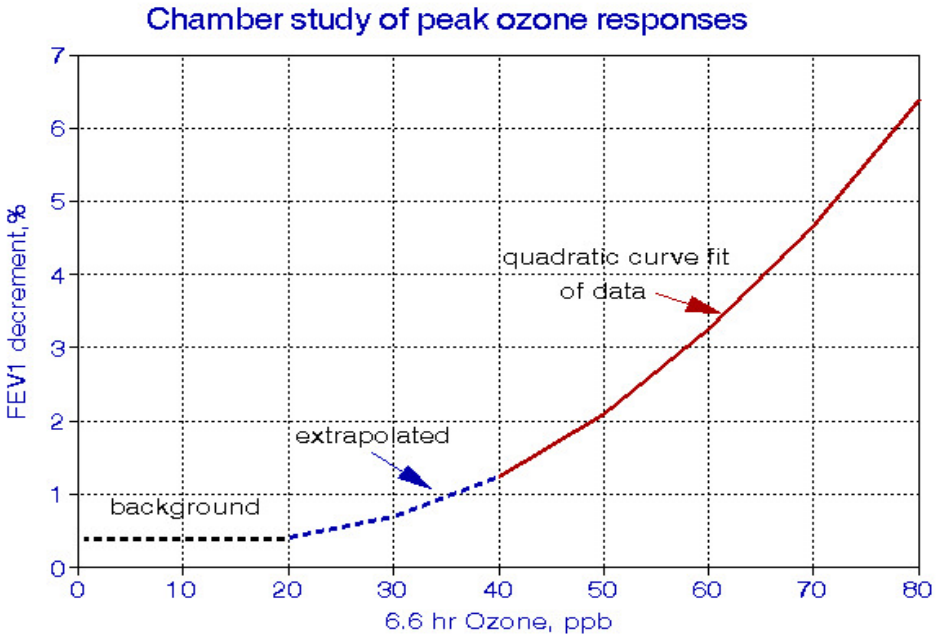

Figure 5. Results of controlled exposures in young healthy adults. Mean decrements in ozone-induced forced expiratory volume in 1 second (FEV_1) after 6.6 hours of exposure. Adapted from Figure ES-3 from the 2019 PA.

Figure 6 compares short-term ozone effects on health subjects' lung function decrements from Figure 5 with daily mortality effects in the U.S. Medicare population (Qian Di et al., 2017). The two C-R relationships are very nearly parallel, implying a 1:1 relationship. However, the FEV_1 data imply a quasi-threshold (as modified in Figure 1), while the mortality data do not, as predicted by Frank and Tankersley (2002) and shown experimentally in impaired mice. I interpret those experiments as supporting the time-series model of Murray and Lipfert (2012). There is another important distinction between non-lethal experiments on humans and statistical analysis of populations.

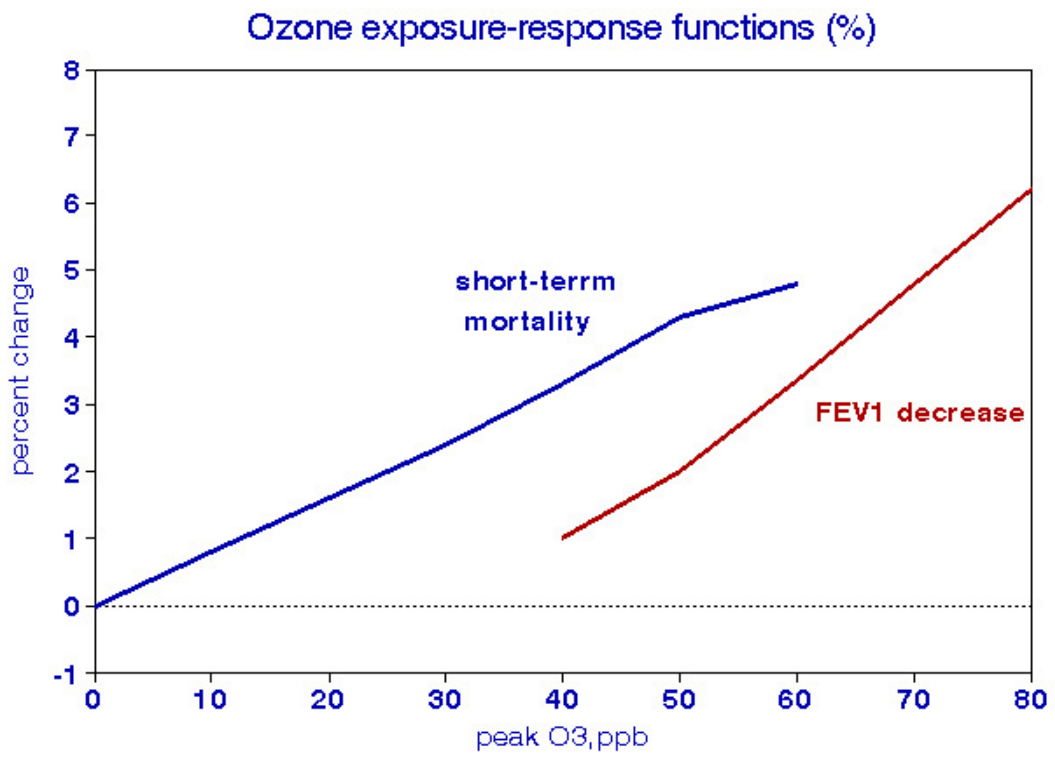

Figure 6. Daily mortality (Qian Di et al., 2017) and lung function decrement (Figure ES-3) as a function of ozone.

Causality in air pollution epidemiology entails five requirements, two of which have been established for peak O_3 (but not long-term mean) levels:

1. Exposure (no). Indoor exposures and daily peaks have not been considered in long-term studies. Initiation of chronic disease only occurs after a latency period and responds to cumulative exposures. This has been shown for smoking but not for air pollution epidemiology. Indoor exposures are not mentioned in Chapter 6.
2. Toxicity (yes). Adverse short-term respiratory effects have been shown in human and animals under specified conditions for selected groups of subjects.
3. Translocation (no). Inhalation of a pollutant is not sufficient to imply contact with an organ and initiation of cardiovascular disease. Associations of O_3 with adverse effects outside the respiratory system are problematic.
4. Susceptibility (yes). Time-series studies have shown that acute mortality is associated with both underlying frailty and daily air pollution peaks. Given the diversity of populations, the notion that a healthy person could be randomly selected to die coincidently with normal levels of ambient air quality is unreasonable.
5. Accountability (no). The ultimate test of causality is whether health has actually improved since the late 1970s in response to peak O_3 levels reduced by a factor of 5 in conjunction with coincident trends in spatial patterns of reduced smoking and improved medical care. A search of PubMed found no support for such improvement. By contrast Lipfert and Wyzga (2018) showed peak O_3 risk coefficients increasing over time.

Ozone – mortality risk coefficients from the literature

I summarized ozone mortality risk estimates for both long-and short-term exposures from my publications and from the literature in Table 1 (note that my publications have not been included in EPA ISAs. In general, there is a lot of heterogeneity among these estimates, even within the same cohort. However, the long-term estimates from my publications are reasonably self-consistent, more so than those from other studies (Table 1(a)). The overall average long-term risk is 0.076. All of the risk estimates in Table 1 are based on mean O_3 concentrations, not the traditional 10 ppb increment. (Note that health effects of $PM_{2.5}$ have traditionally been based on an increment of 10 μgm^3, which is higher than the national average of 8 10 μgm^3, while the 10 ppb increment for ozone is much lower than the national average.)

The short-term (daily) risk estimates presented in Table 1(b) are based on the average of lags 0 and 1 as has been the custom in many studies. I also show the risk estimates as accumulated up to lag 4, based on Figure 6 (a factor of ~3), with a mean of 0.095. The short-term risk estimates are also quite diverse, leading to the conclusion of no significant difference between long and short terms and thus no truly long-term effects.

I found no evidence of O_3 thresholds in short-term risks (Figure 6) and none would be expected with the Murray frailty model. Since the spatial analyses of long-term risks include short-term risks, the conclusion of no threshold applies to all of the studies. This in turn indicates that the demand of the Clean Air Act for an adequate margin of safety cannot be met.

Table 1. Estimates of ozone-mortality risk coefficients from the literature

(a) Long-term all-cause mortality risks based on the mean value of 95%-ile O_3

1. U.S. ecological study at ages 65-74 (Lipfert and Morris, 2002)

mort period	O_3 period	mean risk	lag (y)
1970-74	1970-74	0.0279	0
1979-81	1979-81	**0.0303**	0
1979-81	1970-74	**0.0415**	7
1989-91	1989-91	**0.0612**	0
1989-91	1979-81	**0.0331**	10
1989-91	1970-74	**0.0405**	17
1995-97	1995-97	**0.158**	0
1995-97	1989-91	**0.0608**	6
1995-97	1979-81	0.0261	16
1995-97	1970-74	**0.0409**	24

2. Veterans Cohort studies (Lipfert et al., 2000)

mort period	O_3 period	mean risk	lag (y)
1976-81	1976-81	**0.102**	0
1982-88	1982-88	**0.146**	0
1982-88	1976-81	**0.100**	7
1989-96	1989-96	0.035	0
1989-96	1982-88	0.060	7
1989-96	1976-81	-0.010	14

Bold = $p < 0.05$, overall mean = **0.0825 (0.66–0.99)**

3. Other long-term studies of all-cause mortality based on mean values of the O_3 metric

location (1st author)	period	O_3 metric	mean risk
all US (Di, 2017)	2000-12	annual mean	0.051
all US (Turner, 2016)	1982-04	8-h max	0.107
all US (Jerrett, 2009)	1977-00	daily max	0.005
California (Jerrett, 2013)	1982-00	monthly av'g	-0.02
Canada (Crouse, 2015)	1991-06	8-h max	0.13

mean risk = 0.055 (-.002-0.112)

Table 1 (b) Short-term mortality risks based on mean values of the O_3 metric

location (1st author)	period	O_3 metric	lag 0,1 risk	cumulative risk*
Atlanta (Klemm,	1998-00	max 8-h	0.037-0.064	0.084-0.19
Chicago (Murray, 2012)	1987-00	mean	0.030	0.09
Philadelphia (Lipfert, 2000)	1992-5	mean	0.028-0.04	0.084-0.12
Philadelphia (Lipfert, 2012)	1974-88	daily max	0.014	0.043
US Medicare (Bell, 2004)	1987-00	weekly mean	0.018	0.052
US Medicare (Qian Di, 2018)	2000-12	peak	0.05	0.15

*cumulative risk based on 3x average of lag 0,1 mean risk = **0.095 (0.056-0.13)**

For comparison, ISA Figure 6-8 shows long-term hazard ratios for 9 North American studies based on 10 ppb that would have a mean risk coefficient of about 0.036 when scaled up a mean concentration of 40 ppb. Three foreign studies had statistically significant negative effects. ISAS Figures 6-1 and 6-2 show short-term mortality risk coefficients for the entire year and for the warm season for all causes, cardiovascular, and respiratory deaths for fixed concentration increments. Warm season risks were substantially higher for respiratory deaths but not total or cardiovascular deaths, in spite of the higher ambient concentrations in summer. which suggests co-pollutant effects. Figure 6-1 shows all-cause all-year risk coefficients for 15 short-term studies that average about 1.5% per standard increment that I estimate as 0.044 (0.012-0.072) on the basis of mean concentrations. The ISA studies are for averages of lags 0-2; estimated cumulative risks would be much larger and similar to the values in Table 2(b) above.

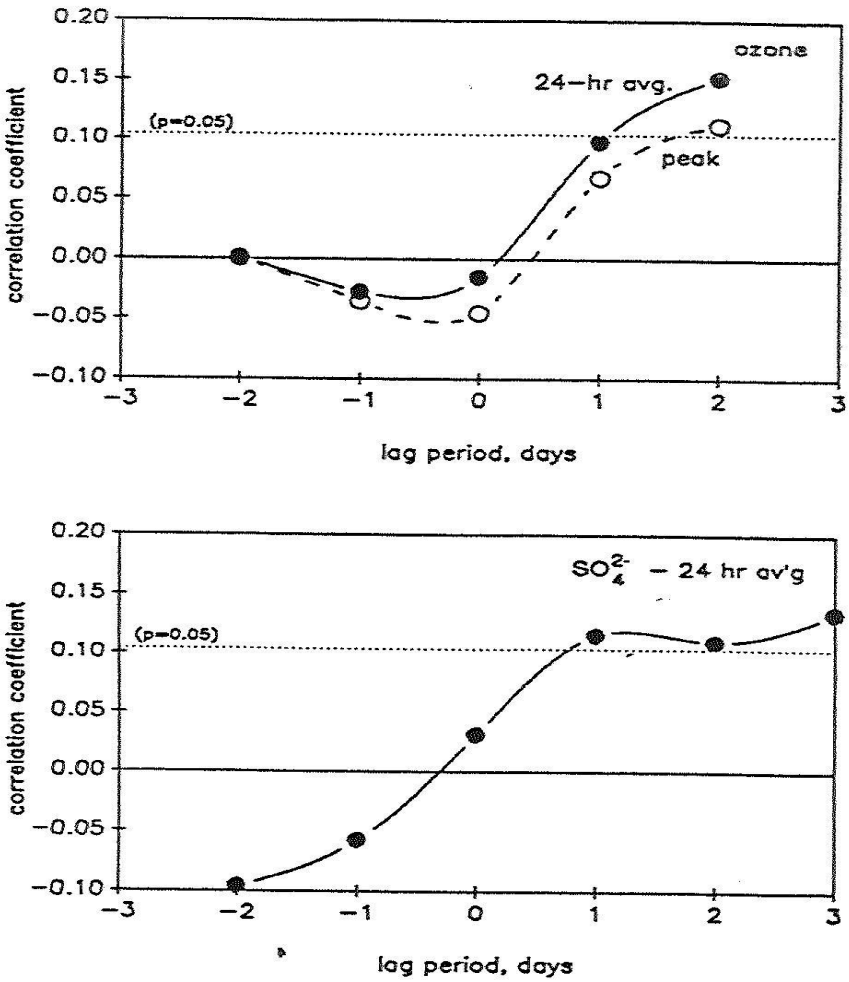

Figure 7. Lag effects on time-series risk coefficients (Lipfert and Hammerstrom, 1992)

Summary of (common sense) ozone epidemiology

I focus on premature mortality as the health endpoint driving cost-benefit analyses. Ozone is a known respiratory irritant associated with symptoms, lung function, and mortality from respiratory diseases. Co-pollutants such as PM may be involved, but PM risks have not been demonstrated experimentally. Ozone exposures vary substantially diurnally and by season but effective control measures must be based on worst-case scenarios and not on long-term averages. Ozone is greatly attenuated indoors but outdoor frequency distributions persist. EPA stated that "exposure has a much more direct link to potential health effects than air quality" (Foley et al., 2003). This principle has been overlooked in more recent years. Indoor exposures are not considered in the discussions of health effects (Chapter 6). Note that peak ozone and temperature are colinear outdoors but not indoors when residential air conditioning is used.

Both short- and long-term associations with all-cause mortality have been shown for specific cohorts and populations, but short-term exposures are included in long-term assessments. Any true long-term effects must thus be based on *differences* between long- and short-term risk estimates. Bona-fide long-term responses that initiate new cases of disease could only could occur as a result of cumulative

exposures following a period of latency. Long-term studies in the ISA have not recognized these precepts.

Short-term (daily) effects have been substantially underestimated in the literature. Most were based on the average of the day of death and the following day (lags 0,1), but the true yield of an event must be the sum over the lag period that may be up to three times higher (Figure 7). In addition, indoor concentrations may be only 20-40% of outdoors, such that the risk per unit of personal exposure must be even greater.

Most of the air pollution epidemiology has considered entire cohorts or populations as if all members were at the same risk; however, healthy subjects are at much less risk than those with previous impairments. Short-term deaths are likely to have resulted from loss of homeostasis (Frank and Tankersley, 2002) that may be exacerbated in the frail elderly most at risk. Time-series analyses based on the Murray-Nelson (2000) model have considered frailty as a necessary factor in addition to air pollution and temperature (Murray and Lipfert, 2012). They found that the elderly subpopulations most at risk comprised a small fraction of those aged 65 and over and that their degrees of prematurity were a matter of days, even over exposure periods up to 15 days. These findings have not been considered in ISAs or cost-benefit analyses. The Murray-Nelson model posits that short-term premature death results from the combination of frailty and pollution exposure, such that *either* extreme frailty or high pollution exposure may be responsible. Accordingly, thresholds in either factor alone are proscribed. Linear C-R functions have been shown for short-term ozone exposures as shown in Figure 6.

Table 1 shows that long-term mortality risks estimated from spatial gradients are no larger than those estimated from time-series analyses of short-term peaks. Since the short-term is included in the long term, I conclude that there are no truly long-term mortality effects associated with O_3 exposures, which is consistent with the strong attenuation of O_3 indoors. I also conclude that there is no evidence for a threshold in mortality responses to ozone, which is supported by:

- lack of threshold in lung function decrements in tests of healthy humans
- lack of threshold in daily mortality responses
- importance of frailty in conjunction with ozone in time-series analyses
- confirmation of loss in homeostasis as the driving mechanism in impaired animals.

Figure 5 shows that a NAAQS of 70 ppb implies a lung function decrement of about 4.7%. If we assume a 1:1 relationship between lung function decrement and risk of premature mortality as seen in Figure 6, the mortality risk over background would be 4.3% or 1 in 23, which most people would find excessive. Reducing that risk to 1 in 100 would require a NAAQS of about 42 ppb, which might be very difficult to attain.

My overall conclusion from the above is that a risk-free NAAQS for ozone cannot be determined at any level above background and certainly not as high as 70 ppb. It thus follows that society must determine a tolerable level of risk, taking into account the presence of extreme frailty. This situation was not considered in the framing of the Clean Air Act.

Summary discussion of the ISA

This is a 1400+ page document for which a thorough review is far beyond the scope of this CASAC question-and-answer investigation. I found the determination of "causality" to be simplistic and notional, as discussed above. As evidence of subjective selection of epidemiology studies, I note that only one of my studies is included (see Table 1 above), but the authors saw fit to mention a study of O_3 exposure and erectile disfunction. (I resisted the opportunity to discuss this further.) Studies with wide confidence intervals were included. There is insufficient linkage between sections, for example between indoor and personal exposures and epidemiology. I found no discussion of accountability, latency in disease incidence, cumulative exposures in epidemiology, comparisons of short- vs. long-term risks, translocation from lung to bloodstream. I conclude that the ISA does not offer convincing evidence of ozone exposure as a cause of long-term health effects in the general population. By contrast, I find the short-term evidence to be more convincing but note that the ISA should compare the two types of studies.

Background references

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Responses to Questions from Dr. James Boylan

Appendix 1 – Atmospheric Source, Chemistry, Meteorology, Trends, and Background

- *Is the discussion on metrics and definitions (Section 1.2) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on sources of U.S. ozone and its precursors (Section 1.3) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on ozone photochemistry (Section 1.4) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on inter-annual variability and longer-term trends in meteorological effects on anthropogenic and U.S. background ozone (Section 1.5) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on measurements and modeling (Section 1.6) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on ambient air concentrations and trends (Section 1.7) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on U.S. background ozone concentrations (Section 1.8) accurate and complete? If not, what additional information needs to be included?*

Sorry, I don't have much to contribute here. I would just point out that for EPA, ambient "ozone" is defined by the "reference" method used to measure it, which applies to inferred health effects as well. It would be of interest to determine how that ambient "ozone" compares to what is used in controlled chamber experiments. It would also be of interest to compare the relationships shown in Figure 1 with actual field experiments.

Background O_3 levels should be discussed in terms of epidemiology and residual risks, including personal and indoor levels, seasonal, and temporal variations, and thresholds. The present discussion of time-activity patterns is inadequate.

Appendix 2 – Exposure to Ambient Ozone

Is the discussion on exposure concepts (Section 2.2) accurate and complete? If not, what additional information needs to be included?

Foley et al. (2003) reported that EPA considered outdoor ambient air quality from fixed ambient monitoring sites to be a "surrogate for exposure". This precept must be directly acknowledged. In this sense, ambient air quality is primarily one of many descriptors of places (county, SMSA, urban vs. rural, etc).

- *Is the discussion on exposure assessment methods (Section 2.3) accurate and complete? If not, what additional information needs to be included?*

- *Is the discussion on personal exposure (Section 2.4) accurate and complete? If not, what additional information needs to be included?*

No. Information on indoor ozone is required including spatial and temporal variations.

- *Is the discussion on copollutant correlations and potential for confounding (Section 2.5) accurate and complete? If not, what additional information needs to be included?*

  No. Co-pollutant data (correlations) should include ambient temperature and should be discussed in terms of temporal (hourly) and geographic (urban vs. rural, regional) distributions, especially high vs. low traffic areas.

- *Is the discussion on interpreting exposure measurement error for use in epidemiology studies (Section 2.6) accurate and complete? If not, what additional information needs to be included?*

  The failure to consider indoor ozone is the major source of exposure error. Because of differences in indoor concentrations co-pollutant effects will differ between outdoor and personal exposures.

Appendix 9 – The Role of Tropospheric Ozone in Climate Effects

- *Is the discussion on ozone impacts on radiative forcing (Section 9.2) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on ozone impacts on temperature, precipitation, and climate related variables (Section 9.3) accurate and complete? If not, what additional information needs to be included?*

I don't see how this is relevant to setting ambient standards, however interesting.

Responses to Questions from Dr. Tony Cox

Questions on causality: My question is: Can valid determinations of manipulative or interventional causation – that is, how and whether changing exposure would change health risks – be made based on observed associations of the types analyzed in the ISA?

No. See my discussion of causality above.

a. *Is this actually a "formal causal framework"?*

   No, it's a list of subjective rationalizations based on studies selected from the literature according to unspecified procedures. Appendix A lists my own studies not included in the ISA and Appendix B lists the results of relevant PubMed searches.

b. *Does the ISA's causal determination framework clearly distinguish between necessary and sufficient causation?*

   No. In this context there will always be exceptions because of the diversity of the populations at risk. The Clean Air Act anticipated this. This issue involves determination of thresholds.

c. *In other words, does a "causal relationship" determination imply a manipulative causal relationship?*

   Not in my opinion.

d. *Can causal determinations be incorrect? (Or, to the contrary, are they performative utterances?)*

   No, I see causality as binary (yes/no).

e. *If causal determinations can be mistaken, then is it clear how uncertainty about which category is correct should be (or has been) resolved in assigning a final causal determination category, as in Table ES-1 p. ES-5) of the ISA?*

   No. I do not.

f. *If causal determinations can be incorrect, then is it clear how observations could be used to test and falsify a given causal determination if it is not correct?*

   Laboratory experiments may determine whether a given type of response *can* happen. Epidemiology is required to determine under what circumstances it *does* happen.

g. *If causal determinations can be incorrect, then is the correctness of each causal determination in table ES-1 formally and transparently evaluated in the ISA? In other words, have formal rules for determining the correctness of the causal determinations in Table ES-1 (p. ES-5) from the data and evidence presented been explicitly stated, applied systematically, and the results documented? (If so, where?)*

No. I find Table ES-1 useless and completely subjective.

h. *Does a determination that an exposure-response (or concentration-response (C-R)) relationship is a "causal relationship" imply that it is entirely causal, with no contribution from incompletely controlled confounding, modeling errors and biases, or other non-causal sources?*

I see causality as binary, not conditional.

i. *Does a determination that a C-R relationship is a "causal relationship" imply 100% certainty that it is causal?*

No. My idea of causality demonstration involves physical determination by experiments, any of which may be subject to error and/or misinterpretation. There has been no longitudinal demonstration of public health benefits resulting from the major abatement of ozone exposure since the 1960s.

j. *Does a determination that a C-R relationship is a "causal relationship" imply that it is causal for every member of a population,* (No) *or might it be deemed "causal" if it is causal for a sensitive subpopulation only?*

Yes, because of the diversity of the population. "Causal" for some portion of the population is still causal but modifiers should be explored

k. *Are the five categories mutually exclusive?*

Probably not, but they don't merit detailed scrutiny.

l. *Can a body of evidence be categorized as "likely to be causal" if the probability of causality based on the evidence is less than 50%?*

No, but there are other issues, such as the magnitude of the pooled risk (see below).

2. Study selection and interpretation.

a. *Is it clear that the ISA's study selection process has successfully provided a comprehensive, trustworthy, and unbiased selection of the best available science on ozone and health effects?*

No. I saw no justification for the studies selected, which included none of mine or my colleagues. (see Appendix A).

b. *Is it clear why results from Moore (2008) are included and cited as "key evidence" but contrary results from Moore (2013) are excluded? More generally, is it clear that study inclusion and exclusion criteria were applied systematically and neutrally to identify and select the best and most up-to-date studies to inform the ISA's conclusions?*

No. Moore 2012 (2013?) cites temperature confounding as a fatal flaw. I would add failure to consider changes that likely varied spatially as well. It seems obvious that temporal changes should be investigated by time-series analysis in a variety of locations. It seems possible that the highly technical aspects of the 2012 Moore paper were beyond the capabilities of the ISA authors (as they are for me as well). These criticisms apply to Tetreault et al. as well.

c. *Are there other studies that are omitted from the ISA that should be included?*

Yes. See Appendices A and B to this response.

d. *Are there studies included in the ISA that should be omitted (e.g., because of uncontrolled confounding, obsolete or incorrect modeling assumptions, conclusions dependent on unverified assumptions, ecological fallacy, lack of causally relevant information, lack of design that can support valid causal inferences, or other methodological problems?)*

Of course, but one must assume that the most egregious examples would have led to rejection by peer review. My choice would be to retain all relevant studies and to compare their findings by methodological flaw. It is equally inappropriate to summarily reject papers based only on self-selected criteria as it is to accept them in that way.

e. *Do you find in the Executive Summary a clear explanation of the extent to which the key evidence supporting the ISA's causal determinations consists of, is sensitive to, or is derived from unverified modeling assumptions, or from modeling assumptions that more recent literature has found to be incorrect or inadequate? Have you found information in the ISA on sensitivity of causal determination conclusions to untested, uncertain, or incorrect assumptions? (If so, where? See Table Annex 6-1, cf p. 6-67 for a discussion of what should be done. Has it been done, and is it clear what the results were?)*

No.

I addressed the following material and questions from Dr. Cox in terms of the ISA's summaries in the executive summary (ES), the integrated summary (IS), and Chapter 6 in the body of the ISA.

b. *Were the epidemiological studies used to support the causal determinations summarized in Table ES-1 (p. ES-5) and Figure ES-2 (p. ES-6) appropriately designed and analyzed to provide valid scientific information and valid <u>causal</u> conclusions about effects of possible future <u>interventions</u> (rather than just conclusions about historical statistical associations)? More specifically, were studies relied on for the "causal" (for short-term respiratory effects) and "likely to be causal" (for short-term and long-term metabolic effects) determinations appropriately designed and analyzed to support valid inferences about manipulative/interventional causality? (See Appendix 3, for a discussion of epidemiological studies. See Table 3-3, p. 3-112, for a "Summary of evidence for a likely to be causal relationship between long-term ozone exposure and respiratory effects.") For these observational studies, were criteria for valid study design and analysis for causal inference (specifically for interventional causation) explicitly stated, systematically applied, and the results transparently presented? (If so, where?) For background on such criteria, see*

Campbell DT, Stanley JC (1963), Experimental and Quasi-Experimental Designs for Research, www.sfu.ca/~palys/Campbell&Stanley-1959-Exptl&QuasiExptlDesignsForResearch.pdf. (My concern here is about whether Table 3-3 and other parts of the ISA seek to draw causal conclusions from non-causal premises and from studies that were neither designed nor analyzed to produce valid causal conclusions or information about effects of future interventions. My key question here is: Is this concern justified?)

c. *Is it clear that the individual studies cited in support of the ISA's causal determinations of "causal" or "likely to be causal" adequately controlled for potential confounding and residual confounding by variables such as income and weather variables? Background: (For background on the importance of confounding by temperature, see e.g., Kai et al. (2018), "Does temperature-confounding control influence the modifying effect of air temperature in ozone-mortality associations?" This article concludes that using a categorical variable (e.g., a season indicator) to control for temperature yields highly significant ozone effects at high temperatures, but also significant residual confounding; and that adjusting for (nonlinear) effects of temperatures "substantially reduced ozone effects at high temperatures and residual confounding.") For example, Table 3-3 cites a study by Tétreault et al. as providing "Key Evidence" of "Cohort studies demonstrating an association with asthma development in children," which the ISA then interprets as "Evidence for a likely to be causal relationship between long-term ozone exposure and respiratory effects."(Emphases added.) In discussing potential confounding, Tétreault et al. state that "We present two confounder models in the results. The first was adjusted for sex and deprivation, whereas the second was adjusted for the same variables as well as the year of birth." The article does not mention temperature or weather variables. Tétreault et al. also note their "lack of information on risk factors at the individual level (e.g. socioeconomic status and smoking). We attempted to control for these factors with adjustments of our models using ecological deprivation variables, which are imperfect and may result in residual confounding." (Emphasis added.)*

   Questions: *Is the ISA well justified in interpreting the statistical association found by Tétreault et al. as key evidence for a "likely to be a causal relationship", given its design and limitations? Is it possible (or plausible) that the association instead reflects uncontrolled or incompletely controlled confounding?*

d. *Is it clear that the individual studies cited in support of the ISA's causal determinations of "causal" or "likely to be causal" have adequately controlled for biases due to exposure estimation errors or exposure misclassification errors? For example, Tétreault et al. caution that "First, individual exposure was modeled and not measured through the follow-up, so the quality of the associations depends on the quality of the exposure models. All associations reported in this study were estimated according to the exposure at the centroid of the residential postal code. This assumes that children would stay at home all day. Because a large proportion of a child's day can be spent outside the home (e.g., at school), where exposure to air pollutants might differ, misclassification bias may have been introduced in our study. Additionally, summer average O3 levels were used to estimate annual averages. Because summer O3 levels are higher than winter levels (Environment Canada 1999) in Canada, we may have overestimated annual average levels. Furthermore, although postal codes circumscribe a relatively small area in urban regions, postal codes may include much larger areas in rural regions. This difference in postal code size could lead to a degree of higher imprecision in exposure estimation in regions of the province that are less densely populated." (Emphasis added.) Does the ISA make adequately clear that the exposure*

concentrations that it reports (e.g., "32.1 ppb mean summer ozone concentration, based on 8-h midday avg" in Table 3-3) are in fact "modeled and not measured" values? Does it adjust correctly (e.g., using appropriate errors-in-variables methods) for potential biases due to such errors before interpreting the results as key evidence of a likely causal relationship? (If so, where?)

e. *Do you find in the Executive Summary, or elsewhere in the ISA, a clear explanation of the extent to which the key evidence supporting the ISA's causal determinations is sensitive to uncontrolled or incompletely controlled confounding and/or ecological associations? Page 3-193 of the ISA states that "Sensitivity analyses with alternate specifications for potential confounding inform the stability of findings and aid in judgments of the strength of inference from results." Is it clear how such sensitivity analyses were applied to individual studies (e.g., in interpreting the Tétreault et al. study as adequate to supply "Key Evidence" of a "likely to be causal" relationship)? Is it clear what the results of these sensitivity analyses were? Does the ISA make clear how such sensitivity analyses were used in informing specific causal determinations, and how sensitive the resulting causal determinations are to incompletely controlled confounding? (If so, where?)*

f. *More generally, is it clear how criteria for individual study quality were applied to each study used in making causal determinations, and what the results were? (See Table Annex 6-1, cf p. 6-67.) Is it clear how the limitations of each individual study were taken into account in causally interpreting their reported associations and in making causal determinations?*

g. *Does the ISA make clear how its causal determinations would change if evidence from associations caused by confounding, residual confounding, measurement error, or unverified modeling assumptions were excluded?*

4. *Is the biological evidence presented in the ISA to support causal determinations correctly stated, correctly interpreted, relevant for predicting effects of changes in the ozone NAAQS, and up-to-date? For example, should the role of the NLRP3 inflammasome in ozone-induced lung injury be discussed? (See e.g., Michaudel C, Couturier-Maillard A, Chenuet P, Maillet I, Mura C, Couillin I, Gombault A, Quesniaux VF, Huaux F, Ryffel B. Inflammasome, IL-1 and inflammation in ozone-induced lung injury. J Clin Exp Immunol. 2016 Mar 23;5(1):33-40; Xu M, Wang L, Wang M, Wang H, Zhang H, Chen Y, Wang X, Gong J, Zhang JJ, Adcock IM, Chung KF, Li F. Mitochondrial ROS and NLRP3 inflammasome in acute ozone-induced murine model of airway inflammation and bronchial hyperresponsiveness. Free Radic Res. 2019 Jul;53(7):780-790. doi: 10.1080/10715762.2019.1630735.) Is NLRP3 inflammasome activation relevant for ozone risk assessment and for determining whether changes in currently allowed ambient concentrations of ozone would affect public health?*
5. *Does the biological evidence presented in the ISA provide well-validated scientific information suitable for predicting the effects on public health of changing NAAQS standard for ozone?*
6. *Is each of the causal determinations summarized in Table ES-1 (especially those labeled "causal relationship" or "likely to be causal relationship") the only possible causal determination conclusion that is justified by, or consistent, with current scientific evidence? Could different causal determinations be equally well justified (or better justified) by the information presented, or by the totality of current scientific evidence?*
7. *Are there changes in the design, analysis, selection, or interpretation of individual studies or in the ISA's processes for interpreting and summarizing them that would improve the validity, credibility, and transparency of the ISA's scientific reasoning and conclusions?"*

Comments on the ISA's "Summaries of evidence" and related material relative to Dr. Cox's questions above

These tables (ES-1, for example) comprise the ISA's entire basis for determining causality and therefore the setting of NAAQS levels. I find them subjective and inappropriate for a scientific document. NAAAQS levels affect the entire nation in terms of air pollution control costs and warnings to the public about unhealthy air, and the ISA should use quantitative methods of evaluation for this purpose, rather than subjective judgements.

For example, the ISA used meta-analyses in summarizing welfare effects but not health effects, despite the latter's key role in cost-benefit analysis. The risk estimates in Tables 6-1 and 6-3 and Figures 6-1, 6-2 and 6-8 should be pooled and weighted by inverse variance to derive overall mean estimates and their confidence intervals. This would provide quantitative measures from which the ISA's users could judge for themselves about consistency across studies and hence causality. Consistency (confidence intervals) and any apparent outliers could indicate whether the heterogeneity among studies may be random or the result of study design and the control of confounders. If the latter, subsets of studies having different confounder controls (especially non-linear temperature effects) should be compared.

I note that lags in in Figures 6-1 and 6-2 are mainly 0-2 days while up to 6-d lag is mentioned on p. IS-28. The synthesis (p. IS-1) does not discuss relevant exposure metrics: annual, 8-d, or daily maximum concentrations. Figures 6-1 and 6-2 pooled these metrics using arbitrary increments (15, 20, 25 ppb) without indicating which studies used which increments; these risk estimates are thus ambiguous at best. I recommend using the overall mean concentration to express risk estimates, which is also useful in comparing pollutants, multi-pollutant model results, and short- vs. long-term risks. It is not clear whether any of the short-term estimates summed risk estimates over the lag period, including distributed lags.

The relative magnitudes of the various health effect indicators must be discussed. We would expect them to decrease according to the severity of the effect (larger risks for asthma attacks compared to premature mortality; larger effects on short-term than long-term effects, as discussed above).

Table 6-1. Short-term effects on mortality

The comments below refer to the table's the six sections of decreasing "evidence".

Section 1. It is not clear how "high quality" is determined.

Section 2. Co-pollutant relationships depend on relative measurement errors and say nothing about the validity of either pollutant.

Section 3. "Support for a linear C-R" does not indicate validity. A noisy relationship will appear to be linear in any event. Thresholds can be obscured by indoor air pollution effects.

Section 4. The validity of cardiovascular effects depends on a biological pathway from lung to heart, which has not been shown specifically. Lack of "consistent human exposure studies" is a red flag. In addition, long-term effects cannot be tested experimentally. Figure 6-2 is inconsistent with cardiovascular effects.

Section 5. No comment.

Section 6. Latitude and temperature are important for *all* long-term studies, even the "high quality" ones. Figure 6-4 indicates nonlinear temperature effects and the absence of thresholds which are not adequately discussed

Table 6-2. Long-term effects on mortality

This table comprises four sections of decreasing "evidence" for long-term associations including four subdivisions for the first (Section 1): limited and sometimes "high quality", for which "consistency" seems to be the main criterion. Each of its four subdivisions deals with different models but the overall impression across the four subdivisions is one of inconsistency.

Section 2. Co-pollutant models with varying correlations. Is the implication that the copollutants pose no independent risk? What does this imply for the single-pollutant models? Why are co-pollutants not considered in short-term studies? Co-pollutant effects vary indoors.

Section 3. The implications of linear vs. sublinear C-R functions on causality should be discussed.

Section 4. Biological plausibility should be the primary consideration.

Summary: these comparisons should be quantitative, not qualitative.

Summary comments on causality and study selection.

Cause (causality) is a noun or verb and not an adjective (causal) as used throughout the ISA. It is binary, like pregnancy.

To preclude subjective selections, *all* peer-reviewed studies should be considered regardless of the journal impact factor or the authors' perceived reputations (which I assume has been termed "high quality"); we assume that the peer review process eliminated obvious errors or inappropriate models. (See my catalogue of long-term morbidity studies (Lipfert, 2015); if a single unsupported investigator can sort through ~400 relevant papers, it should not be too much to ask of the ISA authors.) Studies should be grouped by short- vs. long-term, country, endpoint, time period, season, subject characteristics, and (subjective) compliance with the following criteria:

- Is it likely that the exposure estimates used represent personal exposures of the individuals at risk? This requires indoor exposures to be considered.
- Is it likely that all pertinent confounders have been considered, including co-pollutants and climate?
- Is it likely that the pollutants and confounders are linearly related to risk?
- Are there plausible pathways between lung and target organs?
- Are the implied temporal relationships plausible (lags in time-series studies, latency in long-term studies, previous exposures)?

- Are the subjects of the study representative of the general U.S. public?
- Have interactions been properly considered, such as subject age with long-term exposure?
- Does the magnitude of the mean risk pose an important public health concern (1%, no; 10% yes)?

This protocol would shift the judgement process from the authors' overall conclusions to the internal elements of the study. The question thus becomes, given responses to the above criteria, are the authors' conclusions supported, including their estimated confidence intervals? At this point, the ISA could consider to what extent ambient ozone indeed poses health risks and under what conditions, including time scales, based on pooled risk estimates.

The current ozone ISA does not present coherent or convincing evidence for either long- or short-term mortality effects, in large part due to its format and structure.

Questions from Dr. Mark Frampton

1. Change in causality determination for short-term cardiovascular effects since the 2013 ISA.

Background: Table ES-1 and section ES.4.1 of the Executive Summary, and Appendix 4, cardiovascular (CV) health effects. The 2019 ozone ISA has downgraded the causality determination for short-term ozone exposure and cardiovascular effects from "likely" (2013 ISA) to "suggestive". This was due in part to new human clinical studies of CV effects that are inconsistent with the few studies available in 2013, but also to persistent weaknesses in the epidemiological evidence, as reviewed in Appendix 4.1.

Question 1: Please comment on the strengths and weaknesses of the epidemiology literature with regard to CV effects of short-term ozone exposure. Are there key studies that are missing? Are the remaining weaknesses, along with the other new evidence, sufficient to justify the change in causality determination?

The "likely to be causal" categories are lists of subjective rationalizations based on studies selected from the literature according to unspecified procedures; see my general discussion of causality above in which experimental evidence is key. I see mortality causality as binary, ozone can be deadly or not. Morbidity effects should be evaluated in terms of severity and permanence. Epidemiology is then needed to determine under what conditions and how differences among the studies can be explained. In so doing, the time scales of responses are critical. The time-series studies involving frailty by Murray and colleagues have been ignored; Their model posits that frailty is key in short-term mortality by virtue of inability to maintain homeostasis. In that model, differences within the population at risk are key.

2. Metabolic effects, new determination of "likely" for both short- and long-term exposure.

Background: Table ES-1 and section ES.4.1 of the Executive Summary, and Appendix 5, Metabolic Effects.

"Metabolic effects" include effects on body weight, appetite, body composition, caloric intake, diabetes, glucose, insulin, lipid metabolism, stress responses, and thyroid function. Note that "metabolic effects" differ from the issue of metabolic abnormalities as risk factors for other responses. For example, obesity may affect the pulmonary responses to short-term ozone exposures; this should not be considered a "metabolic effect". This new determination is driven largely by animal toxicology studies, mostly in rodents, and a single human clinical study showing evidence of acute responses in circulating stress hormones.

Question 2: Is there sufficient epidemiological evidence of metabolic effects to justify the "likely" determination for both short- and long-term exposures? Are there additional studies that should be considered?

No. The relevance of metabolic effects depends on the demonstration of pathways from the lung to the organs in question. Missing this information, the results are merely associations. Animal and clinical studies are limited to short-term (daily) effects from peak exposures that are unlikely to relate to translocated mechanisms and subsequent longer-term responses.

3. Change in causality determination for total mortality since the 2013 ISA.

Background: Table ES-1 and section ES.4.1 of the Executive Summary, and Appendix 6, Health Effects-Mortality.

The 2019 ozone ISA has downgraded the causality determination for short-term ozone exposure and total mortality from "likely" (2013 ISA) to "suggestive". However, Figure 6-1 on page 6-6, summarizing the epidemiologic studies of short-term total mortality, shows remarkably consistent evidence for an effect. The newer studies are consistent with the findings reviewed in the 2013 ISA. The rationale for the change is summarized on page 6-20 of the current ISA:

"However, the experimental evidence, specifically from controlled human exposure studies, is not consistent with the studies evaluated in the 2013 Ozone ISA. This contributes additional uncertainty for a biologically plausible mechanism by which short-term ozone exposure could lead to cardiovascular mortality. Lastly, most of the recent studies examined associations between short-term ozone exposure and mortality using ozone data prior to the year 2000, with only Di et al. (2017a) focusing on more recent ozone concentrations."

Although the newer human studies are inconsistent for CV effects, the human studies overall are very consistent for respiratory effects, so there is a plausible pathway for respiratory mortality. In addition, the ISA establishes a new causality category of metabolic effects (see above), with a determination of "likely". Metabolic effects and metabolic syndrome are closely linked with increased risk of CV disease, so this provides a plausible pathway.

Question 3: Please comment on the strengths and weaknesses of the epidemiology literature with regard to short-term ozone exposure and total mortality. Are there key studies that are missing? Does the available evidence justify the change in causality determination for total mortality?

Also please note that, for effects with causal or likely causal determination, the EPA has restricted consideration of epidemiological studies to those in North America (see PECOS Tool, section 6.1.1.1, page 6-3). That was the case for this determination. Are there epidemiological studies of mortality outside of North America that should be considered?

I have existential problems with the evaluation of "causality", which has a double exclusion criterion here: a study must report significant positive risks *and* take place in North America. Since Mexico is included, ethnic differences are involved as well as climatic. I would prefer that *any* study deemed to have sufficient subjects and adequate exposure data be considered, in part to specifically evaluate the roles of climate, traffic density, etc. I searched PubMed for citations with "ozone", "daily", and '"mortality" in abstract or title and found 279 papers of which only 47 involved U.S. populations, only 3 of which were published after 2015. See my Appendix B for a list of the 47 short-term papers and 25 long-term. I selected them by abstract and it is not clear how many of them included independent risk estimates using a valid model. In any event, it is clear that the ISA neglected the overwhelming majority of the available literature of short-term effects on mortality.

Questions from Dr. Sabine Lange

Epidemiology Study Questions

The EPA states in the ISA preamble that "Traditionally, statistical significance is used to a larger extent to evaluate the findings of controlled human exposure and animal toxicology studies. Understanding that statistical inferences may result in both false positives and false negatives, consideration is given to both trends in data and reproducibility of results. Thus, in drawing judgments regarding causality, the U.S. EPA emphasizes statistically significant findings from experimental studies, but does not limit its focus or consideration to statistically significant results in epidemiologic studies."

1) *It has been established that associations found in an epidemiology study can be due to: causation, bias, chance, and/or confounding. If the concept of statistical significance is not useful in epidemiology studies, then how do the study authors/EPA rule out that chance has caused the observed association?*

Essentially, they do not. I take strong issue with the above EPA protocol on statistical significance and note that studies with wide confidence intervals are included. Experimental studies involve defined exposures with no co-pollutants or temperature effects and no measurement error. Variations among studies are thus real and should be analyzed as such. By contrast, epidemiological studies are subject to all of these sources of bias, especially temperature and the treatment of lags. Foley et al. (2003) reported that EPA considered outdoor ambient air quality from fixed ambient monitoring sites to be a "surrogate for exposure", which requires consideration of indoor exposures, by contrast with experimental studies.

Some short-term epidemiology studies use a method that is termed "case-crossover". These studies assess the pollutant concentration on the day of a health effect, and "control" days are those days when a person did not experience that health effect. My understanding is that the intention of this method is to control for intra-individual confounders. These study designs often use days before and after the health event (often matched to day of the week) as control days.

2) *Am I correct in understanding that the intention of ozone case-crossover studies is to compare the ozone concentrations on a day when a health effect occurred for a person, to the ozone concentrations on a day when that health effect did not occur for that person?*

Yes.

3) *If so, then it would be important that some other factor (not related to ozone) did not prevent the health event from occurring on a control day. These studies often use days before and after the health event as control days, but for mortality studies (such as Di et al., 2017), how can a day after death be used as a control day? It doesn't matter what the ozone concentrations are after a person's death, that person would not be able to respond to that concentration. How should we interpret case-crossover studies that use control days after the event (particularly mortality occurred?*

I am not an expert on case-control studies but I question their use in temporal rather than spatial studies. Ozone has both diurnal and seasonal trends as does ambient temperature, its primary confounder (see the Figures 2 and 3 above). Further, acute effects on mortality persist for several

days, perhaps up to a week. Thus "case" days may not be independent of "control" days. Different people with different characteristics die on each day for different reasons. I would rather see both case and control periods extended for say, 3 days or more. The time-series model of Murray and colleagues (not cited in the ISA) considers temporal patterns of subject frailty, ambient temperature and air quality, each over several days. These temporal patterns are much easier to interpret than case-control findings. Di et al. combined spatial and temporal analyses, thus introducing geographic and climate variability (for no particular reason). I would have much rather seen a conventional time-series analysis in each of several locations involving socioeconomic differences as well.

Experimental Study and Dose Concordance Questions

Particularly in the context of known dose information about ozone: total inhaled dose includes concentration, exposure time, and exercise duration; Hatch et al., (2013) have shown that humans and rats that are exposed to ozone at rest achieve similar alveolar ozone doses, and that humans exercising at 5-times a resting ventilation rate achieved an ~ 5-times higher alveolar ozone dose; and that ozone concentrations are 2-10 times lower indoors where people spend most of their time.

4) *What is the importance of dose-concordance in establishing the biological likelihood of ozone-mediated effects occurring at relevant exposure concentrations in humans?*

I fail to see any relevance. Controlled animal and human clinical studies serve only to show what *might* happen under controlled and idealized conditions. Null findings may thus be the most important. By contrast, epidemiology shows what actually *does* happen in the real world, including variability.

5) *Is there evidence that the animal models used to assess ozone effects (largely rats, mice, and non-human primates) are more, less, or similarly sensitive to ozone-mediated adverse effects compared to humans, at approximately equal inhaled doses?*

I don't know but, in my view, such tests should be only qualitative and used to study mechanisms. I don't see them useful to look for a "safe" dose since the actual human doses used in epidemiology remain unknown in part because of indoor effects.

Causality Question

In this ISA I did not find population studies that considered causal pathways when assessing the association between ozone and health endpoints. It has been shown that the type of interaction between variables (e.g. confounding, colliding, mediating) can impact the results of regression analyses if these variables are controlled for in the regression equation.

6) *In the absence of a causality diagram to direct the choice of variables to control in an epidemiological study, how can we judge whether a study has appropriately controlled for confounders, and has not inappropriately controlled for colliders (which can open up pathways between variables that otherwise would not be connected) or mediators (and thereby controlled away the effect)?*

I see causality and confounders in simpler terms: causality in terms of experiments and physiology and confounders in terms of bi-variate correlations and model evaluations with and without potential

confounders. As stated above I believe that most of the mortality relationships are short-term and thus with few potential confounders. I don't think one can ever be sure that all of the long-term potential (spatial) confounders have been adequately controlled.

References

Di, Q., Dai, L., Wang, Y., Zanobetti, A., Choirat, C., Schwartz, J.D., Dominici, F., 2017. Association of Short-term Exposure to Air Pollution With Mortality in Older Adults. Jama 318, 2446. https://doi.org/10.1001/jama.2017.17923

Hatch, G.E., Mckee, J., Brown, J., Mcdonnell, W., Seal, E., Soukup, J., Slade, R., Crissman, K., Devlin, R., 2013. Biomarkers of dose and effect of inhaled ozone in resting versus exercising human subjects: Comparison with resting rats. Biomark. Insights 8, 53–67. https://doi.org/10.4137/BMI.S11102

Questions from Dr. Corey Masuca

Appendix 1 Atmospheric Source, Chemistry, Meteorology, Trends, and Background Ozone

1.3.1 Precursor Sources

Are there not other chemicals besides CO and CH4 that also are contained in the precursor mix of ozone formation with its rapidly forming and degradation in the atmosphere?

Probably, but not with identified health effects at ambient levels. "The dose makes the poison."

Does the singling out of these two constituents of the ozone "cocktail" significant as push toward climate change/global warming instead of just evaluation ozone formation?

Not clear.

1.3.1.2.1 Global Methane

Again, is a teasing out/focusing on CH4 important in discussing the virtual "cocktail" of chemicals that may be associated with ozone formation/degradation?

Not relevant for human inhalation health effects.

1.3.1.2.2 International Emissions of Ozone Precursors

This section focuses on international transport of ozone precursors. What about local/state/regional transport of ozone precursors?

State/local transport is important in devising control strategies but not in evaluating health effects and setting NAAQS.

1.3.1.3.2 Biogenic Volatile Organic Compounds (VOCs)

It has been stated that biogenic VOCs and contributions are greater than anthropogenic sources (i.e., motor vehicles). Is there greater confidence in using models and remote sensing (both with relative degrees of uncertainty) to estimate biogenic ozone source contributions that vehicle emissions estimates (manufacturing vehicle emission standards and testing), in making this assessment?

I'm not sure, but these contributions probably vary with urbanicity and traffic density. We can't study a pollutant that has not been monitored and EPA holds the keys as to what gets monitored, which has been limited to what has already been declared toxic in the absence of such data. I see this as a circular situation closed to new information.

1.4 Ozone Photochemistry

With the advent of monitoring for speciated compounds including PAMS and Near-Road Monitoring (NOy), should there be further discussions about the individual chemicals gleaned from the specialized monitoring.

Not without laboratory work to determine toxicity.

1.5 Inter-Annual Variability and Longer-Term Trends in Meteorological Effects on Anthropogenic and US Background (USB) Ozone

While temperature, wind patterns, cloud cover, and precipitation are highlighted as very important variables in ozone formation, does topography play a role (such as in Birmingham where summertime pollutants are trapped in a "mountainous bowl?"

Yes, to the extent that atmospheric residence time is increased. This is the case with Los Angeles, hence their exemption from national standards. I'm not sure we know much about the "background" ozone in LA.

Are there any independent effects on formation due to relative humidity?

Water vapor plays a role in reducing photochemistry, perhaps by reducing temperature levels.

Appendix 2 Exposure to Ambient Ozone

2.3 Exposure Assessment Methods

While monitoring, including fixed, ambient monitors and personal and microenvironmental monitors are highlighted, what about remote sensing? Biological sampling in blood or tissue?

Personal monitoring is virtually nonexistent, including for ozone. Foley et al. (2003) reported that EPA considered outdoor ambient air quality from fixed ambient monitoring sites to be a "surrogate for exposure". Biological sampling is useful in clinical experiments but not in epidemiology. I'm unaware of any autopsy that identified long-term exposure to air pollution as an underlying cause of death.

2.3.2.1 Spatial Interpolation

*While attempting to quantity concentrations at locations and areas between concentration points is included under **2.3.2 Modeling**, many of these exact same methods (i.e., data averaging, IDW, and kriging) are also utilized for **Monitoring** data shortcomings.*

2.4.1 Time-Activity Data

Is it possible that ozone exposure through time-activity data may be reduced due to temperature alone, as more people tend to avoid time spent outdoors in the summers during extremely warm/hot/humid, stagnant days which are oftentimes conditions for greater ozone formation?

Not likely, because of differential use of air conditioning according to socioeconomic status, for example. Studies of the general public may be misleading, and temporal trends in the use of A/C should be considered in long-term studies, especially with regard to accountability for ozone reductions.

Miscellaneous Question(s)

Due to exposure to ozone being disproportionate for disparate groups (i.e., lower income, children), should this be an emphasis in this section, in lieu of regression analysis confounding/covariate in epidemiological studies for low(er) SES?

Yes, especially in spatial analysis.

Questions from Dr. Steven Packham

Question 1 Background Statement of Fact:

> *Evidence from controlled human exposures is sufficient to conclude with certainty that a causal relationship exists between measurable decrements in FEV1 and subjective symptoms in healthy human adults.*

Question 1: When a causal relationship is conclusive to a high degree of scientific certainty as it is in this case, should this take precedence over causal inference when drafting a NAAQS ISA?

Yes. Figure ES-3 establishes that short-term exposure to O_3 affects lung function. Figure 6 above shows a relationship between FEV_1 change and mortality, thus extending the interpretation of the FEV_1 relationship. Experimental results should take precedence over theory and statistics but care must be taken in selecting experimental subjects.

Question 2 Background Statements of Fact:

1. *The shape of the ozone induced FEV1 and subjective symptoms dose-response curve is a function of the inhaled hourly dosage rate and the cumulative dose inhaled over several hours immediately prior to the onset of the effect.*
2. *The mean cumulative dose threshold for ozone induced FEV1 and symptom effects in healthy adult humans exposed 6.6 hours to ozone concentrations from 60 to 87 ppb is estimated to be 1,362 mg. (Schelegle et al. 2009)*
3. *This is equivalent to inhaling a dose of 2,439 trillion highly reactive oxidizing molecular moieties.*
4. *Whatever the oxidative challenge of PM air pollution is to the human lung, it pales in significance to that of ozone.*
5. *The inhaled hourly dosage rate and cumulative dose thresholds appear to be lower for ozone induced FEV1 and symptom responses than those necessary for inducing clinical signs of injurious pulmonary inflammation.*
6. *Ozone induced FEV1 decrement and subjective symptoms may be species-specific protective and defensive responses and warning signs for human organisms.*
7. *Ozone exposures have been shown to stimulate peripheral mucus flow into central bronchi thereby enhancing particle transport from peripheral to central airways and mucociliary clearance of inhaled particulate matter. This beneficial dose dependent response to ozone "…is of interest since it characterizes the reaction of a primary defense mechanism essential to the protection of mucosal surfaces of the tracheobronchial tree." (Forster et al. 1987)*

Question 2: Given evidence available from controlled human exposures substantiating causal relationships with a number of physiological responses, including beneficially confounding interactions of ozone on PM clearance, should Sub-section ES4.1 Health Effects in the Draft's Executive Summary, and the entire Integrated Synthesis section of the Draft be rewritten?

Yes, for sure!

Question 3 Background Information: Figure ES-3 in the Ozone ISA External Review Draft (shown below) is adapted from the 2013 Ozone ISA which was based on eight human studies published between

1988 and 2013. The 2009 study by Schelegle et al. played a decisive role in the 2015 revision of the O3 NAAQS from 75 to 70 ppb (80 FR 65292 Oct 26, 2015).

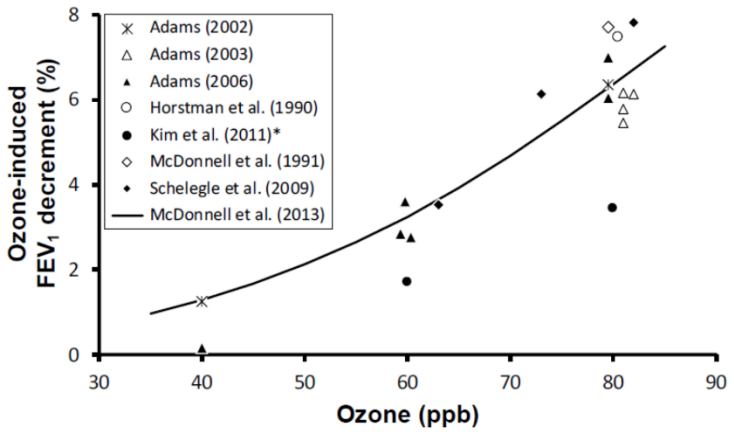


Figure ES-3 *was adapted from Figure 6-1 of 2013 Ozone ISA (U.S. EPA, 2013) which was based on studies by Adams (2006), Adams (2003), Adams (2002), Folinsbee et al. (1988), Horstman et al. (1990), Kim et al. (2011), McDonnell et al. (2013), McDonnell et al. (1991), and Schelegle et al. (2009).*

Figure 1 below (from Schelegle et al. 2009), on the other hand, depicts the actual mean accumulative doses of 31 healthy adult human subjects who completed four 6.6-hour chamber exposures to target mean O_3 concentrations of 60,70, 80, and 87 ppb. The original data presented in this way conveys critical information to toxicologists and biomedical researchers that is "lost in translation" in the concentration/risk-effect picture presented in Figure ES-3.

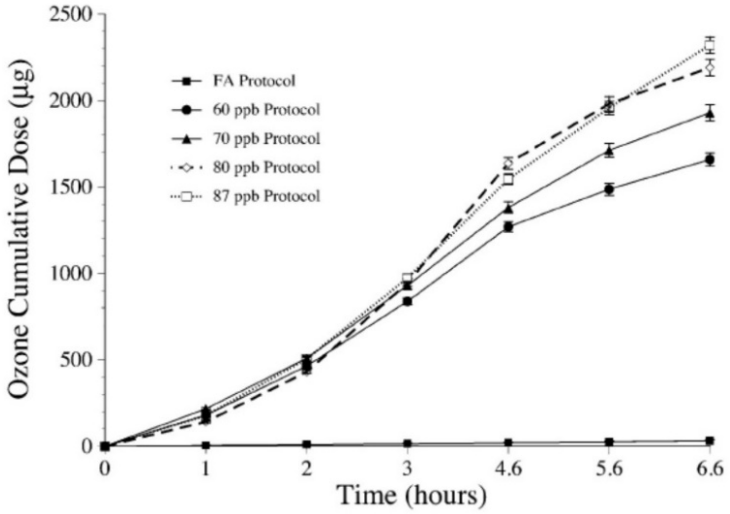
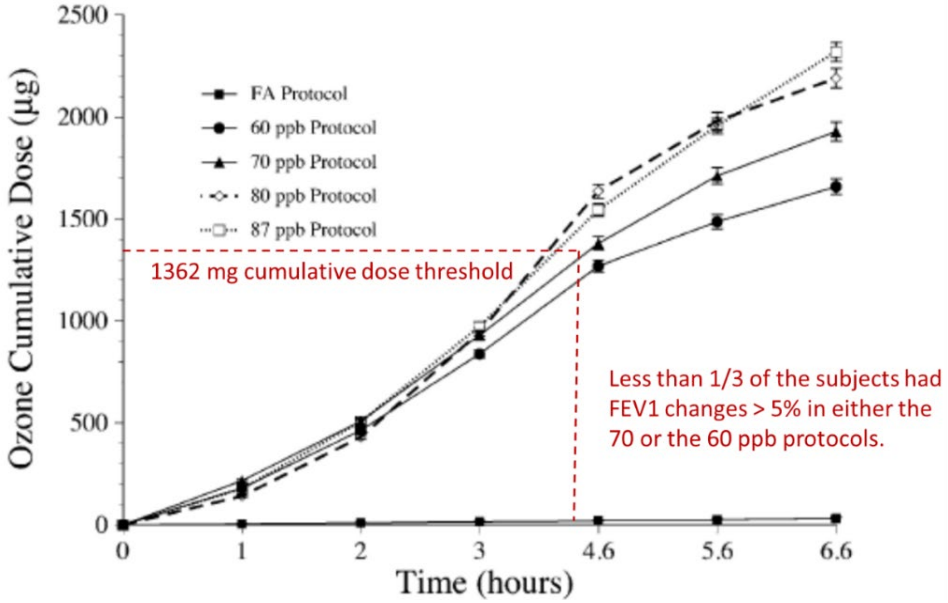


Figure 1. Diagram of mean group values for cumulative dose of ozone (micrograms) against time of exposure for each of the five protocols. Values represent means ± SEM.

To quote Schelegle et al. (2009),

> *"We were able to obtain reliable estimates of a Dose of Onset [i.e., a threshold for the FEV1 effect], using the pooled FEV1from the 80 and 87 ppb ozone exposure protocols, …but not from the pooled FEV1 data from the 60 and 70 ppb ozone exposure protocols. The inability to estimate [a threshold] using the FEV1 data from the 60 and 70 ppb ozone exposure protocols is most likely because <u>less than one third</u> of the subjects had changes in FEV1 <u>greater than 5%</u> in either of these protocols. (Emphasis added)*



Packham Figure 1. Adapted from Schelegle et al. (2009) with toxicological annotations by author, 2019.

The notable differences between Figure ES-3 compared with Packham Figure 1 are driven by how data are interpreted by different scientific disciplines. By superimposing Schelegle's descriptive conclusion-narrative onto the Sigmoid shaped dose-response curves, one sees the beginning of an increased trend of dose-response curve separation between hour 3 and hour 4: Indicative of the cumulative Dose of Onset threshold between the respective exposure protocols.

Figure ES-3 is the product of adapting (i.e., imposing) an ISA Preamble quantal risk-assessment mindset upon graded data collected from continuous response gradients characteristic of living biological organisms. The narrative associated with Figure ES-3 (found on page ES-7) is grossly misleading with respect to the epidemiologically "associated" adverse health effects and completely overlooks the confounding health benefit of enhanced PM clearance stimulated by 200 ppb ozone exposures mentioned above under Question 2 Background Statements of Fact.

The controlled human studies by Folinsbee, Adams, Horstman, Kim, McDonnell and Schelegle, and others cited below in the References and reading list, prove with absolute certainty that exposures to elevated ambient levels of O3 can cause measurable decrements in FEV1 pulmonary test results in healthy adults. These studies document that the effect of O3 on reduced FEV1 volumes is temporary, and suggest that hourly mean ambient O3 concentrations below 70 ppb are not likely to cause FEV1 effects in most healthy adults.

Question 3 Background Statement of Facts:

Several nonmember consultants have expressed reluctance to comment on certain questions because of limited familiarity with pulmonary physiology and inhalation toxicology. Here are few facts to keep in mind.

1. *Lungs have an evolutionary history in which surfactant was key to the evolution of all air breathing species on the surface of the planet, (Daniels and Orgeig (2003.)*
2. *Antioxidant secretions from epithelial Type II cells into the liquid lining of the lungs is one of most important natural defenses the human organism has against naturally occurring ozone levels in the atmosphere near the earth's surface.*
3. *All known effects of ozone on the human respiratory system are dose dependent.*
4. *Ozone stimulation of the respiratory airways evokes a number of organism defensive and adaptive responses in humans.*
5. *Ozone alters tracheobronchial mucociliary function in humans resulting in enhanced transport and clearance of particles deposited in the peripheral air ways, (Foster, et al (1987).*
6. *Ozone is a potent oxidizing agent, (Pryor et al. (1991).*

Question 3 Overarching Conceptual Contexts: An accurate understanding of the causal dose-response relationship between ambient ozone exposure and responses elicited in the human organism opens up a number of important options that could be considered in reviewing and setting NAAQS standards and in how those standards might be used to protect, and even promote, public health. For instance, the realization that the ozone-induced FEV1 effects are temporary, reversible, and occur at a lower inhaled dose than a truly adverse health effect (such as a nonhealing, injurious inflammatory response) could be considered a tenable rationale for classifying them as natural, organism-specific margin-of-safety benchmark indicators.

Another application of hourly MSS inhalation dosage models and thresholds would be to imbed them into web and mobile platform applications for public education and development of user-friendly air quality risk management tools by the EPA. As proof of this concept's possibility, there are two air pollution exposure apps presently in the public domain: A web app http://webapp0.myairhealth.com/# and a free downloadable smartphone app https://apps.apple.com/us/app/myair-health/id790049340.

Question 3: Looking ahead, do you think toxicology, clinical human studies, and biomedical research disciplines should be given more explicit and balanced consideration in the development of the present, and future, O_3 ISAs with the objective to validate causal relationships and determine hourly inhalation dosage rates for adverse inflammatory responses in pulmonary tissues?

Yes, I whole heartedly agree. Experimental research under carefully controlled conditions (including selection of subjects can show what *can* happen under these conditions and *why*, but epidemiology is required to show actually *does* happen in the real world. Statistically significant null findings may thus be particularly important.

However, epidemiology is currently beset with several unsurmountable problems that do not extend to experimental studies:

1. Unknown personal exposures, largely because indoor air is now often dirtier than outdoor (but not for ozone).

2. Limited selection of pollutants of interest. EPA has full control over the selection of pollutants to be monitored in the ambient and makes regulatory rather scientific selections. PM constituents and ultrafines are important cases in point. Perhaps VOCs should also be considered
3. Obsolete cohorts. If EPA had commissioned a new cohort ca. 2000 instead of relying on private (ACS) data that began in 1982, the science would now be in much better shape.
4. The inability to focus on individuals with varying pre-existing conditions.

A downside here is the lack of and difficulty in conducting truly long-term or longitudinal morbidity studies, including experimental studies. I would counter this with an over-arching message: <u>there is no convincing evidence for truly long-term effects on mortality that cannot be explained as the sum of short-term effects.</u> Air quality and experimental research should be moved out of the regulatory arena to a purely scientific one.

Without getting into the details of Schelegle et al. (2009) I would note that variability in individual responses supports the time-series mortality model of Murray et al. based on differences in frailty. Almost all of the extant short-term epidemiology assumes uniform responses throughout the entire population, usually everyone aged 65 and over. Variability in robustness to environmental excursions is responsible for the inability to detect short-term thresholds since in a large population there will always be someone on death's doorstep (for whatever reason) who will succumb to a minor excursion. Society must thus decide on a tolerable level of risk.

Appendix A. Other relevant papers by Lipfert and colleagues not cited in the ISA

Lipfert FW, Morris SC, Wyzga RE. Daily mortality in the Philadelphia metropolitan area and size-classified particulate matter. J Air Waste Manag Assoc. 2000 Aug;50(8):1501-13.

Lipfert FW, Perry HM Jr, Miller JP, Baty JD, Wyzga RE, Carmody SE. The Washington University-EPRI Veterans' Cohort Mortality Study: preliminary results. Inhal Toxicol. 2000;12 Suppl 4:41-73.
Baxter LA, Finch SJ, Lipfert FW, Yu Q. Comparing estimates of the effects of air pollution on human mortality obtained using different regression methodologies. Risk Anal. 1997 Jun;17(3):273-8.

Lipfert FW. A critical review of studies of the association between demands for hospital services and air pollution. Environ Health Perspect. 1993 Jul;101Suppl 2:229-68. Review.
Lipfert FW, Hammerstrom T. Temporal patterns in air pollution and hospital admissions. Environ Res. 1992 Dec;59(2):374-99.

Appendix B.

B-1 Papers involving short-term associations between ozone and daily mortality in U.S. populations.

1: Murray CJ, Lipfert FW. Inferring frail life expectancies in Chicago from daily fluctuations in elderly mortality. Inhal Toxicol. 2013 Jul;25(8):461-79.

2: Ensor KB, Raun LH, Persse D. A case-crossover analysis of out-of-hospital cardiac arrest and air pollution. Circulation. 2013 Mar 19;127(11):1192-9.

3: Sacks JD, Ito K, Wilson WE, Neas LM. Impact of covariate models on the assessment of the air pollution-mortality association in a single- and multipollutant context. Am J Epidemiol. 2012 Oct 1;176(7):622-34.

4: Murray CJ, Lipfert FW. A new time-series methodology for estimatingrelationships between elderly frailty, remaining life expectancy, and ambient air quality. Inhal Toxicol. 2012;24(2):89-98.

5: Zanobetti A, Schwartz J. Ozone and survival in four cohorts with potentially predisposing diseases. Am J Respir Crit Care Med. 2011 Oct 1;184(7):836-41.

6: Peng RD, Bobb JF, Tebaldi C, McDaniel L, Bell ML, Dominici F. Toward a quantitative estimate of future heat wave mortality under global climate change. Environ Health Perspect. 2011 May;119(5):701-6.

7: Chang HH, Zhou J, Fuentes M. Impact of climate change on ambient ozone level and mortality in southeastern United States. Int J Environ Res Public Health. 2010 Jul;7(7):2866-80.

8: Murray CJ, Lipfert FW. Revisiting a population-dynamic model of air pollution and daily mortality of the elderly in Philadelphia. J Air Waste Manag Assoc. 2010 May;60(5):611-28.

9: Ren C, Williams GM, Mengersen K, Morawska L, Tong S. Temperature enhanced effects of ozone on cardiovascular mortality in 95 large US communities, 1987-2000: Assessment using the NMMAPS data. Arch Environ Occup Health. 2009 Fall;64(3):177-84.

10: Katsouyanni K, Samet JM, Anderson HR, Atkinson R, Le Tertre A, Medina S, Samoli E, Touloumi G, Burnett RT, Krewski D, Ramsay T, Dominici F, Peng RD, Schwartz J, Zanobetti A; HEI Health Review Committee. Air pollution and health: a European and North American approach (APHENA). Res Rep Health Eff Inst. 2009 Oct;(142):5-90.

11: Smith RL, Xu B, Switzer P. Reassessing the relationship between ozone and short-term mortality in U.S. urban communities. Inhal Toxicol. 2009 Sep;21 Suppl 2:37-61.

12: Ostro BD, Roth LA, Green RS, Basu R. Estimating the mortality effect of the July 2006 California heat wave. Environ Res. 2009 Jul;109(5):614-9.

14: Medina-Ramón M, Schwartz J. Who is more vulnerable to die from ozone air pollution? Epidemiology. 2008 Sep;19(5):672-9.

15: Zanobetti A, Schwartz J. Is there adaptation in the ozone mortality relationship: a multi-city case-crossover analysis. Environ Health. 2008 May 30;7:22.

16: Basu R, Feng WY, Ostro BD. Characterizing temperature and mortality in nine California counties. Epidemiology. 2008 Jan;19(1):138-45.

17: Ito K, Thurston GD, Silverman RA. Characterization of PM2.5, gaseous pollutants, and meteorological interactions in the context of time-series health effects models. J Expo Sci Environ Epidemiol. 2007 Dec;17 Suppl 2:S45-60.

18: Medina-Ramón M, Schwartz J. Temperature, temperature extremes, and mortality: a study of acclimatisation and effect modification in 50 US cities. Occup EnvironMed. 2007 Dec;64(12):827-33.

19: Bell ML, Kim JY, Dominici F. Potential confounding of particulate matter on the short-term association between ozone and mortality in multisite time-series studies. Environ Health Perspect. 2007 Nov;115(11):1591-5.

20: Sarnat SE, Suh HH, Coull BA, Schwartz J, Stone PH, Gold DR. Ambient particulate air pollution and cardiac arrhythmia in a panel of older adults in Steubenville, Ohio. Occup Environ Med. 2006 Oct;63(10):700-6. 4.

21: Ostro BD, Tran H, Levy JI. The health benefits of reduced tropospheric ozone in California. J Air Waste Manag Assoc. 2006 Jul;56(7):1007-21.

22: Zeger SL, Irizarry R, Peng RD. On time series analysis of public health and biomedical data. Annu Rev Public Health. 2006;27:57-79.

23: Ito K, De Leon SF, Lippmann M. Associations between ozone and daily mortality: analysis and meta-analysis. Epidemiology. 2005 Jul;16(4):446-57.

24: Bell ML, Dominici F, Samet JM. A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. Epidemiology. 2005 Jul;16(4):436-45.

25: Schwartz J. How sensitive is the association between ozone and daily deaths to control for temperature? Am J Respir Crit Care Med. 2005 Mar 15;171(6):627-31.

26: Bell ML, McDermott A, Zeger SL, Samet JM, Dominici F. Ozone and short-term mortality in 95 US urban communities, 1987-2000. JAMA. 2004 Nov 17;292(19):2372-8.

27: Schwartz J. Is the association of airborne particles with daily deaths confounded by gaseous air pollutants? An approach to control by matching. Environ Health Perspect. 2004 Apr;112(5):557-61.

28: Moolgavkar SH. Air pollution and daily mortality in two U.S. counties: season-specific analyses and exposure-response relationships. Inhal Toxicol. 2003 Aug;15(9):877-907.

29: Thurston GD, Ito K. Epidemiological studies of acute ozone exposures and mortality. J Expo Anal Environ Epidemiol. 2001 Jul-Aug;11(4):286-94. Review.

30: Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med. 2000 Dec 14;343(24):1742-9.

31: Ostro BD, Broadwin R, Lipsett MJ. Coarse and fine particles and daily mortality in the Coachella Valley, California: a follow-up study. J Expo Anal Environ Epidem. 2000;10(5):412-9.

32: Moolgavkar SH. Air pollution and daily mortality in three U.S. counties. Environ Health Perspect. 2000 Aug;108(8):777-84.

33: Lippmann M, Ito K, Nádas A, Burnett RT. Association of particulate matter components with daily mortality and morbidity in urban populations. Res Rep Health Eff Inst. 2000 Aug;(95):5-72,

34: Mar TF, Norris GA, Koenig JQ, Larson TV. Associations between air pollution and mortality in Phoenix, 1995-1997. Environ Health Perspect. 2000 Apr;108(4):347-53.

35: Ito K, Thurston GD. Daily PM10/mortality associations: an investigation of at-risk subpopulations. J Expo Anal Environ Epidemiol. 1996 Jan-Mar;6(1):79-95.

36: Moolgavkar SH, Luebeck EG, Hall TA, Anderson EL. Air pollution and daily mortality in Philadelphia. Epidemiology. 1995 Sep;6(5):476-84.

37: Ostro B. Fine particulate air pollution and mortality in two Southern California counties. Environ Res. 1995 Aug;70(2):98-104.

38: Dockery DW, Schwartz J, Spengler JD. Air pollution and daily mortality: associations with particulates and acid aerosols. Environ Res. 1992 Dec;59(2):362-73.

39: Pope CA 3rd, Schwartz J, Ransom MR. Daily mortality and PM10 pollution in Utah Valley. Arch Environ Health. 1992 May-Jun;47(3):211-7.

40: Ramlow JM, Kuller LH. Effects of the summer heat wave of 1988 on daily mortality in Allegheny County, PA. Public Health Rep. 1990 May-Jun;105(3):283-9.

41: Liu T, Zeng W, Lin H, Rutherford S, Xiao J, Li X, Li Z, Qian Z, Feng B, Ma W. Tempo-Spatial Variations of Ambient Ozone-Mortality Associations in the USA: Results from the NMMAPS Data. Int J Environ Res Public Health. 2016 Aug 26;13(9).pii: E851.

42: Hao Y, Balluz L, Strosnider H, Wen XJ, Li C, Qualters JR. Ozone, Fine Particulate Matter, and Chronic Lower Respiratory Disease Mortality in the UnitedStates. Am J Respir Crit Care Med. 2015 Aug 1;192(3):337-41.

43: Madrigano J, Jack D, Anderson GB, Bell ML, Kinney PL. Temperature, ozone, and mortality in urban and non-urban counties in the northeastern United States. Envir Health. 2015 7;14:3.

44: Jhun I, Fann N, Zanobetti A, Hubbell B. Effect modification of ozone-related mortality risks by temperature in 97 US cities. Environ Int. 2014 Dec;73:128-34.

45 Bell ML, Zanobetti A, Dominici F. Who is more affected by ozone pollution? A systematic review and meta-analysis. Am J Epidemiol. 2014 Jul 1;180(1):15-28.

46: Di Q, Dai L, Wang Y, Zanobetti A, Choirat C, Schwartz JD, Dominici F. Association of Short-term Exposure to Air Pollution With Mortality in Older Adults. JAMA. 2017 318(24):2446-2456.

47: Young SS, Smith RL, Lopiano KK. Air quality and acute deaths in California, 2000-2012. Regul Toxicol Pharmacol. 2017 Aug;88:173-184.

B-2 Papers involving long-term associations between ozone and daily mortality

1. Hvidtfeldt UA, Sørensen M, Geels C et al. Long-term residential exposure to PM(2.5), PM(10), black carbon, NO(2), and ozone and mortality in a Danish cohort. Environ Int. 2019 Feb;123:265-272.

2. Sanyal S, Rochereau T, Maesano CN et al.. Long-Term Effect of Outdoor Air Pollution on Mortality and Morbidity: A 12-Year Follow-Up Study for Metropolitan France. Int J Environ Res Public Health. 2018 Nov 8;15(11). pii: E2487.

3. Lipfert FW, Wyzga RE. Revisiting the Veterans Cohort Mortality Study: New results and synthesis. J Air Waste Manag Assoc. 2018 Nov;68(11):1248-1268.

4. Chen K, Wolf K, Breitner S, Gasparrini A et al. Two-way effect modifications of air pollution and air temperature on total natural and cardiovascular mortality in eight European urban areas. Environ Int. 2018 Jul;116:186-196.

5. Nuvolone D, Petri D, Voller F. The effects of ozone on human health. Environ Sci Pollut Res Int. 2018 Mar;25(9):8074-8088.

6. Cakmak S, Hebbern C, Pinault L et al. Associations between long-term PM(2.5) and ozone exposure and mortality in the Canadian Census Health and Environment Cohort (CANCHEC), by spatial synoptic classification zone. Environ Int. 2018 Feb;111:200-211.

7. Robertson S, Miller MR. Ambient air pollution and thrombosis. Part Fibre Toxicol. 2018 Jan 3;15(1):1.

8. Bourdrel T, Bind MA, Béjot Y, Morel O, Argacha JF. Cardiovascular effects of air pollution. Arch Cardiovasc Dis. 2017 Nov;110(11):634-642.

9. Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, Dominici F, Schwartz JD. Air Pollution and Mortality in the Medicare Population. N Engl J Med. 2017 Jun 29;376(26):2513-2522.

10. Cakmak S, Hebbern C, Vanos J, Crouse DL, Burnett R. Ozone exposure and cardiovascular-related mortality in the Canadian Census Health and Environment Cohort (CANCHEC) by spatial synoptic classification zone. Environ Pollut. 2016

11. Turner MC, Jerrett M, Pope CA 3rd et al. Long-Term Ozone Exposure and Mortality in a Large Prospective Study. Am J Respir Crit Care Med. 2016 May 15;193(10):1134-42.

12. Yang WS, Zhao H, Wang X, Deng Q, Fan WY, Wang L. An evidence-based assessment for the association between long-term exposure to outdoor air pollution and the risk of lung cancer. Eur J Cancer Prev. 2016 May;25(3):163-72.

13. Thurston GD, Ahn J, Cromar KR et al. Ambient Particulate Matter Air Pollution Exposure and Mortality in the NIH-AARP Diet and Health Cohort. Environ Health Perspect. 2016 Apr;124(4):484-90.

14. Green R, Broadwin R, Malig B et al. Long- and Short-term Exposure to Air Pollution and Inflammatory/Hemostatic Markers in Midlife Women. Epidemiology. 2016 Mar;27(2):211-20.

15. Atkinson RW, Butland BK, Dimitroulopoulou C et al. Long-term exposure to ambient ozone and mortality: a quantitative systematic review and meta-analysis of evidence from cohort studies. BMJ Open. 2016 Feb

16. Crouse DL, Peters PA, Hystad P et al. Ambient PM2.5, O_3, and NO_2 Exposures and Associations with Mortality over 16 Years of Follow-Up in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Health Perspect. 2015 Nov;123(11):1180-6.

17. Hao Y, Balluz L, Strosnider H et al. Ozone, Fine Particulate Matter, and Chronic Lower Respiratory Disease Mortality in the United States. Am J Respir Crit Care Med. 2015 Aug 1;192(3):337-41.

18. Prueitt RL, Lynch HN, Zu K, Sax SN, Venditti FJ, Goodman JE. Weight-of-evidence evaluation of long-term ozone exposure and cardiovascular effects. Crit Rev Toxicol. 2014 Oct;44(9):791-822.

19. Carey IM, Atkinson RW, Kent AJ et al. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am J Respir Crit Care Med. 2013 Jun 1;187(11):1226-33.

20. Atkinson RW, Carey IM, Kent AJ et al. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology. 2013 Jan;24(1):44-53.

21. Wang XY, Hu W, Tong S. Long-term exposure to gaseous air pollutants and cardio-respiratory mortality in Brisbane, Australia. Geospat Health. 2009 May;3(2):257-63.

22. Jerrett M, Burnett RT, Pope CA 3rd et al. Long-term ozone exposure and mortality. N Engl J Med. 2009 Mar 12;360(11):1085-95.

23. Fischer P, Hoek G, Brunekreef B, Verhoeff A, van Wijnen J. Air pollution and mortality in The Netherlands: are the elderly more at risk? Eur Respir J Suppl. 2003 May;40:34s-38s.

24. Mills PK, Abbey D, Beeson WL, Petersen F. Ambient air pollution and cancer in California Seventh-day Adventists. Arch Environ Health. 1991 Sep-Oct;46(5):271-80.

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

26. Jerrett M, Burnett RT, Beckerman BS et al. Spatial analysis of air pollution and mortality in California. Am J Respir Crit Care Med. 2013 Sep 1;188(5):593-9.

27. Jerrett M, Burnett RT, Ma R, Pope CA 3rd et al. Spatial analysis of air pollution and mortality in Los Angeles. Epidemiology. 2005 Nov;16(6):727-36.

Abstracts of key papers

Frank R, Tankersley C. Air pollution and daily mortality: a hypothesis concerning the role of impaired homeostasis. Environ Health Perspect. 2002 Jan;110(1):61-5.
We propose a hypothesis to explain the association between daily fluctuations in ambient air pollution, especially airborne particles, and death rates that can be tested in an experimental model. The association between airborne particulates and mortality has been observed internationally across cities with differing sources of pollution, climates, and demographies and has involved chiefly individuals with advanced chronic illnesses and the elderly. As these individuals lose the capacity to maintain stable, optimal internal environments (i.e., as their homeostatic capacity declines), they become increasingly vulnerable to external stress. To model homeostatic capacity for predicting this vulnerability, a variety of regulated physiologic variables may be monitored prospectively. They include the maintenance of deep body temperature and heart rate, as well as the circadian oscillations around these set-points. Examples are provided of the disruptive changes shown by these variables in inbred mice as the animals approach death. We consider briefly the implications that the hypothesis may hold for several epidemiologic issues, including the degree of prematurity of the deaths, the unlikelihood of a threshold effect, and the role that coarse, non-combustive particles may play in the association.

Lipfert FW. Long-term associations of morbidity with air pollution: A catalog and synthesis. J Air Waste Manag Assoc. 2018 Jan;68(1):12-28.

ABSTRACT: I searched the National Institutes of Health MEDLINE database through January 2017 for long-term studies of morbidity and air pollution and cataloged them with respect to cardiovascular, respiratory, cancer, diabetes, hospitalization, neurological, and pregnancy-birth endpoints. The catalog is presented as an online appendix. associations with PM2.5 (particulate matter with an aerodynamic diameter <2.5 µm), PM10 (PM with an aerodynamic diameter <10 µm), and nitrogen dioxide (NO2) were evaluated most frequently among the 417 ambient air quality studies identified. Associations with total suspended particles (TSP), carbon, ozone, sulfur, vehicular traffic, radon, and indoor air quality were also reported. I evaluated each study in terms of pollutant significance (yes, no), duration of exposure, and publication date. I found statistically significant pollutant relationships ($P < 0.05$) in 224 studies; 220 studies indicated adverse effects. Among 795 individual pollutant effect estimates, 396 are statistically significant. Pollutant associations with cardiovascular indicators, lung function, respiratory symptoms, and low birth weight are more likely to be significant than with disease incidence, heart attacks, diabetes, or neurological endpoints. Elemental carbon (EC), traffic, and PM2.5 are most likely to be significant for cardiovascular outcomes; TSP, EC, and ozone (O3) for respiratory outcomes; NO2 for neurological outcomes; and PM10 for birth/pregnancy outcomes. Durations of exposure range from 60 days to 35 yr, but I found no consistent relationships with the likelihood of statistical significance. Respiratory studies began ca. 1975; studies of diabetes, cardiovascular, and neurological effects increased after about 2005. I found 72 studies of occupational air pollution exposures; 40 reported statistically significant adverse health effects, especially for respiratory conditions. I conclude that the aggregate of these studies supports the existence of nonlethal physiological effects of various pollutants, more so for non-life-threatening endpoints and for noncriteria pollutants (TSP, EC, PM2.5 metals). However, most studies were cross-sectional analyses over limited time spans with no consideration of lag or disease latency. Further longitudinal studies are thus needed to investigate the progress of disease incidence in association with air pollution exposure.

IMPLICATIONS: Relationships of air pollution with excess mortality are better known than with long-term antecedent morbidity. I cataloged 489 studies of cardiovascular, respiratory, cancer, and

neurological effects, diabetes, and birth outcomes with respect to 12 air pollutants. About half of the studies reported statistically significant relationships, more frequently with noncriteria than with criteria pollutants. Indoor and cumulative exposures, coarse or ultrafine particles, and organic carbon were seldom considered. Significant relationships were more likely with less-severe endpoints such as blood pressure, lung function, or respiratory symptoms than with incidence of cancer, chronic obstructive pulmonary disease (COPD), heart failure, or diabetes. Most long-term studies are based on spatial relationships; longitudinal studies are needed to link the progression of pollution-related morbidity to mortality, especially for the cardiovascular system.