Written comments to the CASAC on Ozone ISA and Policy Assessment (PA) 2019

CASAC meeting December 3-6, 2019

John Dale Dunn, MD, JD, Civilian Lecturer Emergency Medicine Faculty, Carl R. Darnall Army Medical Center, Fort Hood, Texas, Policy Advisor, Heartland Institute, Chicago, IL. Member, Board of Scientific and Policy Advisers, American Council on Science and Health, New York, NY.

The research used to justify ozone regulations does not meet the basic rules for proof of detrimental health effects. In fact the consistent findings of the EPA ozone research is no ambient ozone pollution human health risk and laboratory evidence of fleeting reversible minor pulmonary effects if humans or animals are forced to breath high levels of ozone and exercise.

The results of the findings that ozone is not a risk of harm has resulted in the creation of a harm called haze, so one could ask—why doesn't the EPA regulate fog and mist. The Great Smoky Mountains and other densely forested areas should also be cleared to achieve some aesthetic goal that the haze project has created by torturing the language and intent of the Clean Air Act (which should have been named the Safe Air Act since clean apparently means to the EPA removal of anything identified in the air except the trace gasses, (provided they are natural, not man made) Nitrogen and Oxygen.

Research studies have shown that low relative risk results and pervasive confounders make it very unlikely that the proposed new ozone rules will have measurable beneficial or protective health effects. The EPA has failed to show the previous reduction in ozone levels has produced any benefits.

The EPA should abandon this precautionary-principle driven and junk science justified new standard, and retreat from continued aggressive tightening of ozone and other air quality standards.

Conclusion and recommendation.

There is no health effects science that justifies the current ozone standard. Ozone should go the way of large particles, no longer on the list of EPA targets.

Imagine a government control program that has an end.

Economic and political effects of adoption of the recommendation.

I project that billions of taxpayer dollars and compliance costs could be returned to the citizens as soon as the EPA gives up chasing ozone, a benign component of the natural world.

I also project that a chastened and re-dedicated EPA might, after the end of the ozone campaign, eschew future goose chases, and focus on serious, non-political, scientific inquiries in the public interest.

Hereunder is an extensive critique of the EPA sponsored ozone research and ozone scare policy and regulatory actions that were based on bad research that failed to show that ozone was a criteria pollutant that presented a risk of harm at ambient levels. In fact only extreme exposures and exercise were able to show any impact on humans at all and no research showed that ozone caused asthma. I have removed the sections from the original monograph discussing the disputed claims that global warming will increase ozone, and the reality that what warming that has occurred is in the face of declining ozone levels. What remains is a critique by Joel Schwartz of EPA cited studies for faulty methods, exaggerated and false claims, and the inherent problem of using small associations in uncontrolled population studies to justify assertions of ozone harm. The details are below of data dredging and tortured methods in both epidemiology and toxicology to make the case for aggressive EPA regulation of ozone and ozone precursors. Schwartz shows how EPA sponsored research repeatedly falsifies the claims of harm of ozone exposures, ignores lab studies that show no harm, and uses small association studies to claim proof of causation of harm when they are often the result of data dredging and publication bias using Relative Risks in the range of natural variation noise.

Excerpt from Joel Schwarz Monograph on Ozone

Review and Critique of the Environmental Protection Agency's Analysis and Conclusions Regarding the Effect of Climate Change on Future Ozone Levels and Ozone-Related Health Effects

https://www.heartland.org/publications-resources/publications/review-and-critique-of-the-environmental-protection-agencys-analysis-and-conclusions-regarding-the-effect-of-climate-change-on-future-ozone-levels-and-ozone-related--health-effects

(Omitted is the discussion on predictions of future Ozone levels and the debate about how warming will increase ozone levels when the warming that has occurred has produced a decrease in Ozone levels.)

Ozone at current, historically low levels is not a significant human health concern, and future ozone levels will be much lower, regardless of climate warming. EPA's claims for ozone's most serious health effects—premature death and respiratory and cardiovascular hospitalizations—are based on the results of observational epidemiology studies. However, in cases where observational studies have been tested against randomized controlled trials, the observational study results are nearly always falsified.

Laboratory studies with several different animal species show that animals do not die, even when exposed for the equivalent of many years to ozone at levels nearly ten times greater

than the highest ambient levels. These results make it biologically implausible that ozone at real-world outdoor levels could be causing premature death in humans.

Observational studies generate false indications of risk where no risk in fact exists. EPA's claims for ozone's most serious health effects—premature death and respiratory and cardiovascular hospitalizations—are based on the results of observational epidemiology studies. We show that observational studies generate false indications of risk through data dredging and publication bias. This happens because (1) observational studies inherently allow great flexibility in modeling choices with little or no means of external validation, (2) large datasets are always filled with small chance correlations and the putative effects of ozone are within the same range as these chance correlations, and (4) from among the thousands or millions of superficially plausible models of air pollution and health, researchers seek out models that give statistically significant results. As a result, observational studies tend to confirm the preconceptions of the researchers, rather than provide realistic information on health effects. In cases where observational studies have been tested against randomized controlled trials, the observational study results are nearly always falsified. In its criteria documents and associated reports on ozone's health effects, EPA cites hundreds of air pollution epidemiology studies as evidence of harm from ozone. But implementing an invalid methodology over and over again doesn't improve its validity.

The claim that ozone can kill at real-world exposure levels is biologically implausible. Laboratory studies with hundreds of individual animals representing several different species show that animals do not die, even when exposed for the equivalent of many years to ozone at levels nearly ten times greater than the highest ambient levels. These results make it biologically implausible that ozone at real-world outdoor levels could be causing premature death in humans.

Selective characterization of evidence. In its characterization of ozone's health effects, EPA selectively emphasizes studies and portions of studies reporting harmful ozone effects, while downplaying studies reporting no effects or apparently protective ozone effects. This creates an impression that the evidence for harm from ozone at real-world levels is far more robust and consistent than the full weight of the evidence suggests.

Studies of low-level ozone exposure with human volunteers demonstrate that an 8-hour standard of 85 ppb is more than stringent enough to protect human health with an adequate margin of safety, even from the most mild health effects EPA claims for ozone. A few studies with human volunteers have assessed the effects of ozone at levels below 80 ppb. These studies find small, temporary reductions in lung function that EPA classifies as adverse. But EPA is mistaken on two accounts. First, the subjects in the study had to exercise for the equivalent of six consecutive gym workouts in less than 7 hours just to elicit small, temporary, and medically insignificant effects on lung function. Outside these artificial laboratory conditions, no one is active long enough or intensely enough to elicit even these tiny effects.

Second, EPA ignores the difference between personal exposure and ambient-monitor levels when interpreting these low-exposure studies. As a result of this difference, a 60 ppb personal ozone exposure in a laboratory study is equivalent to at least 100 ppb measured at an ambient ozone monitor. After correcting for this bias, even if EPA is correct that the

minor effects seen in laboratory studies are adverse, these effects do not occur until ozone levels are well above a level equivalent to 85 ppb as measured at an ambient monitor.

The overall result of the above considerations is that the 85 ppb 8-hour ozone standard protects human health with plenty of room to spare. Peak annual ozone levels are already below this level in about 90 percent of the country. Continued ozone-precursor reductions will ensure that the entire country will be well below this level by the time any significant additional warming occurs. Thus, even if warming causes ozone to decrease a bit less than it otherwise would have, ozone levels around the U.S. will still be below a level of concern for human health, with or without climate warming.

Observational studies create false indications of risk where no risk in fact exists. All of the evidence for harm from ozone at realistic levels comes from observational studies and can therefore be discounted.

In making its case for a tougher ozone standard, EPA notes that "The Criteria Document prepared for this review [of the ozone standard] emphasizes a large number of epidemiological studies published since the last review…" Indeed, the Criteria Document (CD) and associated Staff Paper (EPA 2007a) cite hundreds of epidemiological studies that EPA claims provide robust and consistent support for the claim that ozone causes serious harm, even at levels below an 85 ppb, 8-hour standard. What EPA avoids discussing is that these epidemiological studies are all of a type known as an "observational" study and that observational studies have been shown to give spurious results.

Observational epidemiology studies work with non-randomly selected subjects and non-randomly assigned pollution exposures and then use statistical methods to try to remove the biases inherent in non-random data. Unlike controlled clinical or laboratory studies, which can produce direct evidence for cause-effect relationships, the evidence from observational studies is indirect. The implicit assumption in an observational study is that after researchers have controlled for all known sources of bias, any residual correlation between, say, air pollution and risk of an asthma attack, represents a genuine causal connection. However, several lines of evidence indicate that this assumption is false, and that observational studies instead tend to turn up false indications of risk that are statistical figments, rather than real effects.

First, it is nearly impossible to control for all of the biases inherent in non-random data, because most of these biases are either unmeasured or unknown. Even more importantly, incentives for publication bias and data dredging cause an exaggeration of the apparent size of any given health effect reported in the epidemiologic literature and encourage researchers to "find" what they are looking for.

Publication bias refers to the tendency of researchers to seek publication of, and for scientific journals to accept for publication, mainly those studies that find a statistically significant effect, while not publishing studies that do not find an effect. As a result, the real effect of any particular air pollutant, diet, medical intervention, etc., is smaller than the studies in the scientific literature would naïvely lead one to believe.

Data dredging refers to the risk that observational studies can become statistical fishing expeditions that turn up chance correlations, rather than real causal relationships. Think of

the statistical models that researchers use to control for bias in observational studies as having lots of "dials" or "knobs" that researchers can turn in order to "tune" the statistical model to fit the observations. Researchers tend to turn these knobs and dials in ways that maximize the effects they "expect" to find, and are more likely to seek publication of studies that find the expected effect.

Researchers have been aware of these problems for a long time.[1] Here is a recent caution on publication bias from a group of air pollution epidemiologists:

> Publication bias arises because there are more rewards for publishing positive or at least statistically significant findings. It is a common if not universal problem in our research culture…In the field of air pollution epidemiology, the question of publication bias has only recently begun to be formally addressed. (Anderson et al. 2004)

Air pollution epidemiologists have also noted that it is common for researchers to selectively report results for statistical models that maximize the apparent risks of air pollution, rather than the full ensemble of results of their statistical modeling:

> Estimation of very weak associations in the presence of measurement error and strong confounding is inherently challenging. In this situation, prudent epidemiologists should recognize that residual bias can dominate their results. Because the possible mechanisms of action and their latencies are uncertain, the biologically correct models are unknown. *This model selection problem is exacerbated by the common practice of screening multiple analyses and then selectively reporting only a few important results*. (emphasis added) (Lumley and Sheppard 2003)

> *each study can generate a large number of results for various outcomes, pollutants and lags and there is quite possibly bias in the process of choosing amongst them for inclusion in a paper*. (Anderson et al. 2004)

Publication bias and data mining are serious problems not only in air pollution epidemiology but in health research in general. In just the last few years much conventional medical wisdom that was based on observational epidemiology studies has been tested and overturned by randomized controlled trials, which do not suffer from the biases inherent in observational studies.[2] In a recent review of observational studies, Young and Karr reported that 12 recent randomized trials tested 52 different claims from observational studies (Young and Karr 2011). All 52 claims were contradicted by the randomized controlled trials.

---

[1] Publication bias is a well-documented problem in a range of disciplines. See, for example, Montori et al. (2000) and Thornton and Lee (2000).

[2] For example, hormone replacement therapy and Vitamin A turned out not to reduce risk of cardiovascular disease, following a low-fat diet turned out not to reduce risk of heart disease or colorectal and breast cancer, and calcium supplements didn't reduce the risk of osteoporosis (Beresford et al. 2006; Howard et al. 2006; Kolata 2006; Moolgavkar 2005; Prentice et al. 2006; G. D. Smith 2001; Taubes 1995).

A number of epidemiologists and statisticians believe that observational epidemiology methods are not even capable of providing reliable evaluations of health risks, especially when the putative risks are small, as they are for air pollution (Taubes 1995; Ioannidis 2005; G. D. Smith 2001). A number of studies have also provided direct evidence that observational studies of air pollution and health are generating false indications of risk as a result of data mining and publication bias (Anderson et al. 2004; M. L. Bell, Dominici, and Samet 2005; Ito 2003; Keatinge and Donaldson 2006; Koop and Tole 2004).

Because the vast majority of observational studies have been overturned when tested in randomized trials, the prudent course is to conclude that air pollution epidemiology studies are no more valid than other observational studies. Indeed, there is reason to believe that observational air pollution studies are even *less likely* to be valid. The chance that an observational study's results are spurious *increases* as the magnitude of the putative health effect *decreases* (Ioannidis 2005). The putative risks of current levels of air pollution are tiny compared to the putative health risks assessed in medical intervention studies.

EPA cites the large number of observational epidemiology studies claiming harmful effects of low-level ozone as evidence that the harm is real. But implementing an invalid methodology over and over again doesn't improve its validity. Rather, EPA should acknowledge that observational studies are not an appropriate basis for assessing the health effects ozone at or below current ambient levels.

An additional reason to discount epidemiologic studies is their lack of biologic plausibility. Laboratory studies with animals suggest that ozone is not deadly, even at concentrations many times greater than ever occur in ambient air. Researchers have exposed monkeys, rats, and other species to very high levels of ozone (as high as 1000 ppb) for the equivalent of years, yet none of the animals have died.[3] At a 2005 meeting of EPA's Clean Air Science Advisory Committee to discuss a draft of EPA Ozone Criteria Document, Charles Plopper, a professor at UC Davis, expressed skepticism regarding the claim that ozone causes premature mortality, stating "I'm trying to look at it as a biologist and trying to figure out whether [ozone] exposure kills people. And I've never killed a rat in 35 years…and never killed a monkey in 35 years. And I've been accused of using too high [ozone] levels…So I'm trying to figure out does this even make any sense from a biology point of view?"[4]

EPA's Selective Characterization of evidence

Although EPA's Ozone Criteria Document (CD) includes many caveats in its discussions of the evidence on ozone's health effects, the CD overall selectively emphasizes studies and portions of studies reporting harmful ozone effects, while downplaying studies reporting no effects or apparently protective ozone effects. Likewise, the CD is quick to emphasize weaknesses in studies that report little or no harmful effect from ozone, while ignoring weaknesses in studies reporting harmful effects. Summary sections of the CD often draw conclusions that are at odds with the detailed evidence presented in more technical and detailed sections of the CD.

[3] There are dozens of such studies. A few include, (C. Y. Chen et al. 2003; Barr et al. 1990; Barr et al. 1988; Chow, Plopper, and Dungworth 1979; Dodge et al. 1994; Harkema, Plopper, and Hyde 1987; M. G. Lee et al. 2008; Moffatt et al. 1987; Wilson, Plopper, and Dungworth 1984)

[4] CASAC meeting transcript, December 8, 2005, 148.

For example, in a summary in Chapter 8, the CD claims ozone effect sizes are relatively consistent across studies (Environmental Protection Agency 2006, 8–56). However, this claim is based on pooling of results across cities and/or studies, and masks the large heterogeneity of the results between individual cities and even the same city across individual studies. For example, the NMMAPS study (M. L. Bell et al. 2004) reported a range of a -5% to +16% increase in mortality per 10 ppb increase in 24-hour ozone across the 95 cities in the study. Higher ozone was associated with *reduced* mortality in nearly 40 percent of the cities in the study (see Figure 3 in Bell et al. (2004)). A more recent reanalysis of the NNMAPS data has only amplified these concerns (R. L. Smith, Xu, and Switzer 2009).

Nevertheless, EPA draws conclusions based on the pooled results, rather than the individual city results, creating an appearance of consistency that does not in fact exist. The city-by-city data from NMMAPS and other studies cited in the CD demonstrate the huge and biologically implausible range of apparent ozone effects on mortality, from very protective to very harmful.

The CD also fails to note that the pooled result in NMMAPS is sensitive to a few outlier cities. Moolgavkar (2002; 2005) has shown that the NMMAPS pooled PM_{10} mortality association becomes statistically insignificant when just two or three outlier cities are removed from the analysis. Examination of Figure 3 in Bell et al. (2004) suggests that one extreme outlier city and two or three more moderate outliers are driving the statistical association of ozone and mortality as well. The CD demonstrates the great heterogeneity of ozone associations in the technical sections of the document, but the summary sections draw conclusions about consistency that are at odds with this evidence.

In its recent Integrated Science Assessment for ozone EPA continues to ignore evidence against ozone having a causal role in mortality associations. EPA asserts that the mortality effects for ozone have been found at concentrations well below the current 75 ppb standard, citing an analysis of the NMMAPS data that excludes high-ozone days from its analysis (EPA 2012b; Michelle L. Bell, Peng, and Dominici 2006). However, in a follow-up study, Bell et al. (2007) restricted the analysis to days with low ozone, the variability of ozone effects across communities actually widened. When the analysis was restricted to days with ozone less than 20 ppb, the range of individual city ozone-mortality associations for a 10 ppb increase in ozone ranged from -20 percent to +30 percent. It is not plausible that such low ozone exposures could be causing large increases in mortality in some cities and large decreases in mortality in others. With such large variations and such biologically implausible results, the most plausible interpretation is that these are not real ozone effects, but statistical artifacts.

As with the effect of publication bias, model selection bias inflates ozone effect estimates. Koop and Tole used Bayesian Model Averaging (BMA) to conclude, based on data for Toronto, that ozone is unlikely to be associated with daily mortality (Koop and Tole 2004). The CD summarily dismisses this research with a few sentences about BMA's limitations in the introduction to Chapter 7, and does not consider the technique further. Koop and Tole (2004) is not mentioned at all in the Staff Paper.

Yet the problem of model selection bias is becoming widely recognized in air pollution epidemiology, and Koop and Tole (2004) is one of the few efforts to systematically address

the issue. For example, the Health Effects Institute special panel that reanalyzed the GAM time series studies concluded that various model selection choices may "introduce an element of uncertainty that has not been widely appreciated previously" (Health Effects Institute 2003). Likewise, Ito (2003), in the same report, concluded:

> "Weather model specification and the extent of temporal smoothing are not the only factors that can change pollution [Relative Risk] estimates. Others may include the location of monitors, choice of lags, and consideration of distributed lags. These factors can cause differences that vary by up to a factor of two in estimated pollution coefficients."

These problems are compounded by the selective publication of larger and more statistically significant effects. Lumley and Sheppard (2003) cautioned:

> "Estimation of very weak associations in the presence of measurement error and strong confounding is inherently challenging. In this situation, prudent epidemiologists should recognize that residual bias can dominate their results. Because the possible mechanisms of action and their latencies are uncertain, the biologically correct models are unknown. This model selection problem is exacerbated by the common practice of screening multiple analyses and then selectively reporting only a few important results."

Likewise, Smith et al. (2001) similarly warn:

> "From a statistical point of view, the common epidemiological practice of choosing variables (including lagged variables, co-pollutants, etc.) that maximize the resulting effect estimates is a dangerous approach to model selection, particularly when the effect estimates are close to 0 (i.e., RR close to 1.0)."

In fact, Koop and Tole is not the only paper, and BMA is not the only method of demonstrating the effects of model-selection bias. Ito (2003) estimated 1,220 separate air pollution-mortality models for Detroit and substantial fraction suggested a "protective" effect of air pollution on health. More recent work suggests that failing to account for model selection bias can make air pollution effects appear statistically significant when in fact they are not (Roberts and Martin 2010).

Keatinge and Donaldson (2005) showed that changes in adjustment for weather can cause the apparent effect of ozone on short-term mortality to disappear. When they allowed in their model for cumulative effects of heat stress over several days, as well as the additional effects of direct sunshine, which adds to heat stress, the association of ozone with mortality was reduced by 90 percent and became statistically insignificant.

The CD's density plots indirectly show that consideration of publication and model-selection bias would have greatly reduced the health effects attributed to ozone. For example, the density plot for mortality on page 7-128 has 25 percent of the probability on the side of a protective effect for ozone. But for multi-city studies, the chart relies on pooled results, rather than individual city results. For example, NMMAPS includes 95 city results, nearly 40 percent of which suggested a protective effect of ozone. Entering results for individual cities would increase the amount of probably on the side of protective ozone

effects. Furthermore, the density chart relies only on published point-estimate studies, and therefore suffers from publication bias (only partially accounted for by having a few multi-city studies) and model selection bias (not accounted for at all). Accounting for these effects would push still more of the probability toward negative (that is, protective) ozone effects.

The Health Effects Institute's recent APHENA study only amplifies concerns regarding EPA's exaggeration of ozone-mortality associations (Katsouyanni and Samet 2009). In single-pollutant models of ozone and mortality, only 12 of 24 models resulted in a statistically significant relationship between ozone and death in the U.S. Furthermore, when modeling risk of death in those over and under 75 years of age, 10 of 24 models gave statistically significant results for those under 75, and 6 of 24 for those over 75. In models that also controlled for particulate matter, ozone was no longer statistically significant in any of the models. None of these results suggests robust or consistent evidence for ozone as a cause of premature mortality.

Overall, EPA's conclusion of robustness and consistency of ozone associations with mortality and other health effects is mistaken, and its presentation of the evidence creates an appearance of consistency and robustness that does not exist in the full range of research results.

The paragraphs above discuss EPA's general problem of mischaracterizing evidence. Below we point out some additional cases in which EPA's ozone Criteria Document mischaracterizes specific studies, creating a bias toward assuming greater air pollution health effects than the actual results of the studies would suggest.

Children's Health Study Asthma Results: The California Children's Health Study (CHS) assessed the risk of developing asthma due to air pollution in a cohort of 3,535 children with a five-year follow-up (McConnell et al. 2002). According to the CD, "Asthma risk was not higher for residents of the six high-O_3 communities versus residents of the six low-O_3 communities" (p. 7-109). The Staff Paper makes a similar claim (p. 3-24). These claims are mistaken. The risk of asthma was *30 percent lower* in the six high-ozone communities, relative to the six low-ozone communities in the study.[5]

The CD notes that asthma risk was 3.3 times greater for children in high-ozone communities playing three or more team sports (8 percent of the children), though this result was based on a small sample. This means the risk of developing asthma must have been 50 percent lower for the other 92 percent of children in the study (in order to match the 30 percent lower risk of asthma observed for the full cohort).

When the 12 communities were divided into tertiles, increased asthma risk was reported for only the 4 highest ozone communities. These 4 high-ozone communities—all in the eastern portions of the South Coast Air Basin (the Los Angeles metro area)—at the time had by far the highest ozone levels in the country.[6] The study was based on ozone levels

[5] Based on 1-hour ozone levels and this result was statistically significant. Based on 8-hour ozone levels, risk of asthma was 20% lower and the top of the 95% confidence interval for relative risk was 1.0, i.e., a hair short of statistical significance.

[6] They still have the highest ozone levels in the country, but ozone levels there have dropped substantially since the CHS years and are now closer to ozone levels elsewhere.

during 1994-97, when these areas violated the old 1-hour ozone standard dozens of times per year and violated the 8-hour, 85 ppb ozone standard more than a hundred times per year. The rest of the U.S. has ozone levels typical of the medium- and low-ozone areas of the Children's Health Study, for which there was no increase in risk of developing asthma, even in very active children. Thus, this study suggests that even the old federal 1-hour ozone standard is more than protective against the development of asthma.

If the higher asthma risk with higher ozone for very-active children is to be taken as causal, then there is no justification for not taking the lower overall asthma risk as also causal. If so, there are two conclusions that EPA should have drawn: First, overall, higher ozone levels reduce the risk of developing asthma.[7] Second, the federal 1-hour, 125 ppb and 8-hour, 85 ppb ozone standards protect against the development of asthma with a huge margin of safety, even in the most physically active children. The CD and Staff Paper should not have created the impression that a more stringent ozone standard would reduce children's risk of developing asthma.

Another important result from the Children's Health Study is that even after a exposure from birth to ozone exceeding the 1-hour 125 ppb standard more than a hundred days per year, ozone had no effect on teenagers' lung development or lung function (Gauderman et al. 2004).

Multi-City Study of Ozone and Use of Asthma Medication. The CD claims "the strong evidence from the large multicities [sic] study by Mortimer et al. (2002)" (CD, p. 8-44) shows that ozone is associated with increased medication use. But the evidence from this study is not strong. The ozone effect was statistically significant only in a single-pollutant model. It became statistically insignificant when any other pollutant was added as a covariate. The CD creates the false impression that other pollutants had little confounding effect on the results: "In multipollutant models, the O_3 effect was shown to be *slightly* diminished" (CD, p. 7-45; emphasis added). In fact, the ozone effect dropped by 40 percent when NO_2 was added to the model, and dropped to zero when NO_2, SO_2, and PM_{10} were added.[8]

CARB/Kaiser Central Valley Study. This time-series study reported a statistically significant *decrease* in acute health effects with higher ozone levels (van den Eeden et al. 2002). The CD does not mention this study.

Laboratory studies with human volunteers indicate that an 8-hour ozone standard of 85 ppb is protective of human health with room to spare

In both the CD and more recent Integrated Science Assessment (ISA) (EPA 2012b), EPA asserts that laboratory studies with human volunteers provide direct evidence that ozone causes adverse effects at levels below the 85 ppb, 8-hour ozone standard, and even the newer 75 ppb ozone standard. In the CD EPA places special emphasis on studies by Adams

[7] We do not advocate this view. We merely point out that if the study has uncovered a causal relationship between high ozone and increased asthma for children playing three or more team sports, then there is no basis for not considering as causal the statistically significant relationship between high ozone and lower asthma in less-active children.

[8] This was based on only 3 of the 8 cities in the study that had sufficient data on all four pollutants.

(2006; 2002) because at the time they were the only studies that examined respiratory effects associated with ozone exposures for several hours at levels below 80 ppb. The ISA also cites more recent studies that also assessed effects of low ozone levels on human volunteers (Kim et al. 2011; Schelegle et al. 2009).

In these studies, healthy young-adult college students were exposed to ozone at various concentrations (60, 70, 80, and 87 ppb, depending on the study) for 6.6 hours while exercising, and their lung function and subjective symptoms were measured several times during the exposure period. Group-average changes in lung function with 60 ppb ozone were very small. After 6.6 hours, FEV_1 (forced expiratory volume in one second) declined by about 1.7 to 2.7 percent (declines were not statistically significant), depending on the study, returning back to normal within 1 hour after ozone exposure ended. Subjective symptoms were not affected by exposure to ozone.

Schlegle et al. (2009) assessed a 70 ppb exposure and reported a mean reduction in FEV_1 of about 5 percent that took a few hours to return back to normal. Total Symptom Score also increased, from a maximum of about 4 with ozone-free air to a maximum of about 13 with 70 ppb ozone. This is on a scale from zero to 160, so the change in symptoms was quite small.

These changes are small and clinically insignificant. However, EPA expressed concern over the fact that a few subjects experienced larger temporary reductions in lung function. Regarding the Adams studies, EPA reported that after 6.6 hours, 2 of 30 subjects in the Adams studies experienced temporary lung-function reductions in FEV_1 of 10 percent or more, when exposed to ozone at 60 ppb (EPA 2007b, 37828).[9] More recently, Schlegle et al. (2009) also reported that 6 of the 31 subjects in that study likewise experienced temporary FEV_1 reductions greater than 10 percent at both 60 and 70 ppb. Based on these results, EPA concludes that standards of 85 ppb or 75 ppb do not sufficiently protect people from ozone. In its ISA, EPA concludes: "Though group mean decrements are biologically small and generally do not attain statistical significance, a considerable fraction of exposed individuals experience clinically meaningful decrements in lung function" (ISA p. 6-18).

This conclusion is unwarranted for two reasons. First, because of the well-known difference between ozone concentrations measured ambient monitoring stations and actual personal exposures to ozone while outdoors, the personal ozone exposures in the Adams, Schlegle et al., and Kim et al. studies were equivalent to ambient-monitor ozone levels of 100 ppb or more. After accounting for the personal exposure-to-ambient monitor ratio, it is clear that ozone does not have adverse effects at ambient-monitor concentrations below 85 ppb.

Second, even without accounting for the personal exposure-to-ambient monitor ratio, EPA had to make a heroic stretch to find adverse effects in the laboratory ozone studies. As discussed in more detail below, the studies used unrealistically extreme amounts of exercise (equivalent to four or five gym workouts in a row) and the few cases with FEV_1

[9] Adams reported only group-mean results in the two journal articles. However, Adams provided EPA with data on each subject's response to ozone, which EPA analyzed for inclusion in its regulatory documents.

declines of greater than 10 percent could easily have been due to within-subject variability, rather than ozone.

i. Ignoring the difference between personal exposure and ambient-monitor ozone levels causes EPA to great exaggerate ozone's health effects. Once this difference is accounted for, there is no evidence for adverse effects of ozone at levels below 85 ppb (as measured at ambient monitors).

A great deal of evidence indicates that personal ozone exposures—the amount of ozone in the air people actually breathe into their lungs—even while outdoors, are much lower than ambient ozone levels measured at ambient ozone monitors. The reason is that ambient ozone compliance monitors are generally placed several feet above human head-height and away from surfaces, in order to avoid interferences from people and surfaces near the ground that could affect the fidelity and consistency of the ozone measurements. Ozone is very reactive and any nearby surfaces (such as clothing or the ground) reduces the amount of ozone in the air that people actually breathe into their lungs.

Evidence comparing ambient ozone concentrations with personal exposures includes the following:

- Trained technicians in eastern Los Angeles County wore personal ozone monitors and performed scripted activities, such as walking outdoors near or away from a roadway, sitting in a backyard, driving with windows open or closed, performing normal household activities indoors, and so forth, during specific times of the day (Johnson et al. 1996). Personal exposures while outdoors averaged 41 percent lower than hourly ambient ozone levels reported at the nearest monitors. The ratio of personal to ambient ozone level was the same whether the technician was near or away from roadways.
- Outdoor workers in Mexico City experienced average personal ozone exposures 60 percent lower than ambient-monitor levels in a study of thirty-nine shoe-cleaners (O'Neill et al. 2003). All ozone exposures in this study took place outdoors.
- In a study of thirty-six children in Tennessee, those in the top 25 percent for time-spent-outdoors nevertheless experienced personal ozone exposures 80 percent lower than levels measured at ambient monitors (K. Lee et al. 2004).
- A study in Baltimore had a trained technician perform scripted activities to simulate a typical daily schedule of a senior citizen while carrying a personal ozone monitor (Chang et al. 2000). The study reported that personal ozone exposure during the summer averaged 33 percent lower than ambient-monitor levels while outdoors near a roadway, and 11 percent lower while outdoors away from roadways.
- A companion study to the one above measured personal ozone exposures of 15 senior citizens during summer in Baltimore for a total of 12 days each (Sarnat, Koutrakis, and Suh 2000). The highest personal exposures—reflecting more time spent outdoors—were well below ambient-monitor levels. While the highest ambient-monitor level on any day was 54 ppb the highest personal ozone exposure for any of the 15 people in the study was 21 ppb (60 percent lower) and the second highest was 17 ppb (68 percent

lower).[10] As the authors noted, "[P]ersonal exposures to O_3 [ozone], NO_2, and SO_2 were extremely low. Seventy percent of the measured personal O_3, NO_2, and SO_2 values were below their respective LOD [limit of detection], even when ambient concentrations were well above their LOD" (Sarnat, Koutrakis, and Suh 2000, 1188).

- Liu et al. (1997) found that a group of forty children and adults in Alpine, California, experienced average personal ozone exposures 75 percent lower than ambient levels.
- A year-long study of 169 children in Upland and the Crestline area, both high-ozone regions in San Bernardino County, California, reported that personal ozone exposures during the ozone season averaged 61 and 58 percent below the respective ambient levels in the two areas (Geyh et al. 2000).
- A study of 158 asthmatic children in Mexico City reported that personal ozone exposures averaged 77 percent less than ambient-monitor concentrations (Ramirez-Aguilar et al. 2008). The highest personal ozone exposure—reflecting the most time spent outdoors—for any child was 52 percent lower than the *highest* ambient-monitor ozone level and 7 percent lower than the *median* ambient-monitor ozone level during the study.

This difference between ambient ozone concentrations and personal exposures is key for interpreting the laboratory studies. The ozone levels used in laboratory studies such as Adams, Schlegle et al., and Kim et al., are *personal exposures*. To compare them to equivalent ambient-monitor levels, one must account for the fact that personal ozone exposures while outdoors are typically at least 40 percent lower than ozone levels measured at ambient monitors. Or, to turn this around, ozone levels measured at ambient monitors are typically at least 1.67 times greater than concomitant personal outdoor exposures.

Table 3, below, translates the personal ozone exposures used in the laboratory studies into equivalent concentrations at ambient compliance monitors. Because ambient-monitor levels are at least 1.67 times personal exposures, Table 3 uses a conversion factor of 1.67 to go from the personal exposure levels in the Laboratory studies to equivalent ambient levels. The table gives both the average and peak level for each exposure pattern.

Table 3. Comparison of personal ozone exposures used in the Adams, Schlegle et al. and Kim et al. studies with equivalent ambient-monitor concentrations

Laboratory personal ozone exposure protocols			Equivalent ambient-monitor ozone concentration	
Exposure Pattern	6.6-hour Average Personal Ozone	Peak-Hour Personal Ozone Exposure	6.6-hour Average Concentration	Peak-Hour Concentration

[10] In this study, both personal and ambient ozone levels were reported as 24-hour averages. To get a rough idea of equivalent 8-hour and 1-hour levels, multiply by 1.5 and 2.0, respectively. Thus, a 24-hour average of 54 ppb corresponds roughly to an 8-hour level of 85 ppb, and a 1-hour level of 11 ppb. In other words, peak ambient ozone levels during the study were about as high as the old 8-hour standard and well above the new 75 ppb 8-hour standard.

	Exposure Concentration	Concentration		
Filtered Air	0	0	0	0
Triangular	40	50	66	84
Square	60	60	**100**	100
Triangular	60	90	**100**	*150*
Triangular	70	90	**117**	*150*
Square	80	80	**134**	*134*
Triangular	80	150	**134**	*250*

Notes: All values are in parts per billion (ppb). Bold entries signify ozone exposures that exceeded the 8-hour, 75 ppb or 85 ppb ambient standards. Italicized entries signify exposures that also exceeded even the old 1-hour, 125 ppb standard. A "square" exposure pattern means that subjects breathed a constant ozone concentration for the 6.6-hour experiment. A "triangular" exposure pattern means subjects breathed ozone that rose to a peak during the first half of the exposure period and then fell during the second half.

EPA is comparing apples to oranges when it assumes the effects of, say, 60 ppb ozone in the laboratory provides information on the health effects of 60 ppb ozone measured at an ambient compliance monitor. In fact, 60 ppb in the laboratory is equivalent to 100 ppb as measured at an ambient monitor. After converting the personal exposures in Adams (2006) to equivalent ambient levels, we can see that the effective ozone exposures in Adams (2006) were actually much greater than EPA assumes. For example, to get a personal exposure of 60 ppb, the ambient concentration would need to be at least 100 ppb. If anything, Adams (2006) and more recent similar studies (Kim et al. 2011, Schlegle et al. 2009) show that even ozone levels substantially greater than the 8-hour, 75 or 85 ppb standards have little or no effect on people's lung function.

EPA is aware of the difference between ozone concentrations measured at ambient monitors and actual personal exposure concentrations, but ignores this difference in interpreting laboratory studies of the effects of low ozone levels. In its Ozone Criteria Document (EPA 2006) EPA devotes pp. 3-56 to 3-76 to a discussion of personal exposure vs. ambient concentration and cites most of the articles we cite above in the bullet points. However, EPA cites these papers to support the (correct) claim that personal exposures and ambient-monitor levels are *correlated*, meaning that personal exposures tend to rise and fall in concert with ambient-monitor levels. EPA notes this correlation to support the contention that ambient monitors provide a valid measure of ozone exposure for the purposes of observational epidemiology studies. However, EPA omits the fact that these same studies also show that personal exposures, even while outdoors, are *much lower* than ozone levels measured at ambient monitors.

There is, however, one instance where EPA explicitly compares outdoor personal exposures to outdoor ambient-monitor levels. In this case, EPA notes that Brauer and Brook (1997) reported that the personal ozone exposure of farm workers in the lower Fraser Valley (Canada), who spent all of their time outdoors, was only 4 percent lower than

ambient monitor levels (Environmental Protection Agency 2006, 3–74), implying that personal exposure it not much lower than ambient-monitor levels.

EPA's characterization is misleading in three ways. First, Brauer and Brook themselves point out that their personal ozone measurements have a large error and likely a positive bias as well.[11] Second, ambient ozone levels were extremely low in this study—about 15 to 30 ppb on most days and never greater than 50 ppb (as measured at ambient monitors). Third, difference between personal exposure and ambient-monitor ozone was greatest on days with the highest ozone. For example, the five highest-ozone days ranged from 39 to 50 ppb (all other days ranged from 8 to 34 ppb) personal exposure averaged 22 percent lower than ambient-monitor levels (compared with 4 percent lower overall).[12]

In summary EPA mentions the difference between ambient and personal ozone levels when doing so helps EPA make a case for the validity of the observational epidemiology studies (i.e., when EPA notes the *correlation* between personal and ambient ozone), but generally ignores the personal vs. ambient difference when doing so would vitiate EPA's case for harm from low-level ozone (i.e., EPA ignores the fact the outdoor personal ozone exposures are much lower than ambient-monitor levels when interpreting the results of the Adams laboratory studies). Furthermore, in the one case where EPA does compare personal to ambient ozone levels, EPA cites only a single outlier study (in which the study authors themselves cast doubt on the validity of the measurements) to create a false impression that there is little difference between personal and ambient ozone levels.

ii. Even without accounting for the personal exposure-to-ambient monitor ozone ratio, the laboratory results suggest that ozone does not have adverse effects below 85 ppb

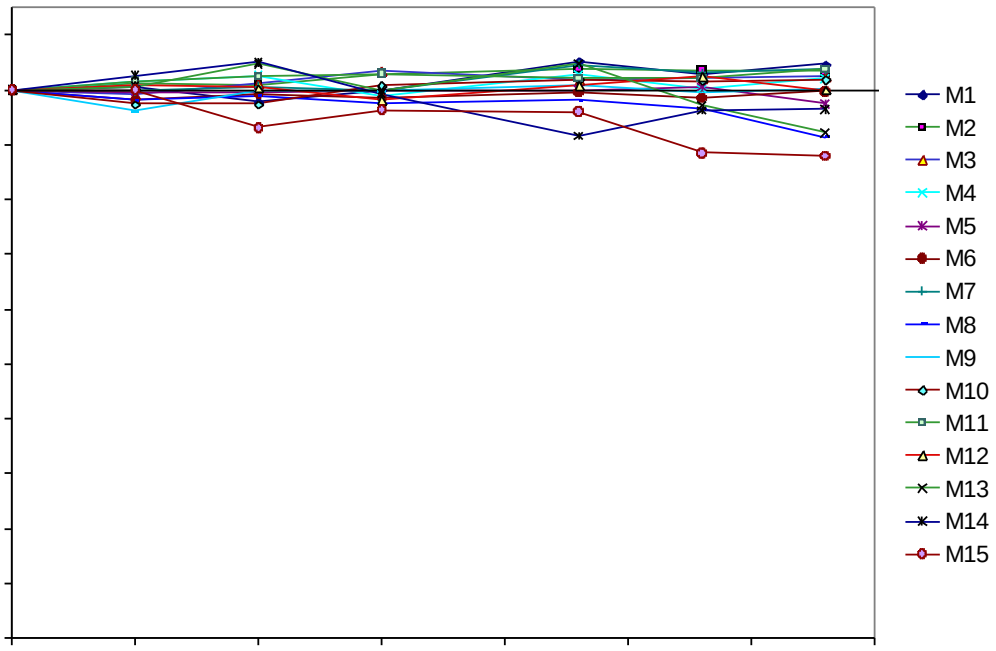
EPA glosses over is how difficult it is to induce even the small ozone effects observed in the laboratory studies, despite the fact that the ozone levels in these studies were effectively much greater than the original 8-hour ozone standard and even the old 1-hour standard.

It is true, as EPA notes, that a couple of subjects experienced FEV_1 declines greater than 10 percent at the 60 ppb exposure in the Adams studies. Figures 10 and 11 display individual results for, respectively, men and women, at the 60 ppb triangular exposure. As the graphs show, one man experienced an FEV_1 decline of 12 percent after 6.6 hours, and one woman experienced a decline of 21%.

Figure 10. Adams (2006) data for men

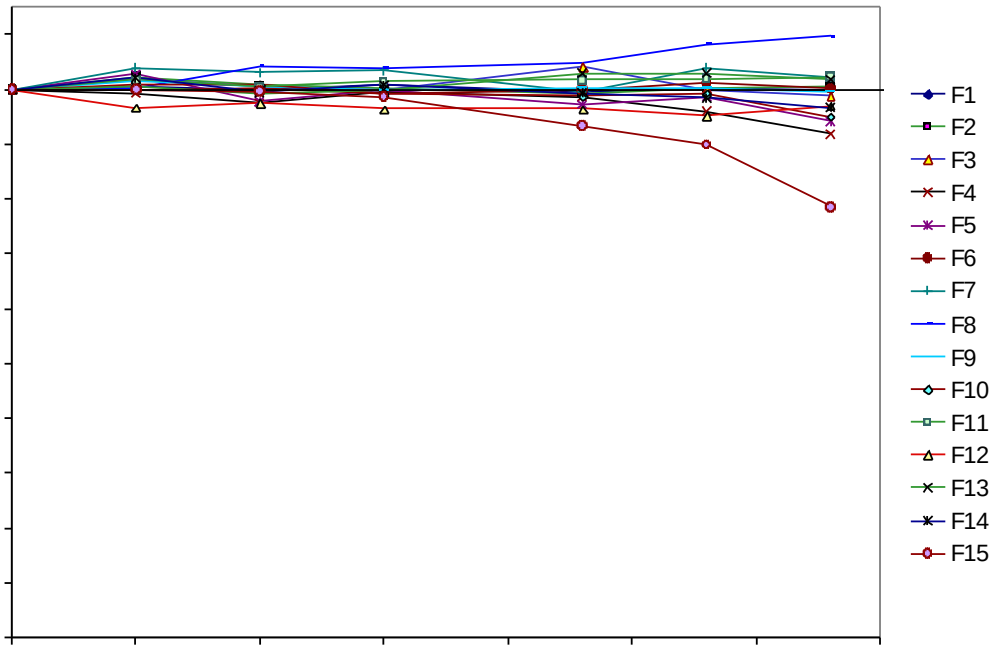
[11] "For some individuals in Group 3 [farm hands working outdoors] personal/fixed ozone ratios were near zero, while for others the ratios were above two (Fig. 1). These extreme values can be attributed in part to random measurement error which we have estimated at 35% (Brauer and Brook 1995)…The high personal-fixed ratios are more difficult to explain and possibly indicate local variability in ozone concentrations or the effect of HNO_3 or some other unidentified interference affecting personal ozone samplers." Brauer and Brook (1997), 2116-17.

[12] See Figure 2(a) in Brauer and Brook (1997).



Source: Data provided by William Adams, Professor Emeritus, UC Davis.

Figure 11. Adams (2006) data for women



Source: Data provided by William Adams, Professor Emeritus, UC Davis.

First, note once again that the ozone exposure was equivalent to at least 100 ppm when translated into ambient-monitor terms, and was therefore effectively at least 18 percent greater than an 8-hour ozone standard of 85 ppb. Thus, even these effects required a relatively high ozone exposure. It certainly does not provide evidence of any effects at ozone levels below an ambient monitor level of 85 ppb.

Second, note that it took more than five hours of continuous ozone exposure before even the most sensitive people began to show any FEV_1 reduction. The subjects spent 50 minutes of every hour performing relatively vigorous aerobic exercise on a treadmill or stationary bicycle. Each 50-minute bout was roughly equivalent to a gym workout. The full 6.6-hour exercise regimen was similar to going on an all-day hike or going to the gym six times in a row in one day.[13] This level of exercise was necessary to raise people's respiration rate high enough so that they would breathe in enough ozone to affect their FEV_1. In other words, it took an unrealistically lengthy bout of relatively vigorous exercise

[13] The average young adult at rest has a respiration rate on the order of 12-18 breaths per minute and a heart rate of about 60-80 beats per minute. In the Adams studies the participants spent 5 hours out of the 6.6 hours of the study (50 minutes per hour, with a 35 minute lunch break in the middle) exercising so as to keep their respiration rate at an average of 26-27 breaths per minute and their heart rate at 123-125 beats per minute. For people in their early twenties (as were the subjects in the Adams studies), the target heart rate for aerobic exercise is 117-165 beats/minute (60%-85% of the recommended maximum safe heart rate for one's age).

even to achieve the small effects that were observed at the 60 ppb personal exposure. To see how unrealistic, the breathing rates in the laboratory studies can be compared with real-world breathing rate data for the general population from Brochu (2006).

In the three laboratory studies, the subjects inhaled air at a rate of 20 liters per minute per square meter of body surface area. This translates into inhalation rates of about 55 cubic meters or air per day (m^3/day) for men and 46 m^3/day for women. In the Brochu (2006) data, the 99th percentile of inhalation rate for any age group is 24 m^3/day for men and 19 m^3/day for women (both for ages 18 to 30).

Since ozone dose is proportional to air inhalation rate, this demonstrates that the ozone doses used in the Adams, Schlegle et al., and Kim et al. studies are much higher than real-world humans would ever experience. And even so, these studies were able to elicit minimal effects on lung function and symptoms.

There is an additional reason why this issue of lengthy exercise is important. The Adams study was performed with physically fit exercise physiology majors from UC Davis. The Schlegle et al. and Kim et al. studies were performed with similar physically fit young adults. EPA claims that these people, being healthy, are less likely to experience significant effects of ozone and that children and the elderly would be more sensitive to ozone's effects. As a result, EPA claims, these laboratory studies place only a lower limit on the effects of low ozone exposures. But this claim ignores the fact that children, the elderly, and those with respiratory diseases are *not capable* of exercising vigorously for the hours in a row necessary to elicit even the small ozone effects reported by Adams. Indeed, as the Brochu (2006) data show, for children and the elderly, 99th percentile inhalation rates are much lower than for the 18 to 30 age group: 12 m^3/day for children ages 3 to 10, and 18 m^3/day for adults over 60. Thus, contrary to EPA's claim, the results of Adams, Schlegle et al., and Kim et al. apply even less to children and the elderly than to young adults.

Conclusion

EPA's ozone modeling is based on 1990s ozone-precursor emissions, making it invalid for assessing the effects of climate warming on ozone levels in the future, when ozone-precursor emissions will be far lower. Indeed, even *current* ozone-precursor emissions are only about half the levels used in EPA's studies.

Research based on more realistic levels of future ozone-precursor emissions shows that ozone levels will be much lower in the future, regardless of warming, and that the effect of warming on ozone—the "climate penalty"—has already been greatly reduced. Since ozone-precursor emissions are dropping rapidly, whatever climate penalty remains will likely disappear within a decade or two, as most remaining ozone-precursor emissions are eliminated by already-adopted measures.

Taken together the weight of the evidence indicates that EPA has exaggerated future ozone levels, the effects of warming on ozone levels, and the health risks from any given level of ozone. In reality, future ozone levels will be below a level of concern for human health, regardless of whether the climate warms.

References

Adams, W. C. 2002. "Comparison of Chamber and Face-mask 6.6-hour Exposures to Ozone on Pulmonary Function and Symptoms Responses." *Inhal Toxicol* 14 (7): 745–64.

———. 2006. "Comparison of Chamber 6.6-h Exposures to 0.04-0.08 PPM Ozone via Square-wave and Triangular Profiles on Pulmonary Responses." *Inhal Toxicol* 18 (2): 127–36.

Anderson, HR, RW Atkinson, JL Peacock, L Marston, and K Konstantinou. 2004. *Meta-analysis of Time-series Studies and Panel Studies of Particulate Matter (PM) and Ozone*. World Health Organization.

Avise, J., J. Chen, B. Lamb, C. Wiedinmyer, A. Guenther, E. Salathé, and C. Mass. 2009. "Attribution of Projected Changes in Summertime US Ozone and PM2. 5 Concentrations to Global Changes." *Atmos. Chem. Phys* 9: 1111–1124.

Aw, J., and M.J. Kleeman. 2003. "Evaluating the First-order Effect of Inter-annual Temperature Variability on Urban Air Pollution." *Journal of Geophysical Research - Atmospheres* 108 (D12): 7–1 – 7–18.

Barr, B. C., D. M. Hyde, C. G. Plopper, and D. L. Dungworth. 1988. "Distal Airway Remodeling in Rats Chronically Exposed to Ozone." *American Review of Respiratory Disease* 137 (4): 924–938.

———. 1990. "A Comparison of Terminal Airway Remodeling in Chronic Daily Versus Episodic Ozone Exposure." *Toxicology and Applied Pharmacology* 106 (3): 384–407.

Bell, M. L., F. Dominici, and J. M. Samet. 2005. "A Meta-analysis of Time-series Studies of Ozone and Mortality with Comparison to the National Morbidity, Mortality, and Air Pollution Study." *Epidemiology* 16 (4): 436–45.

Bell, M. L., A. McDermott, S. L. Zeger, J. M. Samet, and F. Dominici. 2004. "Ozone and Short-term Mortality in 95 US Urban Communities, 1987-2000." *Journal of the American Medical Association* 292 (19): 2372–8.

Bell, Michelle L., Richard Goldberg, Christian Hogrefe, Patrick L. Kinney, Kim Knowlton, Barry Lynn, Joyce Rosenthal, Cynthia Rosenzweig, and Jonathan A. Patz. 2007. "Climate Change, Ambient Ozone, and Health in 50 US Cities." *Climatic Change* 82 (1-2) (January 6): 61–76.

Bell, Michelle L., Jee Young Kim, and Francesca Dominici. 2007. "Potential Confounding of Particulate Matter on the Short-Term Association Between Ozone and Mortality in Multisite Time-Series Studies." *Environmental Health Perspectives* 115 (11) (August 2): 1591–1595.

Bell, Michelle L., Roger D. Peng, and Francesca Dominici. 2006. "The Exposure–Response Curve for Ozone and Risk of Mortality and the Adequacy of Current Ozone Regulations." *Environmental Health Perspectives* 114 (4) (January 23): 532–536.

Beresford, S. A., K. C. Johnson, C. Ritenbaugh, N. L. Lasser, L. G. Snetselaar, H. R. Black, G. L. Anderson, et al. 2006. "Low-fat Dietary Pattern and Risk of Colorectal Cancer: The

Women's Health Initiative Randomized Controlled Dietary Modification Trial." *Journal of the American Medical Association* 295 (6): 643–54.

Bishop, G. A., and D. H. Stedman. 2008. "A Decade of On-road Emissions Measurements." *Environmental Science and Technology* 42 (5): 1651–1656.

Bloomer, Bryan J., Jeffrey W. Stehr, Charles A. Piety, Ross J. Salawitch, and Russell R. Dickerson. 2009. "Observed Relationships of Ozone Air Pollution with Temperature and Emissions." *Geophysical Research Letters* 36 (May 5): 5 pp.

Brauer, M., and J. R. Brook. 1997. "Ozone Personal Exposures and Health Effects for Selected Groups Residing in the Fraser Valley." *Atmospheric Environment* 31 (14): 2113–2121.

Brochu, Pierre, Jean-François Ducré-Robitaille, and Jules Brodeur. 2006. "Physiological Daily Inhalation Rates for Free-Living Individuals Aged 2.6 Months to 96 Years Based on Doubly Labeled Water Measurements: Comparison with Time-Activity-Ventilation and Metabolic Energy Conversion Estimates." *Human & Ecological Risk Assessment* 12 (4): 736–761.

Chang, L. T., P. Koutrakis, P. J. Catalano, and H. H. Suh. 2000. "Hourly Personal Exposures to Fine Particles and Gaseous Pollutants--results from Baltimore, Maryland." *Journal of the Air and Waste Management Association* 50 (7): 1223–35.

Chen, C. Y., A. C. Bonham, C. G. Plopper, and J. P. Joad. 2003. "Neuroplasticity in Nucleus Tractus Solitarius Neurons After Episodic Ozone Exposure in Infant Primates." *J Appl Physiol* 94 (2): 819–27.

Chen, J., J. Avise, B. Lamb, E. Salathé, C. Mass, A. Guenther, C. Wiedinmyer, et al. 2009. "The Effects of Global Changes Upon Regional Ozone Pollution in the United States." *Atmos. Chem. Phys.* 9 (4) (February 16): 1125–1141.

Chow, C. K., C. G. Plopper, and D. L. Dungworth. 1979. "Influence of Dietary Vitamin E on the Lungs of Ozone-exposed Rats. A Correlated Biochemical and Histological Study." *Environmental Research* 20 (2): 309–317.

Dawson, John P., Pavan N. Racherla, Barry H. Lynn, Peter J. Adams, and Spyros N. Pandis. 2009. "Impacts of Climate Change on Regional and Urban Air Quality in the Eastern United States: Role of Meteorology." *Journal of Geophysical Research* 114 (March 14): 11 pp.

Dodge, D. E., R. B. Rucker, K. E. Pinkerton, C. J. Haselton, and C. G. Plopper. 1994. "Dose-dependent Tolerance to Ozone. III. Elevation of Intracellular Clara Cell 10-kDa Protein in Central Acini of Rats Exposed for 20 Months." *Toxicology and Applied Pharmacology* 127 (1): 109–123.

van den Eeden, S. F., Charles P. Quesenberry, Jun Shan, and Frederick W. Lurmann. 2002. *Particulate Air Pollution and Morbidity in the California Central Valley: A High Particulate Pollution Region*. Sacramento: California Air Resources Board.

EPA. undated. "Early Action Compacts - 1997 Ozone Standard". Overviews & Factsheets. http://www.epa.gov/airquality/eac/.

———. 2002. “Kansas City, MO Ozone Maintenance Plan - Second Ten-Year Plan”. http://www.epa.gov/region7/air/rules/missouri/kcozone2-10year.htm.

———. 2006. *Air Quality Criteria for Ozone and Related Photochemical Oxidants*. Washington, DC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=149923.

———. 2007a. *Review of the National Ambient Air Quality Standards for Ozone: Policy Assessment of Scientific and Technical Information, Staff Paper*.

———. 2007b. “National Ambient Air Quality Standards for Ozone; Proposed Rule.” *Federal Register* 72 (132) (July 11): 37818–37919.

———. 2009a. *Assessment of the Impacts of Global Change on Regional U.S. Air Quality: A Synthesis of Climate Change Impacts on Ground-level Ozone Interim Report of US GCRP*. EPA.

———. 2009b. *Assessment of the Impacts of Global Change on Regional U.S. Air Quality: A Synthesis of Climate Change Impacts on Ground-level Ozone; Appendices*.

———. 2009c. *Technical Support Document for Endangerment and Cause or Contribute Findings for Greenhouse Gases Under Section 202(a) of the Clean Air Act*.

———. 2012a. “1970 - 2011 Average Annual Emissions, All Criteria Pollutants.” http://www.epa.gov/ttnchie1/trends/.

———. 2012b. *Integrated Science Assessment of Ozone and Related Photochemical Oxidants (Third External Review Draft)*. http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=242490.

Gauderman, W. J., E. Avol, F. Gilliland, H. Vora, D. Thomas, K. Berhane, R. McConnell, et al. 2004. “The Effect of Air Pollution on Lung Development from 10 to 18 Years of Age.” *New England Journal of Medicine* 351 (11): 1057–67.

Geyh, A. S., J. Xue, H. Ozkaynak, and J. D. Spengler. 2000. “The Harvard Southern California Chronic Ozone Exposure Study: Assessing Ozone Exposure of Grade-school-age Children in Two Southern California Communities.” *Environmental Health Perspectives* 108 (3): 265–70.

Goodman, S. N. 2005. “The Methodologic Ozone Effect.” *Epidemiology* 16 (4): 430–5.

Harkema, J. R., C. G. Plopper, and D. M. Hyde. 1987. “Response of the Macaque Nasal Epithelium to Ambient Levels of Ozone: A Morphologic and Morphometric Study of the Transitional and Respiratory Epithelium.” *American Journal of Pathology* 128 (1): 29–44.

Hauglustaine, D. A., J. Lathière, S. Szopa, and G. A. Folberth. 2005. “Future Tropospheric Ozone Simulated with a Climate-chemistry-biosphere Model.” *Geophysical Research Letters* 32 (24).

Health Effects Institute. 2003. *Revised Analyses of Time-Series Studies of Air Pollution and Health*. Boston.

Hogrefe, C., J. Biswas, B. Lynn, K. Civerolo, J. -Y. Ku, J. Rosenthal, C. Rosenzweig, R. Goldberg, and P. L. Kinney. 2004. "Simulating Regional-scale Ozone Climatology over the Eastern United States: Model Evaluation Results." *Atmospheric Environment* 38 (17): 2627–2638.

Howard, B. V., L. Van Horn, J. Hsia, J. E. Manson, M. L. Stefanick, S. Wassertheil-Smoller, L. H. Kuller, et al. 2006. "Low-fat Dietary Pattern and Risk of Cardiovascular Disease: The Women's Health Initiative Randomized Controlled Dietary Modification Trial." *Journal of the American Medical Association* 295 (6): 655–66.

Ioannidis, J. P. 2005. "Why Most Published Research Findings Are False." *PLoS Medicine.* 2 (8).

Ito, K. 2003. "Assocations of Particulate Matter Components with Daily Mortality and Morbidity in Detroit." In *Revised Analyses of Time-Series Studies of Air Pollution and Health*. Boston: Health Effects Institute.

Ito, K., S. F. De Leon, and M. Lippmann. 2005. "Associations Between Ozone and Daily Mortality: Analysis and Meta-analysis." *Epidemiology* 16 (4): 446–57.

Jacob, D. J., and D. A. Winner. 2009. "Effect of Climate Change on Air Quality." *Atmospheric Environment* 43 (1): 51–63.

Johnson, T, K Clark, K Anderson, A Geyh, and W Ollison. 1996. "A Pilot Study of Los Angeles Personal Ozone Exposures During Scripted Activities." In *Measurement of Toxic and Related Air Pollutants*, 358–365. Research Triangle Park, NC: Air and Waste Management Association.

Jung-Hun Woo, Shan He, Efthimios Tagaris, Kuo-Jen Liao, Kasemsan Manomaiphiboon, Praveen Amar, and Armistead G. Russell. 2008. "Development of North American Emission Inventories for Air Quality Modeling Under Climate Change." *Journal of the Air & Waste Management Association* 58 (11) (November): 1483–1494.

Katsouyanni, Klea, and Jonathan Samet. 2009. *Air Pollution and Health: A European and North American Approach (APHENA)*. Boston: Health Effects Institute. http://pubs.healtheffects.org/getfile.php?u=518.

Keatinge, W. R., and G. C. Donaldson. 2006. "Heat Acclimatization and Sunshine Cause False Indications of Mortality Due to Ozone." *Environmental Research* 100 (3): 387–93.

Kim, Chong S., Neil E. Alexis, Ana G. Rappold, Howard Kehrl, Milan J. Hazucha, John C. Lay, Mike T. Schmitt, Martin Case, Robert B. Devlin, and David Diaz-Sanchez. 2011. "Lung Function and Inflammatory Responses in Healthy Young Adults Exposed to 0.06 Ppm Ozone for 6.6 Hours." *American Journal of Respiratory and Critical Care Medicine* 183 (9) (May 1): 1215–1221.

Knowlton, K., J. E. Rosenthal, C. Hogrefe, B. Lynn, S. Gaffin, R. Goldberg, C. Rosenzweig, K. Civerolo, J. Y. Ku, and P. L. Kinney. 2004. "Assessing Ozone-related Health Impacts Under a Changing Climate." *Environmental Health Perspectives* 112 (15): 1557–63.

Kolata, Gina. 2006. "Big Study Finds No Clear Benefit Of Calcium Pills." *New York Times*. February 16, 2006.

http://www.nytimes.com/2006/02/16/health/16bones.html?_r=1&pagewanted=all.

Koop, Gary, and Lise Tole. 2004. "Measuring the Health Effects of Air Pollution: To What Extent Can We Really Say That People Are Dying from Bad Air?" *Journal of Environmental Economics and Management* 47: 30–54.

Lee, K., W. J. Parkhurst, J. Xue, A. H. Ozkaynak, D. Neuberg, and J. D. Spengler. 2004. "Outdoor/Indoor/Personal Ozone Exposures of Children in Nashville, Tennessee." *Journal of the Air and Waste Management Association* 54 (3): 352–9.

Lee, M. G., A. M. Wheelock, B. Boland, and C. G. Plopper. 2008. "Long-term Ozone Exposure Attenuates 1-nitronaphthalene-induced Cytotoxicity in Nasal Mucosa." *American Journal of Respiratory Cell and Molecular Biology* 38 (3): 300–309.

Levy, J. I., S. M. Chemerynski, and J. A. Sarnat. 2005. "Ozone Exposure and Mortality: An Empiric Bayes Metaregression Analysis." *Epidemiology* 16 (4): 458–68.

Liao, Hong, Wei-Ting Chen, and John H. Seinfeld. 2006. "Role of Climate Change in Global Predictions of Future Tropospheric Ozone and Aerosols." *Journal of Geophysical Research* 111 (June 17): 18 pp.

Liu, L. J., R. Delfino, and P. Koutrakis. 1997. "Ozone Exposure Assessment in a Southern California Community." *Environmental Health Perspectives* 105 (1): 58–65.

Lumley, T., and L. Sheppard. 2003. "Time Series Analyses of Air Pollution and Health: Straining at Gnats and Swallowing Camels?" *Epidemiology* 14 (1): 13–4.

McConnell, R., K. Berhane, F. Gilliland, S. J. London, T. Islam, W. J. Gauderman, E. Avol, H. G. Margolis, and J. M. Peters. 2002. "Asthma in Exercising Children Exposed to Ozone: a Cohort Study." *Lancet* 359 (9304): 386–91.

Mickley, L.J., D.J. Jacob, B. D. Field, and D. Rind. 2004. "Effects of Future Climate Change on Regional Air Pollution Episodes in the United States." *Geophysical Research Letters* 31: L24103.

Moffatt, R. K., D. M. Hyde, C. G. Plopper, W. S. Tyler, and L. F. Putney. 1987. "Ozone-induced Adaptive and Reactive Cellular Changes in Respiratory Bronchioles of Bonnet Monkeys." *Exp Lung Res* 12 (1): 57–74.

Montori, V. M., M. Smieja, and G. H. Guyatt. 2000. "Publication Bias: a Brief Review for Clinicians." *Mayo Clinic Proceedings* 75 (12): 1284–8.

Moolgavkar, S. H. 2002. *Review of Chapter 8 of the Criteria Document for Particulate Matter (comments Submitted to EPA)*.

———. 2005. "A Review and Critique of the EPA's Rationale for a Fine Particle Standard." *Regulatory Toxicology and Pharmacology* 42 (1): 123–144.

Mortimer, K. M., L. M. Neas, D. W. Dockery, S. Redline, and I. B. Tager. 2002. "The Effect of Air Pollution on Inner-city Children with Asthma." *European Respiratory Journal* 19 (4): 699–705.

Murazaki, K., and P. Hess. 2006. "How Does Climate Change Contribute to Surface Ozone Change over the United States?" *Journal of Geophysical Research* 111 (D5).

Nakicenovic, Ndbojsa, and Rob Swart. 2000. *Special Report on Emissions Scenarios*. IPCC. http://www.ipcc.ch/ipccreports/sres/emission/index.php?idp=0.

O'Neill, M. S., M. Ramirez-Aguilar, F. Meneses-Gonzalez, M. Hernandez-Avila, A. S. Geyh, J. J. Sienra-Monge, and I. Romieu. 2003. "Ozone Exposure Among Mexico City Outdoor Workers." *Journal of the Air and Waste Management Association* 53 (3): 339–46.

Prentice, R. L., B. Caan, R. T. Chlebowski, R. Patterson, L. H. Kuller, J. K. Ockene, K. L. Margolis, et al. 2006. "Low-fat Dietary Pattern and Risk of Invasive Breast Cancer: The Women's Health Initiative Randomized Controlled Dietary Modification Trial." *Journal of the American Medical Association* 295 (6): 629–42.

Racherla, P. N., and P. J. Adams. 2008. "The Response of Surface Ozone to Climate Change over the Eastern United States." *Atmospheric Chemistry and Physics* 8 (4) (February 22): 871–885.

Racherla, Pavan N., and Peter J. Adams. 2009. "U.S. Ozone Air Quality Under Changing Climate and Anthropogenic Emissions." *Environmental Science & Technology* 43 (3) (February 1): 571–577.

Racherla, Pavan Nandan, and Peter J. Adams. 2006. "Sensitivity of Global Tropospheric Ozone and Fine Particulate Matter Concentrations to Climate Change." *Journal of Geophysical Research* 111 (D24) (December 16).

Ramirez-Aguilar, M., A. Barraza-Villarreal, H. Moreno-Macias, A. M. Winer, P. Cicero-Fernandez, M. G. Velez-Marquez, M. Cortez-Lugo, J. J. Sienra-Monge, and I. Romieu. 2008. "Assessment of Personal Exposure to Ozone in Asthmatic Children Residing in Mexico City." *Salud Publica De Mexico* 50 (1): 67–75.

Roberts, Steven, and Michael A. Martin. 2010. "Does Ignoring Model Selection When Assessing the Effect of Particulate Matter Air Pollution on Mortality Make Us Too Vigilant?" *Annals of Epidemiology* 20 (10) (October): 772–778.

Sarnat, J. A., P. Koutrakis, and H. H. Suh. 2000. "Assessing the Relationship Between Personal Particulate and Gaseous Exposures of Senior Citizens Living in Baltimore, MD." *Journal of the Air and Waste Management Association* 50 (7): 1184–98.

Schelegle, Edward S., Christopher A. Morales, William F. Walby, Susan Marion, and Roblee P. Allen. 2009. "6.6-Hour Inhalation of Ozone Concentrations from 60 to 87 Parts Per Billion in Healthy Humans." *American Journal of Respiratory and Critical Care Medicine* 180 (3) (August 1): 265–272.

Schwartz, Joel, and Steven F. Hayward. 2008. *Air Quality in America*. Washington, DC: American Enterprise Institute.

Smith, G. D. 2001. "Reflections on the Limitations to Epidemiology." *Journal of Clinical Epidemiology* 54 (4): 325–31.

Smith, Richard, Peter Guttorp, Lianne Sheppard, Thomas Lumley, and Naomi Ishikawa. 2001. *Comments on the Criteria Document for Particulate Matter Air Pollution*. NRCSE Technical Report Series. EPA.

Smith, Richard L, Baowei Xu, and Paul Switzer. 2009. "Reassessing the Relationship Between Ozone and Short-term Mortality in U.S. Urban Communities." *Inhalation Toxicology* 21 Suppl 2 (September): 37–61.

Steiner, Allison L., Shaheen Tonse, Ronald C. Cohen, Allen H. Goldstein, and Robert A. Harley. 2006. "Influence of Future Climate and Emissions on Regional Air Quality in California." *Journal of Geophysical Research* 111 (D18).

Tao, Zhining, Allen Williams, Ho-Chun Huang, Michael Caughey, and Xin-Zhong Liang. 2007. "Sensitivity of U.S. Surface Ozone to Future Emissions and Climate Changes." *Geophysical Research Letters* 34 (April 27): 5 pp.

Taubes, G. 1995. "Epidemiology Faces Its Limits." *Science* 269 (5221): 164–165+167.

Thornton, A., and P. Lee. 2000. "Publication Bias in Meta-analysis: Its Causes and Consequences." *Journal of Clinical Epidemiology* 53 (2): 207–16.

Wilson, D. W., C. G. Plopper, and D. L. Dungworth. 1984. "The Response of the Macaque Tracheobronchial Epithelium to Acute Ozone Injury. A Quantitative Ultrastructural and Autoradiographic Study." *American Journal of Pathology* 116 (2): 193–206.

Woo, Jung-Hun, Shan He, Efthimios Tagaris, Kuo-Jen Liao, Kasemsan Manomaiphiboon, Praveen Amar, and Armistead G Russell. 2008. "Development of North American Emission Inventories for Air Quality Modeling Under Climate Change." *Journal of the Air & Waste Management Association (1995)* 58 (11) (November): 1483–1494.

Wu, Shiliang, Loretta J. Mickley, Daniel J. Jacob, David Rind, and David G. Streets. 2008a. "Effects of 2000–2050 Changes in Climate and Emissions on Global Tropospheric Ozone and the Policy-relevant Background Surface Ozone in the United States." *Journal of Geophysical Research* 113 (D18) (September 27).

Wu, Shiliang, Loretta J. Mickley, Eric M. Leibensperger, Daniel J. Jacob, David Rind, and David G. Streets. 2008b. "Effects of 2000–2050 Global Change on Ozone Air Quality in the United States." *Journal of Geophysical Research* 113 (March 19): 12 pp.

Young, S. Stanley, and Alan Karr. 2011. "Deming, Data and Observational Studies." *Significance* 8 (3): 116–120. doi:10.1111/j.1740-9713.2011.00506.x.

Zeng, G., J. A. Pyle, and P. J. Young. 2008. "Impact of Climate Change on Tropospheric Ozone and Its Global Budgets." *Atmospheric Chemistry and Physics* 8 (2): 369–387.