November 29, 2011

U.S. Environmental Protection Agency
Office of Environmental Information (OEI) Docket
Mail Code: 2822T
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Draft Integrated Science Assessment for Ozone and Related Photochemical Oxidants - Second External Review Draft; Docket ID No. EPA-HQ-ORD-2011-0050

Submitted Electronically

The Alliance of Automobile Manufacturers appreciates the opportunity to provide comments on the Second External Review Draft "Integrated Science Assessment for Ozone and Related Photochemical Oxidants."

Attached please find our comments prepared by Jon Heuss and George Wolff of AIR Improvement Resource, Inc.

If you should have any questions, please contact Giedrius at (248) 915-8836.

Sincerely,

Giedrius Ambrozaitis
Director, Environmental Affairs

Attachment

Review and Critique of the U. S. Environmental Protection Agency's Second External Review Draft of the "Integrated Science Assessment for Ozone and Related Photochemical Oxidants"

By
Jon M. Heuss
George T. Wolff
Dennis F. Kahlbaum
Air Improvement Resource, Inc.

Prepared for
The Alliance of Automobile Manufacturers

November 28, 2011

Executive Summary

Air Improvement Resource, Inc. (AIR) reviewed the second draft Integrated Science Assessment (ISA) focusing on the portions of the document that are important to providing the Administrator with the most relevant science with which to judge the health effects of ozone and establish a primary ozone standard which will protect the public health with an adequate margin of safety. The ISA evaluates controlled human exposure studies, animal toxicology, and short- and long-term term epidemiology and makes determinations of the weight of evidence for ozone causing health effects in various categories. AIR identified many issues with the draft ISA's evaluation of the data.

AIR comments focus on the background of ozone uncontrollable through reduction in US man-made emissions, the human clinical studies of ozone effects and their interpretation in terms of the public health, and the epidemiological studies of associations of ozone with health endpoints and their interpretation in terms of public health.

Background Ozone

With regard to background ozone, there is substantial new information that the background is higher than EPA estimated in the previous review. The new higher background estimates affect consideration of both the primary and secondary standards. Importantly, the background is higher than average when ozone exceeds 0.060 ppm, particularly in the intermountain West. The recent modeling also provide strong evidence that Canadian and Mexican emissions significantly enhance the background and this enhancement is occurring on high ozone days and can be a major contributor to exceedances of the 0.075 ppm standard. As a result, we strongly recommend that the background that includes Canadian and Mexican emissions be used in conducting the risk

assessments and in determining the degree of emission controls required to reach attainment with any ozone standard, especially in the Eastern two-thirds of the US and in the Southwestern US.

Controlled Human Exposures

The controlled human exposure studies provide a strong body of information on the dose-response of effects of 1-to-3 hour and 6- to 8-hour exposures to ozone. The first effects - transient, reversible FEV1 decrements - are the body's reflexive reaction to the presence of an irritant gas unrelated to sensations of discomfort. Such effects occur after exposures to 0.08 ppm for 6 to 8 hours when the subjects are exercising at a rate that would be considered strenuous when carried out intermittently for an eight-hour period. There are now several studies of exposure to 0.060 ppm with exercise that all indicate very small group mean changes in FEV1, changes of the same magnitude as the accuracy of repeat FEV1 measurements. Importantly, respiratory symptoms were not affected by ozone exposure at the 0.060 ppm level.

The public health significance of the first effects of ozone is not adequately discussed in the ISA. According to the American Thoracic Society guidelines, the functional changes at 0.06 ppm would not be considered as adverse. The knowledge of the basic nature and extent of functional effects has not changed since the 1997 and 2008 reviews. The fact that personal exposures to ozone are only a fraction of the monitored levels provides a large margin of safety from the first effects identified in controlled human studies for the vast bulk of the population as they go about their daily activities. In addition, the existence of a substantial threshold for the first physiological effects in controlled studies is not consistent with EPA's assumption that the more severe effects suggested by some epidemiological studies have no threshold.

Epidemiological Studies

The epidemiological or observational studies of the association of ozone with various health endpoints continue to be difficult to interpret. As more studies are published, the fundamental weaknesses of this body of information have become more apparent. For example, publication bias is now known to exaggerate the apparent strength and consistency of association. Limitations due to issues of model selection and stochastic variability add substantially to the uncertainty. In addition, the issue of confounding raises the possibility that a positive association for ozone or any other pollutant in a single-pollutant model may be an indicator of some other pollutant rather than evidence of an independent effect of that pollutant. EPA's practice of making causality determinations for broad categories of effects is misleading because the evidence of causality for the various health endpoints varies widely.

The second draft ISA continues to over-rely on the positive ozone associations in the literature, discount evidence from studies that report null results, and avoid a rigorous and balanced discussion of biological plausibility. As a result, the second draft continues to inappropriately weigh the evidence from epidemiology with regard to ozone health

effects. For example, as each criteria pollutant has been reviewed, EPA is claiming or has claimed independent respiratory effects that are considered as causal or likely causal for four different criteria pollutants based on single-pollutant models.

While there is evidence of small acute FEV1 changes, the lack of consistent evidence implicating ozone as being associated with inflammation or respiratory symptoms in observational studies is an important finding that needs to be considered as the ISA evaluates the biological plausibility of even more severe effects such as daily hospital admissions and mortality.

With regard to hospital admissions and mortality, the overall results of a large multi-continent Health Effects Institute (HEI) study do not support EPA's claims of causal relationships between ozone and mortality or between ozone and hospital admissions. The ISA uses selected results from the HEI study and the literature in general to claim consistent or generally positive effects on mortality and hospital admissions. However, the full pattern of results for these endpoints demonstrates a wide range from positive to negative associations in individual cities in multi-city studies and a regional and seasonal pattern of combined associations that is not consistent with ozone causality.

The overall evidence for cardiovascular effects from current ambient ozone concentrations is weak and inconsistent. The ISA acknowledges the lack of a consistent cardiovascular morbidity signal and weak evidence for biological plausibility for ozone-induced cardiovascular morbidity. Therefore, the body of evidence is <u>not</u> suggestive of a causal relationship between relevant short-term exposures to O_3 and cardiovascular effects.

With regard to chronic mortality, the ISA focuses on one positive study, Jerrett et al. (2009), as showing a chronic respiratory mortality signal for ozone. However, the respiratory mortality signal is present only for females in spite of the fact that males would be expected to receive higher ozone doses by being outside exercising more than females. In addition, the regional results reported by Jerrett et al. show no respiratory mortality effect in Southern California, the Northeast, or the Industrial Midwest, the regions of the country with the highest historic man-made ozone exposures. Moreover there are several other chronic mortality studies that do not report an ozone effect. Finally, the presence of a chronic respiratory mortality signal is not coherent with the lack of an acute respiratory mortality signal in the HEI multi-continent study. For these reasons, the evidence for a chronic ozone mortality effect is much weaker than indicated in the ISA.

Review and Critique of the U. S. Environmental Protection Agency's Second External Review Draft of the "Integrated Science Assessment for Ozone and Related Photochemical Oxidants"

By
Jon M. Heuss
George T. Wolff
Dennis F. Kahlbaum
Air Improvement Resource, Inc.

Prepared for
The Alliance of Automobile Manufacturers

November 28, 2011

Introduction

The U. S Environmental Protection Agency (EPA) is in the process of reviewing the National Ambient Air Quality Standards (NAAQS) for ozone (O_3) with the issuance of the second external review draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants[1] (ISA) in September 2011. Air Improvement Resource, Inc. (AIR) reviewed the draft with a focus on the portions of the ISA that are important to providing the Administrator with the most relevant science with which to judge the health effects of ozone and establish a primary ozone standard which will protect the public health with an adequate margin of safety. AIR and the Alliance of Automobile Manufacturers (Alliance) participated in the previous review of the ozone standard that resulted in the 8-hour standard being set at 0.075 ppm.[2] AIR and the Alliance also participated[3] in the re-consideration of the ozone standard that was initiated by Administrator Jackson in January 2010. Finally, AIR and the Alliance provided public comments[4] on the first draft ISA.[5]

The following comments focus on the policy relevant background, the human clinical

[1] U. S. Environmental Protection Agency, Second External Review Draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants, EPA/600/R-10/076b, Sept. 2011.
[2] Comments of the Alliance of Automobile Manufacturers on EPA's Proposal to Revise National Ambient Air Quality Standards for Ozone, 72 Fed. Reg. 37,818 (July 11, 2007), dated Oct. 9, 2007.
[3] Comments of the Alliance of Automobile Manufacturers on EPA's Proposal to Revise National Ambient Air Quality Standards for Ozone, 75 Fed. Reg. 2992 (Jan. 19, 2010), dated Mar, 22, 2010.
[4] J. M. Heuss and George T. Wolff, Review and Critique of the U. S. Environmental Protection Agency's First External Review Draft of the "Integrated Science Assessment for Ozone and Related Photochemical Oxidants," Air Improvement Resource, Inc. Report, Prepared for The Alliance of Automobile Manufacturers, May 2011.
[5] U. S. Environmental Protection Agency, First External Review Draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants, EPA/600/R-10/076a, Mar. 2011.

studies of ozone effects and their interpretation in terms of the public health, and the epidemiological studies of associations of ozone with health endpoints and their interpretation in terms of public health.

The choice of policy relevant background of ozone (the ozone that cannot be reduced through control of US man-made emissions) is particularly important since it affects the risk estimates that the Agency will use later in the NAAQS review process and provides a limit to how stringent a standard can be and still be achieved throughout the US. As detailed in previous submissions (Alliance October 9, 2007 and March 22, 2010 comments), the Alliance has been concerned that EPA has underestimated the relevant background in the prior review. As discussed below, there is now substantial new modeling and other information that supports the Alliance view.

The human clinical studies of ozone are important since these data provide a strong and consistent body of information on the dose-response of effects of 1- to 3- hour and 8-hour exposures to ozone. Although there are now more studies of 6- to 8-hour exposures to low ozone concentrations while exercising heavily, EPA's estimate of the dose-response curve at low concentrations has not changed appreciably. The most important issue with regard to these data is how to translate the results into human risk as people go about their daily life.

The epidemiological or observational studies of the association of ozone with various health endpoints continue to be difficult to interpret. As more studies are published, the fundamental weaknesses of this body of information have become more apparent. Public comments from several groups have detailed these concerns and inconsistencies.[6] However, the ISA continues to gloss over these issues and fails to address the concerns and inconsistencies that have been raised in public comments. As a result, the draft ISA continues to overstate the consistency and weight of evidence for ozone effects from epidemiologic studies.

Before discussing the evidence for individual categories of potential effects, it is appropriate to make some general comments on the organization of the document. Chapter 6 reviews, summarizes, and integrates the evidence for various health outcomes related to short-term ozone exposures. As such, it is the main place in the document where ozone health effects are discussed and will be the focus of AIR comments. However, the information in other chapters is important as it illuminates and informs the discussion and integration in Chapter 6. Therefore, we provide comments on other chapters as needed to aid in the integrative discussion.

Chapter 6 is organized by major health effect categories (e.g., respiratory, cardiovascular,

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[6] C. R. Long, et al. "Comments on U.S. EPA's Causality Determinations for Short-term and Long-term Ozone Exposures and Mortality in the Integrated Science Assessment for Ozone and Related Photochemical Oxidants, First External Review Draft," May 5, 2011. Available as Attachment B at: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-ORD-2011-0050-0009; J. E Goodman, "Comments on the 'Integrated Science Assessment of Ozone and Related Photochemical Oxidants' EPA Document EPA/600/R-10/076A; released March 2011." Available as Attachment 1 to Docket ID EPA-HQ-ORD-2011-0050-0007; Alliance comments, supra note 4.

mortality). Within each category, the evidence is organized by health endpoint (e.g., lung function, pulmonary inflammation) and then by specific scientific discipline (e.g., controlled human exposure, epidemiology, and toxicology). Each major section (e.g., respiratory, cardiovascular, mortality) concludes with an integrated summary of the findings and a conclusion regarding causality. The determination of causality is made for each broad health effect category, such as respiratory effects, for example. While the overall organization is reasonable, making causality determinations for such broad categories is misleading because the evidence of causality for the various respiratory endpoints varies dramatically. To lump the evidence together and draw a conclusion regarding causality for such a large category is scientifically unsound. Instead, separate determinations should be made for sub-categories of effects.

I. Policy Relevant Background

A. EPA's Choice of Background Ozone Values Has Profound Consequences on the Risk Assessment and the Degree of Emission Reductions Required to Meet a NAAQS.

Because of the way EPA conducts their risk assessments, most of the annual health risk from ozone exposure accumulates on days when the ambient ozone concentrations are above background but below the NAAQS. Thus, the choice of the background level is a critical determinant of the amount of relative risk on any given day.[7] For example, Smith[8] has shown that if EPA had used a background value of 40 ppb (0.040 ppm) instead of the range of 15-35 ppb, 92 to 100% of EPA's estimated risk would have disappeared.

The background concentration represents the minimum concentration that is achievable if all US anthropogenic emissions were eliminated. Consequently, if the background is underestimated, the degree of control required to meet any NAAQS will be underestimated and chronic nonattainment will prevail.

As a result, it is important that the background be properly determined so that the real risk can be estimated and that there can be a reasonable expectation that the NAAQS can be attained after a control strategy is designed and implemented. In the previous review of the ozone NAAQS, EPA introduced a new term, Policy Relevant Background (PRB), which they define as "the distribution of O_3 concentrations that would be observed in the US in the absence of anthropogenic (man-made) emissions of precursor emissions (e.g., VOC, NO_x, and CO) in the US, Canada, and Mexico."[9] The differences between this

[7] McDonald-Buller, E.C., Allen, D.T., Brown, N., Jacob, D.J., Jaffe, D., Kolb, C.E., LeFohn, A.S., Oltmans, S., Parrish, D.D., Yarwood, G. and Zhang, L. (2011), *Environ. Sci. Technol.*, doiorg/10.1021/es2022818.

[8] Smith, A. E. (2011), Comments to CASAC on Reconsideration of the Ozone National Ambient Air Quality Standard in Advance of February 18, 2011 CASAC Conference Call. Available at http://yosemite.epa.gov/sab/sabproduct.nsf/7401CA2E8A7B7E6C85257831006377AB/$File/API+-+Smith+Comments.pdf.

[9] U.S. EPA (2007), Review of the National Ambient Air Quality Standards for Ozone: Policy Assessment of Scientific and Technical Information OAQPS Staff Paper, EPA-452/R-07-003, Jan. 2007.

definition and the definition previously used for background are that the current definition refers to a distribution of concentrations rather than a range or a fixed value and it explicitly excludes anthropogenic precursor emissions in Mexico and Canada. EPA does not include emissions from our two neighboring countries because the Agency unrealistically assumes that such emissions can be fixed by international agreements. This has not happened and it will not happen. In reality, the states that receive ozone impacts from Mexico and/or Canada are being penalized by EPA because they will need to implement additional control measures to offset these foreign emissions.

EPA further states: " As a result of long-range transport of O_3 and its precursors from anthropogenic sources within North America, estimates of PRB O_3 concentrations cannot be derived solely from measurements of O_3, and must be based on modeling." This represented a major departure from the way background was estimated in the past which was based ambient measurements in air masses entering the US. Specifically, EPA used the global photochemical transport model GEOS-Chem[10] to estimate PRB.

In the following sections, two aspects of the PRB O_3 will be discussed. First, the latest modeling results will be examined to determine whether the results are more realistic than the estimates derived in the previous review. Second, the consequences of excluding Canadian and Mexican emissions from the definition of PRB will be examined. Because of the way EPA defines PRB (i.e.; they exclude US, Mexican and Canadian emissions), PRB is identical to the North American Background (NAB). Because many authors use NAB and PRB interchangeably, they will be used interchangeably in these comments. The term US background (USB) will refer to the US background ozone with Mexican and Canadian anthropogenic emissions included.

B. New Policy Relevant Background Estimates Are Higher Since the Last Ozone Review

For the last review, the estimates of PRB/NAB were based on runs of the GEOS-Chem model applied to the 2001 warm season (April to November). The model output consisted of hourly gridded ozone estimates in 2^o latitude and 2.5^o longitude grid cells for the entire US. These outputs were used to generate monthly average diurnal profiles for each cell for April through October. Each mean monthly profile was then used in the risk assessment by applying the nearest grid cell's monthly profile to each of the twelve urban areas used by EPA in the risk assessment.

The mean profiles for each urban area were plotted in Appendix 2a of the 2007 Staff Paper.[11] An example of these profiles (for Detroit) is reproduced here as Figure 1. As seen from the figure, there is not much hourly variation in the estimated NAB profile.

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[10] Fiore, A., Jacob, D.J., Liu, H., Yantosca, R.M. Farlie, T.D. and Li, Q. (2003), "Variability in surface ozone background over the United States: Implications for air quality policy," *J. Geophys. Res.*, doi:10, 1029/2003JD003855.

[11] U.S. EPA (2007), Review of the National Ambient Air Quality Standards for Ozone: Policy Assessment of Scientific and Technical Information OAQPS Staff Paper Appendices to OAQPS Staff Paper, EPA-452/R-07-003, Jan. 2007.

This is the case for the other eleven urban areas as well. In general, April has the highest concentrations and August has the lowest summer concentrations. A broad afternoon/evening peak is observed with relatively constant concentrations from 1300 to 2300. Using these graphs, estimates of the 8-hour afternoon maximum concentrations of the NAB for April and August for each urban area were made and these are presented in Table 1. April and August were selected because they represent the months that generally experience the maximum and minimum PRB, respectively, during the ozone season. The monthly estimates fall within a range of 15-35 ppb with a mean of about 25 ppb. In April, the NABs range from a low of 27 ppb at a number of Eastern and Midwest cities to a high of 34 ppb in Sacramento while in August they range from a low in Sacramento of 15 ppb to a high of 28 ppb in Houston. In previous comments (May, 2011) on the first draft of the ISA,[12] AIR, Inc.[13] showed that these estimates of NAB were unrealistically low compared to analysis performed using ambient air measurements.

Since May 2011, additional GEOS-Chem modeling results have been presented by Zhang et al., (2011)[14] and ICF International (2011)[15] which have led to increases in the NAB estimates. Since the original Fiore et al. (2003) results were published, GEOS-Chem has undergone significant upgrades. The model now includes improved chemistry and physics and stratospheric ozone chemistry, updated meteorology and emissions and a much higher resolution grid of 0.5 x 0.6 km over North America. Both Zhang et al. and ICF used improved versions of the GEOS-Chem model. Zhang et al. used v8-02-03 and ICF used v9-01-01 versions of the model. For the new runs, both groups modeled the years 2006-2008.

The results from both groups are similar. On average, Zhang et al. report the overall average US NAB increased by 4 ppb from the 2001 modeling results used in the 2007 EPA Staff Paper. However, this increment varies spatially and temporally. For spring (March-May) ICF reports the US mean 8-hour NAB to be 33.2 ppb with ranges of 37.8 to 41.7 ppb in the West and 29.3 to 32.6 ppb in the East. For summer (June-August) the US mean was 30.0 ppb while the West ranged from 33.9 to 40.4 ppb and the East from 22.9 to 34.2 ppb. These values are a few ppb higher than the numbers presented in Table 1. Both groups also found higher NAB at the elevated sites (>1.5 km) in the intermountain West (includes the states of ID, MT, WY, NV, UT, CO, AZ, NM) compared to the lower elevation sites. For the high elevation sites, ICF reported a mean of 42.0 ppb while

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[12] U.S. EPA (2011), Integrated Science Assessment for Ozone and Related Photochemical Oxidants, EPA/600/R-10/076A, Mar. 2011.

[13] Wolff, G.T. (2011), Comments on Policy Relevant Background As Discussed in EPA's Draft Integrated Science Assessment for Ozone and Related Photochemical Oxidants. Available as Attachment B at: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-ORD-2011-0050-0009.

[14] Zhang, L; Jacob, DJ; Downey, NV; Wood, DA; Blewitt, D; Carouge, CC; Van donkelaar, A; Jones, DBA; Murray, LT; Wang, Y. (2011), "Improved estimate of the policy-relevant background ozone in the United States using the GEOS-Chem global model with 1/2° × 2/3° horizontal resolution over North America," *Atmos. Environ*. 45:6769-6776.

[15] ICF International (2011), "Modeling for North American Background Concentrations," Contract No. EP-C-09-009, Oct. 28, 2011.

Zhang et al. reported a mean of 40±7 ppb. At the lower elevation sites their respective NABs were 30.0 ppb and 27±8 ppb.

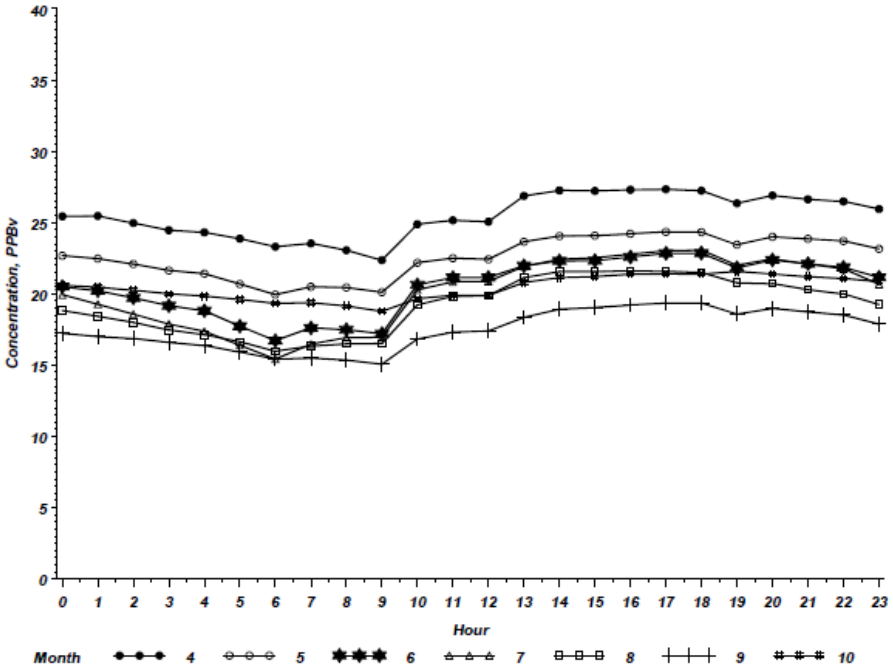

Figure 1: Diurnal NAB (PRB) ozone patterns in the Detroit CSA.[9]

CSA	April	August
Atlanta, GA	28 ppb	22 ppb
Boston, MA	30	20
Chicago, IL	32	23
Cleveland, OH	27	22
Detroit, MI	27	22
Houston, TX	31	28
Los Angeles, CA	32	20
New York, NY	27	22
Philadelphia, PA	28	23
Sacramento, CA	34	15
St. Louis, MO	28	26
Washington, DC	27	23

Table 1: Maximum 8-hour afternoon ozone NAB estimates by month for GEOS-Chem. These estimates were made from graphs which appeared in Appendix 2a of the EPA 2007 Staff Paper.[11]

However, the biggest differences in the new results were reported by Zhang et al. on days when the total ozone concentrations exceeded 60 ppb. They state:

> We also find that the PRB is higher than average when ozone exceeds 60 ppbv, particularly in the intermountain West. The annual 4th-highest PRB value in the model (representing the minimum standard achievable through suppression of North American anthropogenic emissions) is typically in the 35-45 ppbv range over the East and the West Coast but 50-60 ppbv in the intermountain West. Whereas previous GEOS-Chem studies found no occurrences of PRB ozone exceeding 60 ppbv, we find here some occurrences in the intermountain West. The high PRB values in that region compared to the proposed revisions of the ozone NAAQS (60-70 ppbv) suggest that special consideration may be needed in the NAAQS-setting process.

These results are shown in Figure 2. The top two maps show the mean maximum 8-hour NAB ozone across the US in the spring and summer, respectively while the bottom two maps show the NAB for days when the total ozone exceeded 60 ppb. Note that the NAB above 40 and 50 ppb are not just confined to the intermountain West, especially in the spring, but also cover parts of the Midwest and Great Lakes Region. This underscores the inappropriateness of EPA using monthly mean maximum 8-hour NAB concentrations in their risk assessments.

Further evidence that the use of monthly mean NAB is inappropriate is shown in plots of the hourly paired-in-time GEOS-Chem NAB and total ozone results that were prepared by Nichole Downey[16] (a coauthor on Zhang et al., 2011). Two such plots, for Denver and Boston for 2006 are shown in Figures 3 and 4. Although the two graphs are significantly different, they show frequent occurrences of NAB as high as 40 to 60 ppb in Denver and up to 40 ppb in Boston. Clearly the use by EPA of monthly average NABs on the order of those in Table 1 instead of the paired-in-time concentrations would result in: 1) a significant underestimation of the actual NAB, 2) the overestimation of the perceived health risk and, 3) a underestimation of the degree of control required to meet a NAAQS.

In general, these new GEOS-Chem modeling results appear to produce more realistic estimates of short-term NAB, at least in the Western US. Zhang et al. state: " The model captures the frequency of high-ozone events up to about 70 ppbv but fails to reproduce events of exceptionally high ozone that may be due to stratospheric or wildfire influences." In addition, the predicted NAB concentrations appear to be in line with NAB estimates of others who have used various data screening techniques and statistical techniques to estimate NAB from ambient measurements in the Western US.[17,18,19,20,21]

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[16] Blewitt, D., Personal Communication October 24, 2011.

[17] Oltmans, S.J., Lefohn, A.S., Harris, J.M. and Shadwick, D.S. (2008), "Background ozone levels of air entering the west coast on the US and assessment of longer-term changes," *Atmos. Environ.* 42:6020-6038.

[18] Parrish, D.D., Miller, D.B. and Goldstein, A.H. (2009), "Increasing ozone in marine boundary layer inflow at the west coast of North America and Europe," *Atmos. Chem. Phys.* 9:1303-1323.

[19] Zhang et al. (2008), "Transpacific transport of ozone pollution and the effect of recent Asian emission increases on air quality in North America: an integrated analysis using satellite, aircraft, ozonesonde, and surface observations," *Atmos. Chem. Phys.* 8:6117-6136.

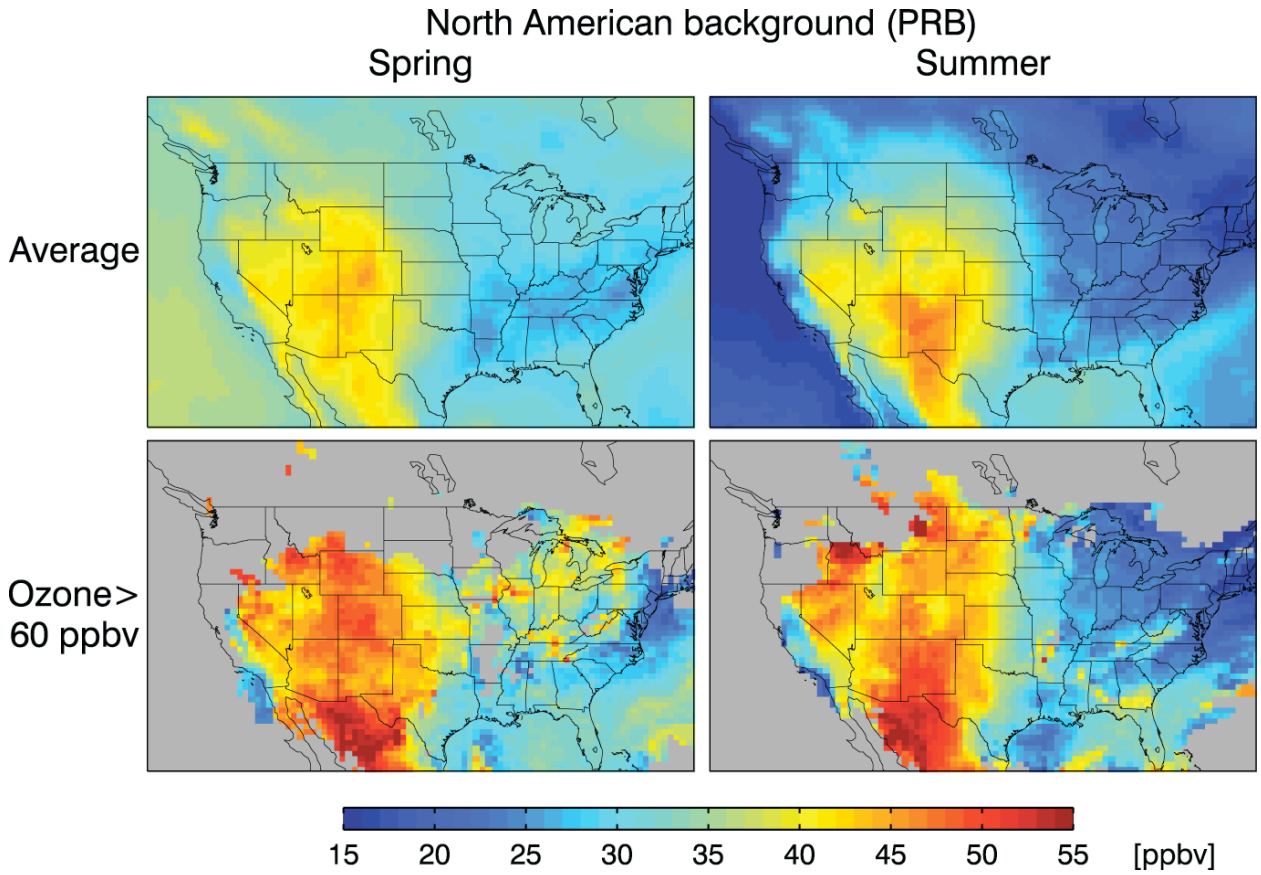

Figure 2: North American background (NAB) 8-hour ozone concentration in surface air for spring and summer 2006. The top panels show seasonal means while the bottom panels show the means for days with ozone > 60 ppb. Gray areas in the bottom panels had no days with ozone > 60 ppb.[14]

[20] Oltmans, S.J. et al. (2010) "Enhanced ozone over western North America from biomass burning in Eurasia during April 2008 as seen in surface observations," *Atmos. Environ.*44:4497-4509.
[21] Jaffe, D. (2011), "Relationship between surface and free tropospheric ozone in the Western U.S.," *Environ. Sci.Technol.* 45;432-438.

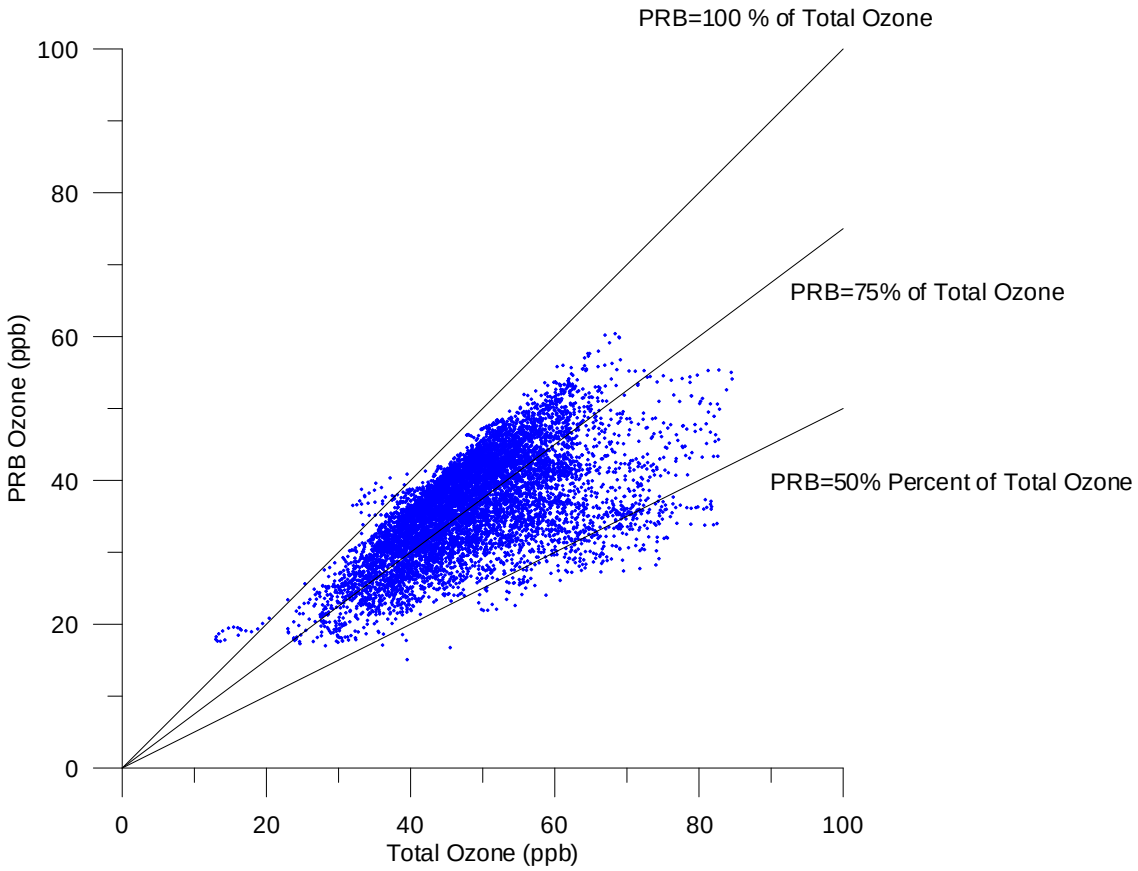

Figure 3: Scatter plot of paired-in-time hourly PRB and total ozone predictions for Denver, CO for 2006 using GEOS-Chem.[16]

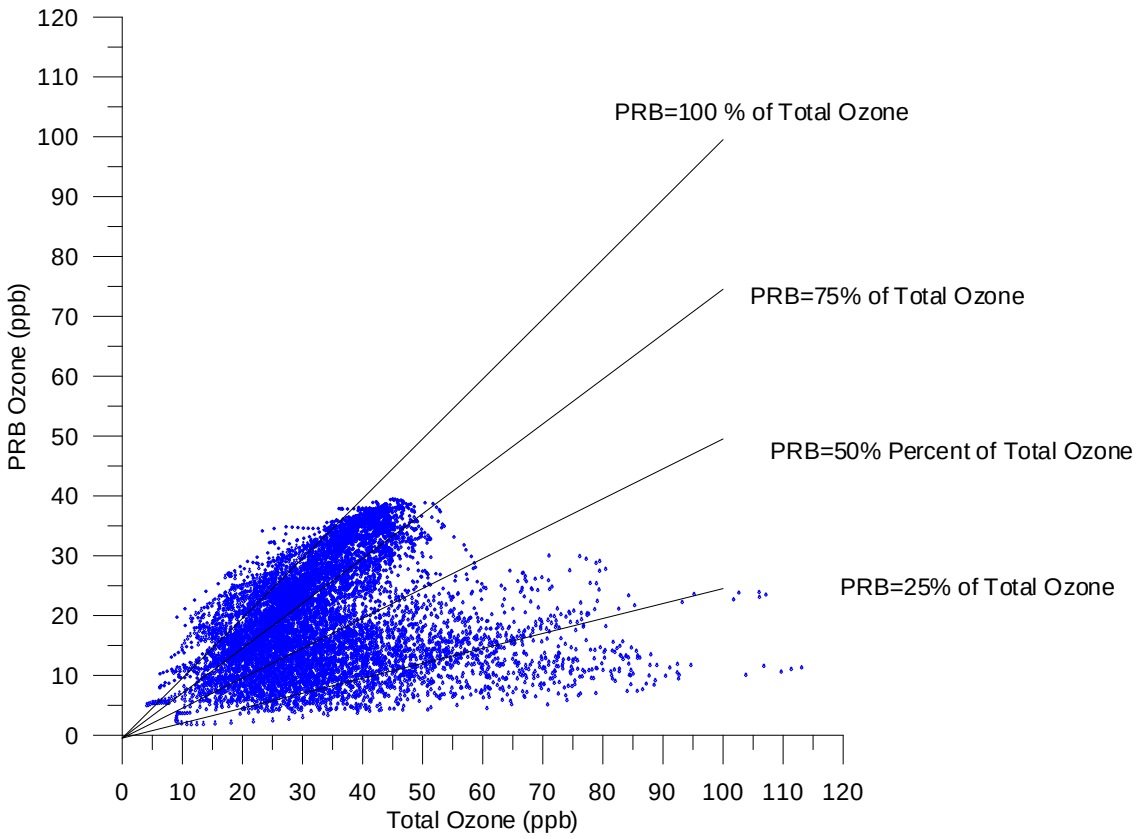

Figure 4: Scatter plot of paired-in-time hourly PRB and total ozone predictions for Boston, MA for 2006 using GEOS-Chem.[16]

Thus it appears that the new model estimates of NAB provide more reasonable estimates of the ozone concentrations in the air masses entering the Western US providing short-term, 8-hour estimates are used rather than monthly averages. Although some of the highest peaks are still not reproduced, the frequency of high ozone events up to about 70 ppb is reproduced. It also appears that there is better agreement between the model NAB results and the estimates made from analyzing Western US air quality data. However, a rigorous comparison of these new results with ambient data needs to be done to assess model performance.

C. PRB as Defined by EPA is Inappropriate for the Eastern Two-Thirds of the US and the Southwestern US.

To estimate NAB, the new modeling by ICF and Zhang et al. and the earlier modeling of Fiore et al. (2003) and EPA simply zeroed out US, Canadian and Mexican anthropogenic emissions of VOCs, NO_x, and CO and calculated the resulting ozone concentrations across the US. Using the 2006-2008 emissions and the latest version of GEOS-Chem, ICF also conducted a modeling run where they shut down US anthropogenic emissions but left in the Canadian and Mexican anthropogenic emissions. This run produced US background ozone (USB) and it should be representative of what is coming into the US across any border or coastline. The mean seasonal 8-hour maximum USB concentrations are summarized and compared to the NAB in Table 6-3 of the ICF International (2011) report. The mean enhancement (USB-NAB) from March through August of the USB due to Canadian and Mexican contributions is summarized by site in Table 2.

An examination of the spatial distribution of the enhancement reveals the following. For sites in the intermountain West removed from the US-Mexican border, the enhancement is generally small (less than 2 ppb), which is consistent with a relatively minor contribution of Canadian and Mexican sources to the NAB in this region. However, for the Western sites close to the Mexican Border (Joshua Tree, Chiricahua, AZ and Big Bend, TX), the mean enhancement is about 5 ppb. In Big Bend, it increases to 8 ppb. Similarly, for the sites near the Canadian Border (Theodore Roosevelt National Park in North Dakota and Unionville, MI, the mean enhancement is about 5 ppb. The greatest enhancements are seen in Upstate New York (Huntington Forest = 9.0 ppb) and in Maine at Acadia National Park where the mean enhancement is 22.0 ppb. Similar enhancements and geographic patterns have been reported by Wang et al. (2009)[22] who used an earlier version of GEOS-Chem (v7-02-01) and modeled the June-August period of 2001.

However, just as it was shown that it is inappropriate to use monthly average NAB, it is inappropriate to use mean monthly USB values or mean monthly enhancements. Both

[22] Wang, H., Jacob, D.J., Le Sager, P., Streets, D. G., Park, R.J., Giulliland, A.B. and van Donkelaar, A. (2009), "Surface ozone background in the United States: Canadian and Mexican pollution influences," *Atmos. Environ.* 43:1310-1319.

ICF and Wang et al. present time series plots for selected sites. In Figure 5, the time series from ICF for Big Bend is reproduced. This clearly shows frequent USB excursions

Site Location	State	USB-PRB
Mt. Rainier NP	WA	2.40
Pinnacles NM	CA	1.47
Joshua Tree NM	CA	5.00
Lassen NP	CA	1.13
Chiricahua NM	AZ	5.06
Great Basin NP	NV	2.56
Pinedale	WY	1.85
Rocky Mtn NP	CO	1.91
Caddo Valley	AR	2.41
Konza Prairie	KS	2.80
Theodore Roosevelt NP	ND	4.64
Big Bend NP	TX	8.05
Unionville	MI	4.86
Salamonie Reservoir	IN	3.77
Oxford	OH	3.72
Perkinstown	WI	3.61
Cadiz	KY	2.58
Great Smoky Mtns NP	TN	2.43
Blackwater NWR	MD	5.57
Acadia NP	ME	21.98
Penn State	PA	5.11
Huntington Wildlife Forest	NY	9.03
Sumatra	FL	3.63

Table 2: GEOs-Chem derived differences between mean daily maximum 8-hour ozone USB and NAB for the 2006, 2007 and 2008 simulations. These values were calculated the values presented in Table 6-3 in ICF Kaiser (2011).[15]

of 50 ppb, a few of 60 ppb and one of 70 ppb. In addition, there are numerous times when the USB is 20 ppb greater than NAB. On three occasions, when the ozone exceeded the 75 ppb NAAQS, the USB ranged from the low 60s to 70 ppb.

Figure 6 is the Unionville, MI time series from Wang et al. On several occasions, the USB approached or exceeded 40 ppb and on three occasions, the ozone exceeded the 75 ppb NAAQS while the Canadian contribution exceeded 10 ppb causing exceedances of the 75 ppb NAAQS. Further, there are two occasions when the Canadian enhancement exceeded 30 ppb.

Clearly these modeling exercises provide strong evidence that Canadian and Mexican emissions significantly enhance the USB and this enhancement is occurring on high ozone days and can be a major contributor to exceedances of the 75 ppb NAAQS. As a result, we strongly recommend, that the USB be used instead of the PBR in conducting

the risk assessments and in determining the degree of emission controls required to reach attainment with any NAAQS, especially in the Eastern two-thirds of the US and in the Southwestern US.

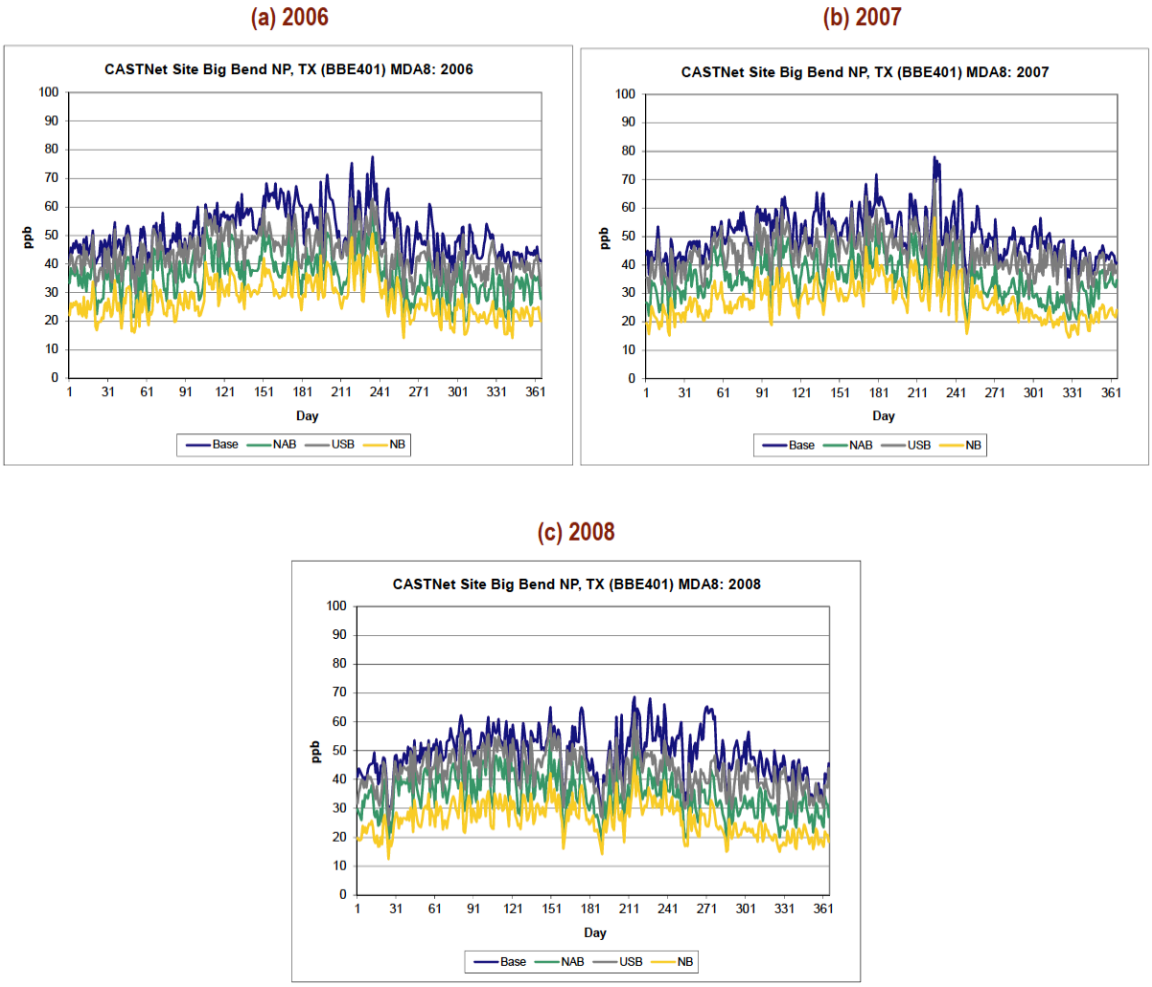

Figure 5: Daily 8-hour maximum ozone concentrations for Big Bend NP, TX. Blue line is the total ozone from the base case, grey is the USB, green is the NAB and the yellow line is the natural background (NB).[15]

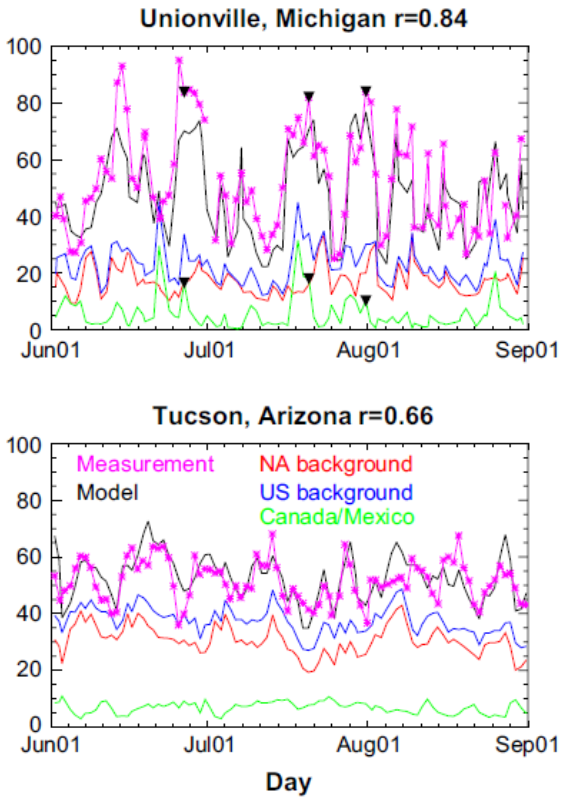

Figure 6: Jun–Aug 2001 time series of daily-8 h-max ozone concentrations at one US site in the northeast (top) and southwest (bottom) where Canadian and Mexican influences are particularly strong. Model results (black line) are compared to observations (magenta line with stars). Also shown are the USB (blue line), the NAB (red line), and the Canadian and Mexican pollution enhancement (green line) determined by difference of the USB and the NAB. Black triangles highlight days when observed ozone exceeds 75 ppb and Canadian/Mexican enhancement exceeds 10 ppb. The r is the correlation coefficient between modeled values and observations.[22]

D. The Higher Background Estimates Affect Consideration of Both the Primary and Secondary Standards

The Alliance comments[23] on the Administrator's July 2007 proposal to revise the primary and secondary standards included detailed comments on the limitations of the Agency's approach to estimating background. The new estimates discussed above confirm many of the Alliance's concerns. In particular, the Alliance was concerned that the fact that the extremes of background were not being considered would negatively affect the choices for both the primary and secondary standards. The Alliance pointed out that EPA and CASAC relied on an inadequate model in recommending secondary standards that fall within the range of uncontrollable background. The overall pattern of W126, the exposure metric proposed in 2007, suggested both a contribution from US man-made emissions and a background component that could involve biogenic emissions, agricultural emissions, long-range transport from non-US sources and a stratospheric component. Figures 7 and 8 show the distribution of W126 across the country for 2009 and 2010. W126 levels greater than 7 ppm-hr. exist in many locations throughout the country, including many rural and remote inter-mountain Western sites well-removed from anthropogenic emission source areas. Although EPA incorrectly assumed at the time that W126 was not confounded by background, the new background estimates show that is not the case.

E. Summary of Policy Relevant Background

1. The use of the mean monthly PRB (NAB) by EPA significantly underestimates the NAB and results in an overestimation of the health risks and jeopardizes the ability of states to develop viable state implementation plans that will lead to attainment of the NAAQS.

2. The use of PBR (NAB) concentrations is inappropriate for the Eastern two-thirds of the US and the Southwest US because of the significant impact Mexican and/or Canadian emissions have on ozone concentration in these states. Since EPA does not have the authority to make these emissions disappear, daily 8-hour paired-in-time estimates of USB should be used instead of NAB estimates in the risk assessments and in the development of state implementation plans.

3. The most recent GEOS-Chem estimates of USBs appear to be more realistic, however, these estimates need to be verified with rigorous model performance evaluations.

4. The new higher background estimates affect consideration of both the primary and secondary standards.

[23] Alliance comments, supra note 2, pp. 40-47 and 56 -58.

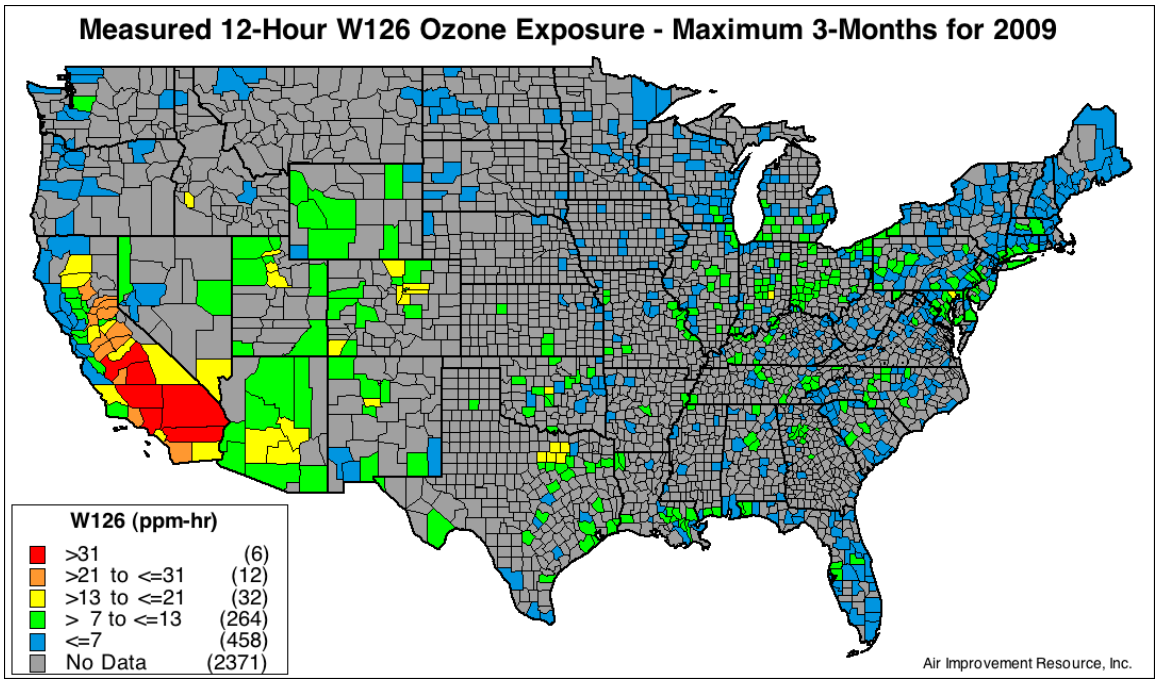

Figure 7: W126 exposure for maximum 3 months in 2009.

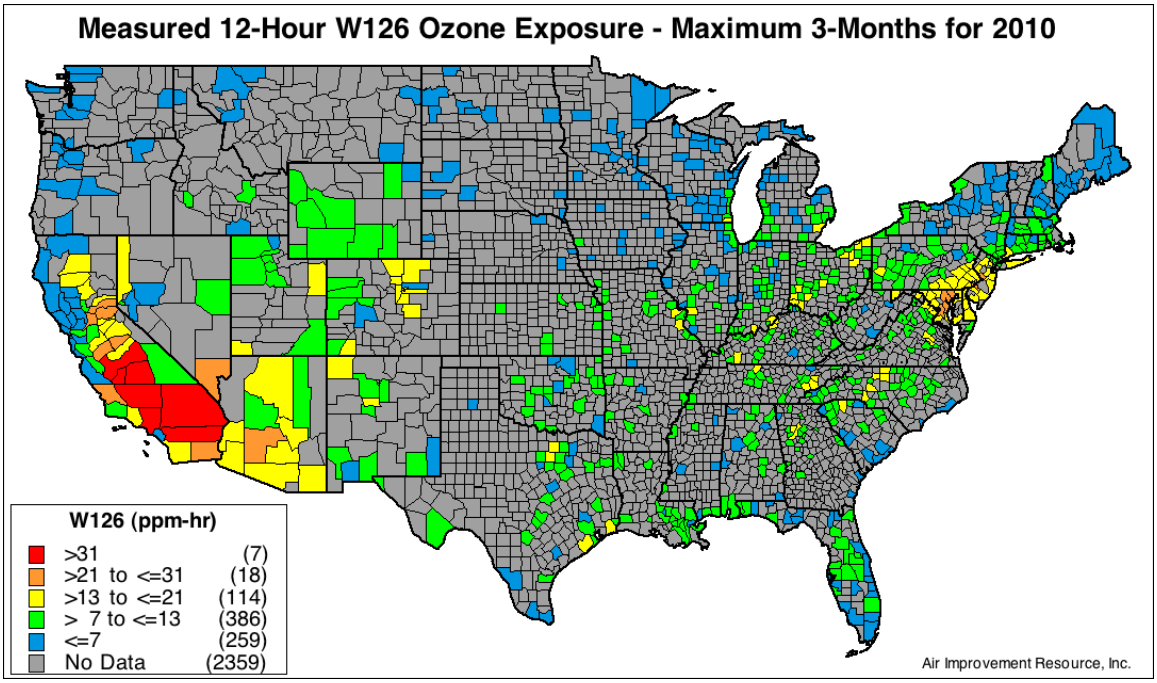

Figure 8: W126 exposure for maximum 3 months in 2010.

II. Human Clinical Studies and Their Interpretation

As indicated in the ISA,[24] the controlled human exposure studies provide a strong and quantifiable body of information on the dose-response of effects of 1- to 3-hour and 6- to 8-hour exposures to ozone. The first effects, which are transient and reversible FEV1 decrements, are the body's reflexive reaction to the presence of an irritant gas unrelated to sensations of discomfort. Such effects occur after exposures to 0.08 ppm for 6 to 8 hours when the subjects are exercising at a rate that would be considered strenuous when carried out intermittently for an eight-hour period. Whether such effects occur at 0.06 or 0.07 ppm has been highly controversial since the answer depends on how the baseline is evaluated, how the precision of the test is considered, how the day-to-day variability of a subject is evaluated, and how the data are statistically analyzed. During the previous review, the Adams (2006) study was the only study available at concentrations below 0.08 ppm. The Schelegle et al. (2009) and Kim et al. (2011) studies are now also available.[25] As noted in the ISA these studies now all indicate very small group mean changes in FEV1 at 0.060 ppm, with an average response (adjusted for the response to filtered air) of 2.7 %. This small change is of the same magnitude as the accuracy of repeat FEV1 measurements, + or – 3 %. Importantly respiratory symptoms were not affected by ozone exposure at the 0.060 ppm level.

A. The Public Health Significance of the First Effects of Ozone Are Not Adequately Discussed in the ISA

The important question is not whether these small changes in the performance of lung function tests are statistically significant; the important question is their medical or public health significance. The ISA does not adequately lay the groundwork for answering this question. The ISA refers to several publications regarding guidelines for determining clinically meaningful FEV1 changes. Two of the references (ATS, 1991 and Pellegrino et al., 2005) discuss the use of lung function testing to evaluate various obstructive and restrictive disease states that result in changes in lung function. For example, the Pellegrino et al. (2005) review discusses lung function changes as they relate to progressing disease or the response of disease states to therapy. Pellegrino et al. do not discuss the clinical significance of the kind of transient, reversible changes caused by ozone. They do note, however, that statistical significance and clinical significance do not follow one another. They point out that two lung function measurements that are statistically indistinguishable may provide reassurance in a patient receiving therapy for a disease that is otherwise rapidly progressive. They note that the same tests may be very disappointing if one is treating a disorder that is expected to improve dramatically with the therapy prescribed. They also point out that a statistically significant change may be of no clinical importance to the patient.

The more relevant American Thoracic Society guidelines that are not referenced in the

[24] ISA, supra note 1 at p. 6-2.
[25] Literature referred to by author and date without a footnote is references included in the ISA.

ISA are guidelines regarding what constitutes adverse air pollution effects. The 1999 Guidelines indicate:[26]

> The committee recommends that a small, transient loss of lung function, by itself should not automatically be designated as adverse. In drawing the distinction between adverse and nonadverse reversible effects, this committee recommended that reversible loss of lung function in combination with the presence of symptoms should be considered adverse.

Therefore, the ISA should discuss the symptom results for the human clinical studies along with the FEV1 results to provide appropriate information to the reader.[27] In the Adams (2006) study, the total mean symptom scores were only 2-4 units at 0.04 and 0.06 ppm out of a possible total score of 160. Adams indicated that the differences in the symptoms between the 0.04 and 0.06 ppm exposures and the filtered air control were not statistically significant. Kim et al. (2011) also indicate that the symptom scores were not different between ozone and clean air. Schelegle et al. (2009) indicate that the symptom scores were increased at 0.07 and 0.08 ppm but not at 0.06 ppm.

Thus, according to the ATS guidelines, the functional changes at 0.06 ppm would not be considered as adverse. The ISA should expand on the clinical and public health relevance of the functional effects. The basic nature and extent of functional effects has not changed since the 1997 and 2008 reviews. There is now data between 0 and 0.08 ppm, but the assumption made in 1997 was that functional effects, albeit small, do occur below 0.08 ppm. In the 1997 review, single incidences of the effects at 0.08 ppm (for either healthy or asthmatic subjects) were not considered to be adverse by CASAC and EPA staff. Nothing in the body of controlled studies has changed to alter that view. If anything, the growing evidence that the functional effects are caused by activation of neural reflexes, as discussed in greater detail in Section 5.2.3 of the Dosimetry chapter, should reduce the concern over isolated transient, reversible lung function decrements.

Instead of referring to the July 1999 ATS guidelines for adverse health effects of air pollution, the ISA refers to the 1999 guidelines for methacholine and exercise challenge testing. In contrast to normal individuals where exercise usually results in a small increase in FEV1, exercise induces airway narrowing in the majority of patients with asthma. The guidelines relate to testing of potential asthmatics to determine whether exercise induces bronchoconstriction. The ISA indicates that greater than a 10 % change in FEV1 is considered abnormal and uses that fact to infer that a greater than 10 % change in FEV1 that is ozone-induced is clinically important. This is not warranted since the 10 % change due to exercise induced bronchoconstriction is actually a narrowing of the airways and a 10 % ozone-induced change is not a narrowing of the airways but instead is an inhibition of maximal inspiration during the test due to ozone's effect on

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[26] "What Constitutes an Adverse Health Effect of Air Pollution? ", Official Statement of the American Thoracic Society Adopted by the ATS Board of Directors, July 1999, *Am. J. Respir. Crit. Care Med*., 161, 665-673, 2000.

[27] In the draft ISA respiratory symptoms are discussed as a separate category of effects in Section 6.4, but only epidemiological studies are discussed at that point.

neural receptors, as first proposed by Hazucha et al. (1989) and as documented in Chapter 5. This difference is very important and should be acknowledged in the ISA.

The ISA uses the 10 % response cutoff to claim that:[28]

> 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.

There are several problems with this claim. First, as noted by public comments on the first draft ISA,[29] the studies of exposure to 0.06 ppm with exercise were not designed to assess individual responses. To determine whether lung function changes for a given individual were due to ozone, an acceptable study design would include repeat measurements for each individual and utilize a scientifically acceptable statistical test on the data for each individual. Second, the individual data that is available demonstrates sufficient variability (with examples of individual responder's responses at 0.06 ppm greater than at 0.08 ppm) such that EPA's assumption that all FEV1 changes are due to the ozone exposure cannot be supported. Within-subject variability needs to be understood and accounted for before the ozone-induced effect can be determined. Third, the sample size is too small to generalize the results. Fourth, as noted above, EPA's claim regarding the 10 % response cut-off is not soundly based. Instead, the ISA should discuss the public health significance of ozone-induced FEV1 changes at 0.060 ppm with exercise in light of the neural reflexive mechanism and the lack of any respiratory symptoms.

Since the first effects on the performance of lung function tests occur at 0.50 ppm in sedentary individuals, the vast bulk of personal exposures of either the general population or the susceptible population are far below the thresholds for the first effects identified in controlled studies. For example, the data on indoor/outdoor ratios and personal exposures in Section 4.3 clearly show that personal exposures are only a fraction of the levels measured at ambient monitors. Typically, personal exposures average a quarter or less of the ambient measurements, even for school children that spend an average of two hours per day outdoors. Even for a group of camp counselors, the personal exposures averaged less than half of the ambient measurements. The first draft ISA concluded that "Another important finding is that the magnitude of personal exposures is smaller than concentrations reported at fixed-site monitors due to time spent indoors and the low indoor penetration of O_3."[30] The second draft indicates "personal-ambient ratios are typically 0.1- 0.3"[31] although individuals spending substantial time outdoors such as outdoor workers may experience higher ratios. This important finding needs to be included in the integrative discussion in Chapter 6. It provides a large margin of safety from the first effects identified in controlled human studies for the vast bulk of the population as they go about their daily activities.

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[28] ISA, supra note 1 at pp.. 6-14
[29] Goodman Rpt., supra note 6.
[30] ISA, supra note 5 at pp. 4-8.
[31] ISA, supra note 1 at pp. 4-42.

Other effects on the respiratory system occur at higher concentrations as ozone triggers other responses in the body's defense mechanisms. The presence of inflammatory markers has been studied in many human clinical studies. The ISA refers to a meta-analysis of 21 studies (Mudway and Kelly, 2004) which showed that neutrophil influx in healthy subjects is associated with total ozone dose (i.e., the product of ozone concentration, exposure duration, and ventilation rate). The studies included in Mudway and Kelly evaluated inflammatory markers in exposures that ranged from 0.08 to 0.60 ppm ozone with varying degrees of exercise and durations from 1 to 6.6 hours. The ISA notes that the presence of neutrophils in the lung has long been accepted as a hallmark of inflammation and is an important indicator that ozone causes inflammation in the lungs. Neutrophilic inflammation of tissues is indicative of activation of the innate immune system. It is normally followed by processes that clear the evidence of acute inflammation.

The immune system responses noted by EPA as the first indications of "inflammation" are physiological processes that occur in all living organisms under the stimuli of daily life. The first reported changes (that occur in humans with heavy exercise after 1- to 3-hours above a threshold of 0.18 to 0.20 ppm) are small and reversible and well within the range of physiological variability. They fall into the category of biochemical markers that the American Thoracic Society indicates do not necessarily imply adversity. The 2000 review by Mudway and Kelly[32] notes that for neutrophils transiting into the lung - one of the earliest of these responses - it is not clear if the response should be considered beneficial (functioning to clear necrotic cells) or detrimental (leading to an active inflammation with tissue injury). The 2006 Criteria Document noted that generally, "the initiation of inflammation is an important component of the defense process; however, its persistence and/or its repeated occurrence can result in adverse health effects."

Since the threshold for even the first indications of an inflammatory response is as high or higher than that for the reflexive FEV1 response, the likelihood of persistent or repeated lung function decrements or inflammation is very small. For example, the typical ambient concentrations of ozone in recent years are quite low compared to the thresholds for the first physiological effects as determined from controlled exposure studies. The ISA indicates that "the median 24-h avg, 8-h daily max, and 1-h daily max O_3 concentrations across all US sites reporting data to AQS between 2007 and 2009 were 29, 40, and 44 ppb, respectively."[33] When one considers that the median 8-h daily maximum ozone concentration across the country is 0.040 ppm and the personal exposures of the population are typically only a small fraction of the monitored concentration, it is clear that the day-in day-out exposures of the population are typically way below the threshold for the first physiological effects.

In addition, the possibility that peak exposures result in effects also needs to be considered. The 99th percentile of the 8-h daily maxima is 0.080 ppm and the 4th highest

[32] I. Mudway and F. Kelly, "Ozone and the Lung: A Sensitive Issue," *Mol. Aspect. Med.,* 21, 1-48 (2000).
[33] ISA, supra note 1 at pp. 3-117.

daily 8-h maxima now range from about 0.065 to 0.085 as shown in Table 3-4 and Figure 3-44 of the ISA, with many sites still exceeding the current 0.075 ppm standard. Although these peak concentrations overlap with the thresholds for the first effects, it should be borne in mind that a subject has to be outside, exercising at the time and place of high ozone for there to be an exposure that could cause an effect. In order to calculate the risk, all these factors need to be taken into account. This is discussed in greater detail below. The role of exercise is particularly important. For example, the threshold for inflammatory changes in the Mudway and Kelly (2004) meta-analysis at a 1-hour ozone concentration of 0.12 ppm is a ventilation rate greater than 10 times the resting rate. The threshold at an 8-hour ozone concentration of 0.08 ppm is a ventilation rate greater than 3 times the resting rate. The various new studies of exposure to 0.060 ppm while exercising all utilize an experimental protocol that is quite strenuous compared to the normal range of human activity. In the Kim et al. (2011) study, the heart rate of the subjects with either ozone or filtered air averaged 127 or 128 beats per minute over the 6.6-hour test period. This means that the heart rate was higher during the six 50-minute exercise periods. While such a heart rate is common with exercise, it is not common to exercise at such a rate for such a long time. In fact, it is not unlike the heart rate achieved by a typical marathon runner who runs at between 70 and 80 % of their maximum heart rate, typically 135 beats per minute, for most of the race.

Thus, the results of the clinical studies cannot be used directly to claim effects below the current standard. Rather, they must be used to evaluate the risk by mapping the results onto realistic exposure/activity patterns. Although this is done in a separate Risk Assessment, the science supporting the key data and assumptions that go into the Risk Assessment should be fully vetted in the ISA. The current draft ISA is deficient in this regard.

B. There Are Key Factors Influencing the Risk of Pulmonary Effects that Need To Be Covered in the ISA

Neither the first draft ISA nor the second draft ISA addresses several key factors and issues. Instead the drafts provided a short summary of the APEX model EPA used in the Risk Assessment in the 2008 Review in Section 4.4.2 of the first draft and in Section 4.5 of the second draft that indicate that the model works rather well. In contrast, during the 2008 review, the Alliance provided comments on at least five ways in which the clinical exposure and risk assessment was biased, overstating the exposures and risks that would accompany any of the alternative standards under consideration.[34] The final ISA should address several of these concerns.

First, the ISA should acknowledge that human ozone exposures near a monitor are lower than the monitor measures. The 2006 CD acknowledged that ozone exposure is lower at "breathing" height compared to "measurement" height (3-15 meters). For example, Wisbeth et al. (1996)[35] measured the increment between ozone at 2 and 10 meters and

[34] Alliance comments, supra note 2 at pp. 13-17.

[35] A. Wisbeth, G. Meiners, T. Johnson, and W. Ollison *"Effect of monitor probe height on measured ozone concentration,"* Paper No. 96-RA111.02, presented at the 89th Annual Meeting of the Air & Waste

reported an average 13 percent difference. In addition to the height differential, ozone monitors are also sited in open areas removed from sources so as to capture the highest ozone concentrations expected in an area. Since downwind sites are usually the design value sites, they will dominate the upper tail of the ozone distribution and yet may not reflect the overall outdoor exposures in the vicinity of the site. If people spend time outdoors in closer proximity to streets or in areas with more surface area (buildings, etc.) to quench ozone, their exposures will be below that measured at the monitor. The APEX model assumes that whatever ozone is interpolated from the monitor measurement is the actual ozone exposure in the outdoors microenvironment. The 2007 Langstaff Memorandum acknowledged the issue of vertical variation in ozone but indicated that the Agency did not plan to address it due to a lack of data. This vertical difference was corrected in the vegetation risk assessment in the previous review but not in the human risk assessment. In the vegetation risk, the metric summing concentrations of 0.06 ppm and higher was halved with a 10 percent vertical correction.[36] By analogy, a vertical correction in the human risk assessment would likely halve the number of human exposures of concern at ground level. Because this effect would correct a bias in the exposure calculations, it is particularly important that the ISA include a discussion of the difference between ozone at person height and at measurement height. In contrast to this omission in Chapter 3, the difference in ozone exposure between plant height and measurement height is discussed in Chapter 9.

Second, since exercise or ventilation rate is such an important factor in assessing risk for ozone effects, the ISA should include a discussion of the distribution of ventilation rates in the human population. The APEX model predicts more elevated ventilation rate occurrences than observed in real world data. Langstaff acknowledged that the "values produced by the ventilation rate algorithm may exhibit an excessive degree of variability."[37] The final sensitivity analysis for APEX includes a comparison of predicted ventilation rates with mean values in the literature, but the upper tails of the distribution which impact the risk estimates were not compared.[38] This was an important oversight because the upper percentiles of ventilation rate are responsible for the exposures that cause the perceived risk. In the comparison of the APEX modeled values with the measured ventilation rates from Brochu et al. (2006),[39] the model over-predicted mean daily ventilation rates for persons below age 11 and over age 40. More importantly, the model had a much higher standard deviation at all ages.

This suggests that the upper percentiles of ventilation rates in the model are substantially above those measured in a database of over 30,000 person-days from a cohort of over 2,200 free-living individuals between the ages of 3 and 96. The following Figure 9

Management Association, Nashville, TN, June 1996.

[36] 2007 SP, supra note 8 at pp. 7-46 and 7-47.

[37] Draft Langstaff Memorandum at p. 42.

[38] J. Langstaff, Technical Memorandum, *Analysis of Uncertainty in Ozone Population Exposure Modeling*, Jan. 31, 2007 at 52 (EPA-HQ-OAR-2005-0172-0174).

[39] P. Brochu, J. Ducre-Robitaille, and J. Brodeur, 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, Int. J. Hum. Ecol. Risk. Asses., 12, 736-761 (2006).

shows that the APEX model EPA used in the prior risk assessment significantly

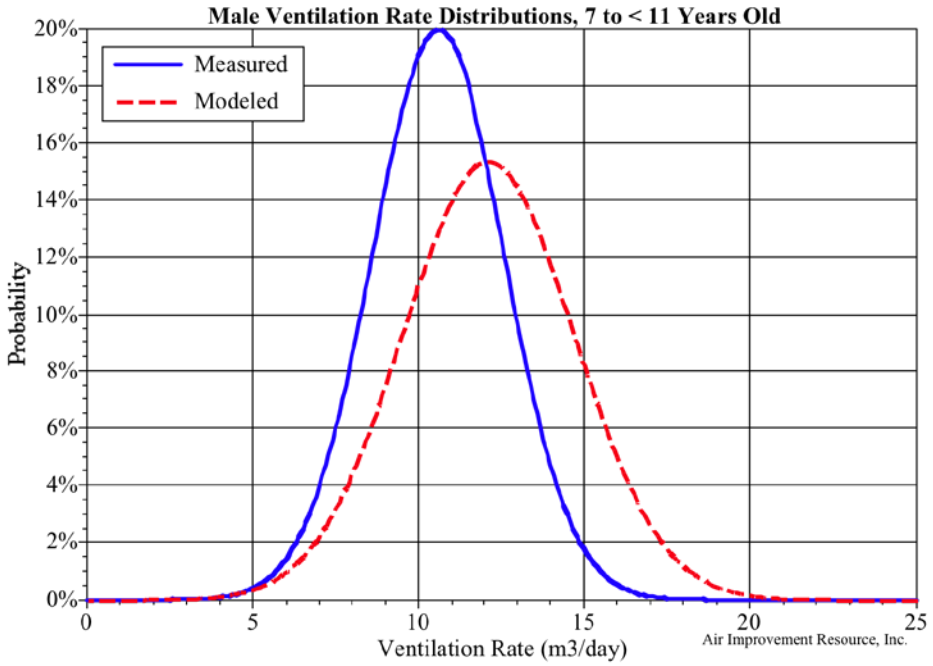

Figure 9: Comparison of measured vs. modeled daily ventilation rates for 7- to 10-year old boys.

overestimates the breathing rates of male children, particularly for the upper tails of the distribution that are responsible for the exposures of concern evaluated by the Agency. The data underlying these distributions (means and standard deviations) come from Table 25 in the 2007 Langstaff Memorandum on uncertainty in the exposure model. In fact, of the 16 comparisons in Table 25, for eight age groupings each of males and females, 15 had substantially higher modeled ventilation rates compared to the data reported by Brochu et al., 2006 at the upper end of the distribution.

The 1997 EPA analysis had also over-estimated the number of high ventilation rates in the population. That analysis used an algorithm to assign ventilation rates based on individuals who exercised regularly and were motivated to reach a high ventilation rate. As a result, the 1996 Staff Paper acknowledged that the analysis allowed more high ventilation rates (hence greater risk) than would actually occur in the populations of interest - outdoor workers, outdoor children, etc. Because of the importance of the methodology for assigning ventilation rates to the estimated risk, the ISA should include a detailed discussion of the methodology and data involved.

Third, the shape of the dose-response for 8-hour exposures below 0.08 ppm should be discussed in the ISA. With the additional data accumulating at 0.06 ppm, it is now clear that the functional changes below 0.08 ppm are less than linear. In the 2007 Staff Paper, EPA assumed a mix of linear and logistic responses below 0.08 ppm based on the concern that with the limited data at 0.060 ppm, a linear response could not be ruled

out.[40] Even though there was no data below 0.08 ppm in the 1997 review, EPA assumed a linear response below 0.08 ppm. Thus, as data accumulates, the estimated risk below 0.08 ppm has been reduced. In addition, the key response factor used in the Risk Assessment was the likelihood of FEV1 decrements of greater than 10 % or 15 %. Therefore, the quality and characteristics of the data on the distribution of FEV1 changes and the rationale for choosing particular cutpoints need to be fully vetted in the ISA.

Fourth, the fact that the relevant non-US background is now estimated to be higher than in the previous review needs to be factored into the integrative discussion. Background is important since the 2007 Staff Paper indicated:[41]

> For assessing risks remaining upon just meeting a standard, EPA has decided as a matter of policy that only risks in excess of PRB are relevant to the decision, and thus staff judges it is still appropriate to estimate risks in excess of estimated PRB levels.

Thus, as the background is increased, the risk attributable to any given ambient level will decrease. Another issue related to the presence of background that was raised in public comments on the first draft ISA[42] is that the use of Filtered Air (FA) may not be an appropriate control exposure because the 0.00 ppm FA that is generated in the laboratory does not exist under ambient or indoor air conditions.

C. A Number of Additional Facts Need to be Considered in the Integrative Synthesis

As the ISA discusses the implications of the clinical findings, the findings from toxicology and epidemiology are also discussed. However, other factors need to be included in the mix of considerations. There needs to be an acknowledgement that the studies establishing the first subtle physiological effects demonstrate threshold behavior. There needs to a more detailed discussion of the public health implications of the FEV1 and other changes identified in controlled human studies. There needs to be a greater consideration of real world exposures and how seldom such effects occur in human population at current ozone levels.

The toxicological and clinical findings need to be interpreted in relation to the body's natural defense mechanisms. The ISA indicates "the first line of defense against oxidative stress is antioxidants-rich ELF which scavenges free radicals and limit lipid peroxidation."[43] Toxicological findings for ozone are discussed both in Chapter 5 Dosimetry and in sections of Chapter 6. Even though there are many references in these sections to the body's natural defenses against the presence of an irritating and oxidizing gas, there is insufficient consideration of the issue of dose-response in the summary and

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[40] 2007 SP, supra note 8 at pp. 5-20.
[41] 2007 SP, supra note 8 at pp. 5-80.
[42] M. Hazucha and A. Lefohn, "Comments Provided for Consideration to the CASAC Ozone Review Panel on the EPA's First External Review Draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants to be held on May 19-20 2011," May 5, 2011.
[43] ISA, supra note 1 at p. 6-19.

integrative sections of the ISA. The discussion of mechanisms of action does not include sufficient discussion of the doses that are required to elicit the various effects and pathways. The question of biological plausibility involves two factors, the kinds of effects an agent may cause and the levels of the agent that are necessary to cause the effects. The question of dose-plausibility needs to be fully discussed in the ISA.

With regard to this issue, Oberdorster et al. (2005)[44] make several important points. For one, a careful evaluation of exposure–dose–response relationships is critical to the toxicologic assessment of an agent. Secondly, although high dose studies may be used in a first proof-of-principle approach, it is mandatory to follow up and validate results using lower concentrations resembling realistic exposures. Finally, the 500-year old phrase "the dose makes the poison" can also be paraphrased as "the dose makes the mechanism." The mechanistic pathways that operate at low realistic doses are likely to be different from those operating at very high doses when the cell's or organism's defenses are overwhelmed.

The threshold nature of the clinical effects is acknowledged in the ISA. For example, the ISA indicates:

> A delay in onset of O_3-induced pulmonary function responses has been noted in numerous studies. Recently the delay was characterized in terms of changes in breathing frequency (Schelegle et al., 2007). In humans exposed for 1-2 hours to 120-350 ppb O_3 while exercising, no change in breathing frequency was observed until a certain cumulative inhaled dose of O_3 had been reached. Subsequently, the magnitude of the change in breathing frequency was correlated with the inhaled dose rate (Schelegle et al., 2007). These investigators proposed that initial reactions of O_3 with ELF resulted in a time-dependent depletion of ELF antioxidants, and that activation of neural reflexes occurred only after the antioxidant defenses were overwhelmed (Schelegle et al., 2007).

The threshold nature is also evident in the studies of respiratory effects of human subjects at rest in which 0.50 ppm for two hours is the minimum dose needed to elicit an effect. However, the implications of the threshold nature of these effects are not fully acknowledged or weighed in the integrative sections of the ISA. The existence of a substantial threshold for the first physiological effects in controlled studies is not consistent with the assumption that the more severe effects suggested by some epidemiological studies have no threshold. Such assumptions are not consistent with either the general principals of toxicology or the specific findings of ozone toxicological studies. Rhomberg et al. (2011)[45] discusses these issues in detail.

The public health implications of transient, reversible FEV1 changes need to be considered carefully in the integrative synthesis. Public comments during the previous

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[44] G. Oberdorster, et al., *Environ. Health Perspect*.,113: 823–839 (2005).

[45] Rhomberg, LR; Goodman, JE; Haber, LT; Dourson, M; Andersen, ME; Klaunig, JE; Meek, B; Price, PS; McClellan, RO; Cohen, SM. 2011. "Linear low-dose extrapolation for noncancer health effects is the exception, not the rule." *Crit. Rev. Toxicol*. 41:1-19.

review have established that a variety of environmental exposures and stresses to which many people, including children, are routinely exposed produce changes in pulmonary function tests of the same magnitude as observed from ozone below 0.08 ppm. Many children experience minor exposures and stresses that result in transient FEV1 decreases of 10-15%. Further, in some cases, these routine changes or effects occur consistently rather than infrequently, i.e. once per year.[46] As noted above, an important question in interpreting the ozone clinical studies is not whether there are small changes in the performance of lung function tests, but what these small changes mean for public health given the involuntary reflex mechanism causing the changes. The small group mean changes that are at issue are well within the range of normal measurement variability and even the responders/outliers in the data are no more than the 10 to 20% changes which are considered moderate and potentially of health concern in the 2007 Staff Paper.

Another consideration is whether persons with asthma, the elderly, and particularly children, are more sensitive and experience larger decrements in lung function due to O_3 exposure than do healthy volunteers. The ISA summarizes the available data, noting that children, adolescents, and young adults (<18 years of age) appear, on average, to have nearly equivalent spirometric responses to O_3, but have greater responses than middle-aged and older adults when exposed to comparable O_3 doses.[47] The ISA goes on to indicate that symptomatic responses to O_3 exposure, however, appear to increase with age until early adulthood and then gradually decrease with increasing age. This was the state of the evidence in 1996 and is still the state of the evidence in 2011. Noting that the ISA also indicates that asthmatics are at least as sensitive as healthy subjects, studies of healthy young adults are likely the most sensitive means to evaluate lung function test decrements with symptoms, which are the physiological changes that ATS views as adverse.

In the 1997 review, single incidences of the FEV1 effects at 0.08 ppm (for either healthy or asthmatic subjects) were not considered to be adverse by CASAC and EPA staff. The 1996 Staff Paper included extensive discussion of how to interpret the clinical results in terms of public health.[48] Large functional changes, > 20 % FEV1 decrements, and severe symptomatic responses were indicated as clearly adverse. Moderate functional changes and symptoms were discussed in relation to interference with normal activity for both healthy and asthmatic individuals. For asthmatics, the Agency and CASAC concluded that moderate responses, when repeated, should be considered adverse. After considerable discussion there was consensus on CASAC that single, acute moderate functional responses should <u>not</u> be considered adverse for healthy individuals. Rather the staff indicated that the number of exposures resulting in moderate responses should be considered a factor in determining adversity for healthy individuals. In addition, the category of moderate functional changes without symptoms or with minimal symptoms

[46] NAM, Attachment 2, Critical Review of the Health Data in EPA's 2008 Proposed NAAQS for Ozone Cited in the Current 2010 Proposed Rulemaking, Docket ID No. EPA–HQ–OAR–2005–0172-12439.4 at pp. 1-7.
[47] ISA, supra note 1 at pp. 6-17.
[48] U. S. Environmental Protection Agency, Review of the National Ambient Air Quality Standards for Ozone: Assessment of the Scientific and Technical Information, OAQPS Staff Paper, EPA-452/R-96-007, June 1996 at pp. 62-72.

was not specifically addressed in previous reviews.

As CASAC has indicated, for ethical reasons, controlled exposure studies involve effects that are relatively mild and reversible, including changes in pulmonary function and increased evidence of inflammatory changes. Controlled studies of asthmatics and Chronic Obstructive Pulmonary Disease (COPD) patients have been conducted with intermittent exercise at substantially higher ozone exposures than the current standard, resulting in group-mean FEV1 decrements as high as 20 to 25 %, suggesting that such effects are relatively mild with regard to clinical or public health significance.[49]

When these factors are considered along with the low current personal exposures of ozone, documented in Chapter 3 of the ISA, the likelihood of major debilitating health effects from current ambient ozone concentrations is extremely small.

III. Epidemiological Studies and Their Interpretation

A. The Limitations of Air Pollution Epidemiology Are Not Adequately Considered in the ISA

In contrast to the science regarding human clinical effects which, while refined, has not changed substantively since the 1997 review, the available epidemiological evidence has increased dramatically. However, along with an outpouring of studies has come increased understanding of the limitations of the epidemiological evidence. For example, publication bias is now known to exaggerate the apparent strength and consistency of association. Limitations due to issues of model selection add substantially to the uncertainty. There is substantial evidence that stochastic variability adds substantially to the uncertainty. In addition, the issue of confounding raises the possibility that a positive association for ozone or any other pollutant in a single-pollutant model may be an indicator of some other pollutant rather than evidence of an independent effect of that pollutant. While one possibility is that ozone may be an indicator of the mix of photochemical oxidants, other possibilities also need to be acknowledged.

The ISA does not adequately discuss these methodological limitations and concerns. It should clearly state that air pollution time-series epidemiology studies suffer from problems associated with publication bias, model uncertainty, model selection issues, lack of adequate control for confounding variables such as other pollutants and weather, and exposure misclassification arising out of the poor correlation between ambient monitors and personal exposure and consider these limitations in the integrative discussions. In a June 2006 letter to the Administrator, CASAC confirmed this view in evaluating mortality time-series studies, noting that "[b]ecause results of time-series studies implicate all of the criteria pollutants, findings of mortality time-series studies do not seem to allow us to confidently attribute observed effects specifically to individual pollutants."[50]

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[49] See Table AX6-3 in Vol. II of 2006 Ozone CD.
[50] R. Henderson, CASAC Letter, EPA-CASAC-06-07, June 5, 2006 at p. 3.

Despite detailed public comments from the Alliance[51] as well as from other parties,[52] that raised these methodological limitations and concerns with regard to the first draft ISA, the second draft continues to over-rely on the positive ozone associations in the literature, discount evidence from studies that report null results, and avoid a rigorous and balanced discussion of biological plausibility. As a result, the second draft continues to inappropriately weigh the evidence from epidemiology with regard to ozone health effects.

There are severe limitations to the use of epidemiology to identify interactions and to evaluate causality. A meta-analysis by Steib et al.[53] evaluated 109 acute mortality studies from around the world. They report that there are positive associations with mortality (with a wide range in the individual cities) for all the major pollutants in single pollutant models and that for each, when other pollutants are included, the association with the first pollutant, on average, is decreased. In fact, the patterns in single-pollutant epidemiological studies were very similar for all the criteria pollutants.

The studies evaluated by Steib et al. are all subject to publication bias. To avoid publication bias that would inflate the apparent association, investigators have carried out large multi-city analyses. In fact, the patterns in single-pollutant associations in multi-city epidemiological studies are also very similar for all the criteria pollutants. The individual-city associations in large multi-city studies also cover a biologically implausible wide range from strongly negative to strongly positive, a finding which is readily apparent but seldom discussed.

There is also strong evidence for unrecognized stochastic variability in associations within a given city. Ito[54] re-analyzed the 1220 separate air pollution mortality and morbidity associations that were included in the original Lippmann et al. (2000) HEI study of Detroit. As shown in Figure 10, there was a wide range of negative and positive risks in Detroit when all pollutants, lags, and endpoints were considered. Ito showed in separate figures that the wide range of associations occurred for each pollutant. Although the focus in the original Lippmann study, as it is in almost all the published literature, was on the positive associations, Ito's plot shows that there are many negative associations in the data. Although there may be somewhat more positive associations than negative associations, there is so much noise or variability in the data, that identifying which positive associations may be real health effects and which are not is beyond the capability of current methods.

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[51] Alliance ISA comments, supra note 4.
[52] ISA public comments, supra note 6.
[53] D. Steib, S. Judek, and R. Burnett, "Meta-analysis of time series studies of air pollution and mortality: Effects of gases and particles and the influence of cause of death, age, and season," *J. Air & Waste Manage. Assoc.*, 52, 470-484 (2002) and Stieb et al., *J. Air & Waste Management Association*, 53, 258-261, 2003.
[54] K. Ito, pp. 143-156, "Revised Analyses of Time-Series Studies of Air Pollution and Health", *HEI Special Report*, May 5, 2003.

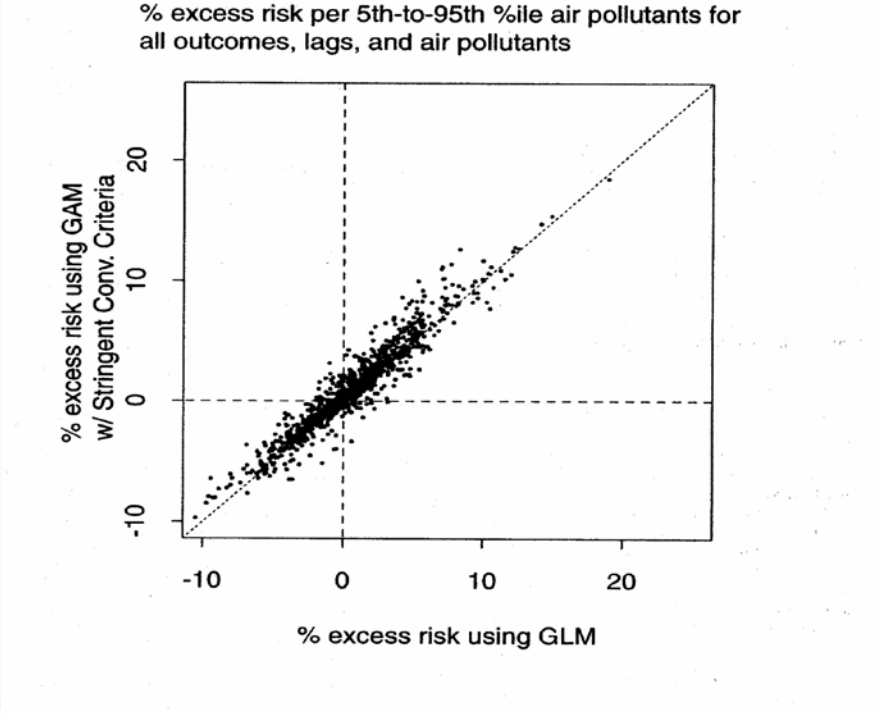

Figure 10 - Comparison of air pollution risks calculated with the General Additive Model (GAM) versus the General Linear Model (GLM) from Ito (2003).

Although EPA is planning on evaluating pollutants in a multipollutant context in the future, the ozone ISA must start that process now by acknowledging and discussing the full range of results for the many studies that evaluated multiple pollutants. Since the 2004 National Research Council report on air quality management in the U. S. recommended that EPA address multiple pollutants in the NAAQS review and standard setting process, there have been several papers/reviews discussing how to do this.[55] At a February 2011 EPA/HEI Workshop on Multipollutant Risk Assessment, EPA staff indicated that the Agency will develop a Multipollutant Science Assessment (MSA) in parallel with the current ISAs for individual pollutants. EPA will be developing the MSA over the next several years and plans to have the MSA inform the NAAQS decisions for single pollutants in coming years.

As each criteria pollutant has been reviewed, EPA is claiming or has claimed independent respiratory effects that are considered as causal or likely causal for four different criteria pollutants and is using selected single-city single-pollutant associations for that pollutant to set the NAAQS. In the recently completed NO_2 review, EPA used a cluster of five

[55] Dominici et al. (2010). 'Protecting human health from air pollution: Shifting from a single-pollutant to a multipollutant approach," . *Epidemiology*, 21, 187-194; Greenbaum and Shaikh (2010). 'First steps toward multipollutant science for air quality decisions," *Epidemiology*, 21, 195-197; Hidy and Pennell (2010). "Multipollutant air quality management" *J Air Waste Manage Assoc*, 60, 645-674; Mauderly et al. (2010). 'Is the air pollution health research community prepared to support a multipollutant air quality management framework?" *Inhal Toxicol*, 22(S1), 1-19; Vedal and Kaufman (2011). "What does multi-pollutant air pollution research mean?" *Am J Respir Care Med*, 183, 4-6; National Research Council (2004). "Air Quality Management in the United States", *National Academies Press*, Washington DC.

selected single-pollutant NO_2 associations that were cited as being "positive, and often statistically significant" to establish the level of the new 1-hour NO_2 standard.[56] The Agency also claimed that single-pollutant NO_2 associations were generally robust to the inclusion of other pollutants. In the recently completed SO_2 review, EPA cited ten studies that reported mostly positive and sometimes statistically significant single-pollutant SO_2 associations and then used SO_2 associations in three cities that remained statistically significant in multi-pollutant models with PM to set the level for the new 1-hour SO_2 standard.[57] In the draft PM Policy Assessment, selected single-pollutant individual city associations are being used to evaluate a range for a potential 98th percentile PM_{10} standard. In the January 2010 Agency proposal to re-visit the ozone NAAQS, EPA cited epidemiological evidence as a main reason to support the low end of the proposed range for a revised primary standard.[58] Although the Administration made a decision not to proceed with the ozone reconsideration, the over-reliance on selected single-pollutant epidemiological associations continues in the draft ISA. Only in the case of the recent decision to retain the current CO standards, has the Administrator discounted the epidemiological associations with CO as possibly acting as a surrogate for other pollutants.

B. Major Revisions Are Needed to Accurately Reflect the State of Science

In recognition that the Agency is moving toward a multipollutant approach, and in preparation for that approach, the ozone ISA requires major revision. Revisions are necessary in the way the individual epidemiological studies are presented and discussed in the text in Chapters 6 and 7, in the way the data are summarized in Tables and Figures, and in the way the material is evaluated and integrated together. In addition, there need to be revisions to the earlier supporting chapters to provide an accurate context for the integrative discussion.

1. Revisions Are Needed in the Main Text - The current text focuses on selected ozone associations and presents results for multi-pollutant models only to the extent they change the ozone associations. Since many of the studies cited evaluated multiple pollutants in single pollutant models, the overall pattern of associations for the other pollutants needs to be discussed. If the patterns of association are similar for other pollutants for a specific endpoint, that should be brought out in the text. Where available, data on spatial and temporal variations in associations should be discussed. For example, when multi-city studies are discussed, usually only the combined associations are discussed. In addition, the full range of individual-city associations should be documented. When seasonal results are discussed, usually summer or warm season and all-year results are presented. In addition, winter or cold season results whenever available should be documented. Specific examples are given below.

2. Revisions Are Needed in the Figures - The data presentation in the many figures in Chapter 6 provides a misleading impression of the overall patterns and consistency of the

[56] 75 *Fed. Reg*.r 6501, Feb. 9, 2010.
[57] 75 *Fed. Reg*. 35548, June 22, 2010.
[58] 75 *Fed. Reg*. 2997, Jan. 19, 2010.

epidemiological data. By plotting only selected single-city associations, by omitting the wide range of individual city associations in multi-city studies, by including meta-analyses that are known to overestimate positive associations due to publication bias, and by providing only limited information on the associations with other pollutants in the same or other studies, the ISA gives a false impression of the consistency of the data. Instead, the full range of individual-city associations in multi-city studies should be shown. Again, specific examples are given below.

3. Revisions Are Needed in the Integrative Synthesis - The current text is written with a bias to include all the arguments for ozone causing health effects. Instead, the text should weigh the evidence, both pro and con for ozone causing various effects at or below the current NAAQS. The current integrative synthesis ignores the issue of dose plausibility, leaves out consideration of personal exposures to ozone, and omits discussion of whether other pollutants might cause the same effects. As such it overstates the case for ozone having independent effects.

People are exposed to a wide variety of gases and particles in both indoor and outdoor environments. The lung has various defense mechanisms that help it continuously deal with these materials. The lung and respiratory system typically deals with a wide range of inhaled gases and particles without activating an inflammatory response. However, it is also capable of responding with an inflammatory response to a serious infective challenge. Ozone is both a natural constituent of the atmosphere and a pollutant. Although ozone is very toxic at high levels, it is also a natural constituent of the atmosphere with typical personal exposures below the outdoor background level. The issue for the ISA is at what doses does ozone overwhelm the body's defenses and cause concern. Therefore, a detailed discussion of the various potential effects in the context of the defense mechanisms and dose plausibility should be a major part of the integrative synthesis.

4. Revisions Are Needed in Chapter 3 to Support the Integrative Synthesis - The discussion of ambient mixtures should include a discussion of seasonal differences including both other criteria pollutants and other photochemical oxidants. Although the ISA title refers to ozone and other photochemical oxidants, there is little or no discussion of the other photochemical oxidants in the draft. The section on ozone measurements indicates that other oxidants are not measured in routine monitoring networks, but that data are available from specialized studies. Because of the potential importance of the role of other photochemical oxidants in health effects, the ISA should include estimates of the concentrations of other oxidants from both measurements and photochemical model calculations. Estimates should be provided by season and location, since warm season associations are cited at many places in the ISA as being higher than all-year or cold season associations.

An additional important consideration is the level of ozone and other pollutants. In the U. S., peak ozone levels and the levels of other pollutants have been decreasing for over 40 years. Thus, the interpretation of older studies should include consideration of the higher concentrations to which the population was exposed at the time of the study. In

order to provide such information for ozone, the long-term trends in ozone should be included in the ISA.

For example, Figures 11 and 12 show the trend in peak 1-hour and 8-hour ozone concentrations at monitoring sites across the country from 1975 to 2010. Figures 13 and 14 show the trend in June through August average daily maximum 1-hour and 8-hour ozone concentrations from 1975 to 2010. These figures show the progress that the nation's ozone control program has made. There has been dramatic progress in reducing the 1-hour and 8-hour daily maxima at the highest ozone sites that are dominated by man-made ozone. The lowest ozone sites are a mix of some near-source sites in urban areas in which ozone is suppressed by the continual presence of nitric oxide and a larger number of rural and remote sites. The 5th percentile ozone lines on these figures actually increase from 1975 to 1985 because the precursor control programs that reduced the maxima in and downwind of cities also reduced the nitrogen oxides concentrations in near-source areas. While the ozone at the highest ozone sites has continued downward, the lack of progress at lower ozone sites in recent decades is indicative of the presence of a substantial background of uncontrollable ozone as documented in Section I of these comments.

C. There are Important Issues with the Data for Specific Health Endpoints that Need to be Considered in the ISA

In the following, the epidemiological evidence for the most important heath endpoints is discussed and related to what is known about ozone effects from controlled studies. In the first sub-section, the evidence with regard to lung function and inflammatory markers is discussed. Next, there is a separate sub-section discussing the results of the multi-continent APHENA study that evaluated ozone associations with hospital admissions and mortality. The APHENA study is important because it is the largest multi-city study available and is discussed at several points in the ISA. This is followed by sub-sections discussing other endpoints discussed in the ISA.

D. The ISA Is Misleading with Regard to the Role of Ozone in the Air Pollution Mix with Regard to Lung Function and Other Respiratory Effects

1. The Discussion of Lung function Effects Is Misleading - The ISA presents the results for ozone/lung function associations but neglects to point out that many of the studies evaluated other pollutants and report many similar associations for those pollutants in single pollutant models. For example, the O'Connor et al. (2008) study evaluated five pollutants including ozone in a group of 861 asthmatic children in seven U. S. inner-city communities. The authors report stronger and significant positive associations of lung function parameters with three other pollutants compared to ozone in single-pollutant models. For asthma symptoms and missed school days, other pollutants also had stronger associations than ozone. Thus, the ISA gives a misleading impression of the role of ozone in the air pollution mix with regard to lung function and other respiratory effects.

In addition, the normal procedure of evaluating multiple lung function parameters at multiple lags and then reporting only the strongest associations increases the risk of false positives being highlighted in the ISA. For example, Pellegrino et al. (2005) warn that when too many indices of lung function are tracked simultaneously, the risk of false-positive indications of change increases.

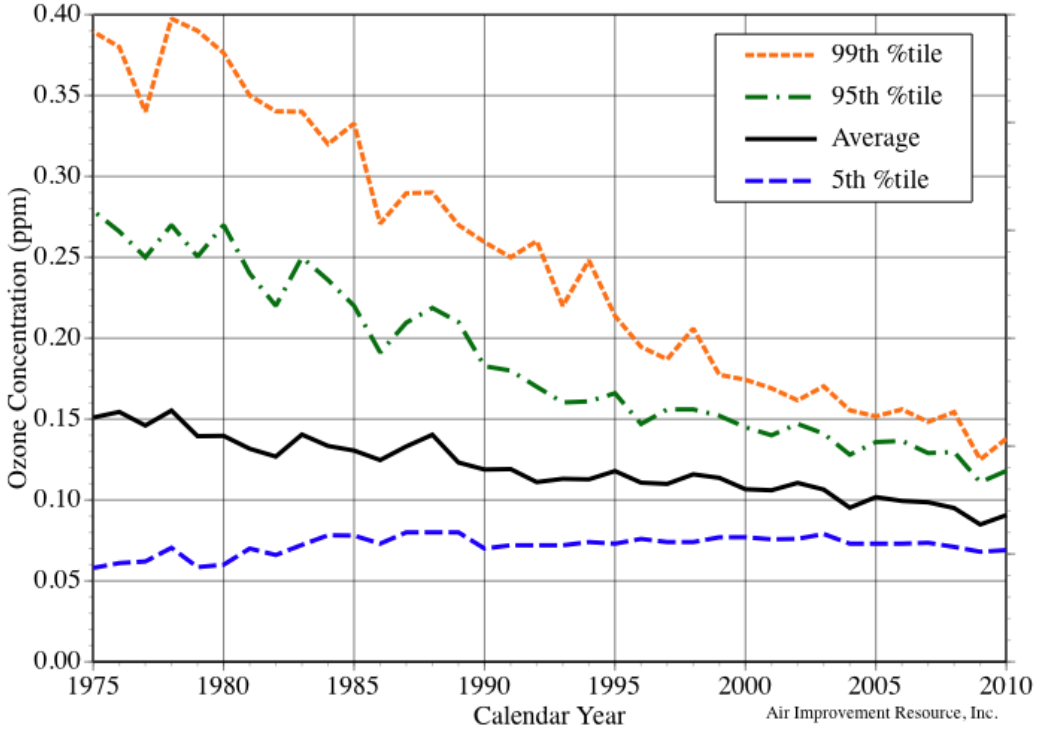

Figure 11: Highest annual 1-hour ozone concentrations for all US monitoring locations from 1975 to 2010.

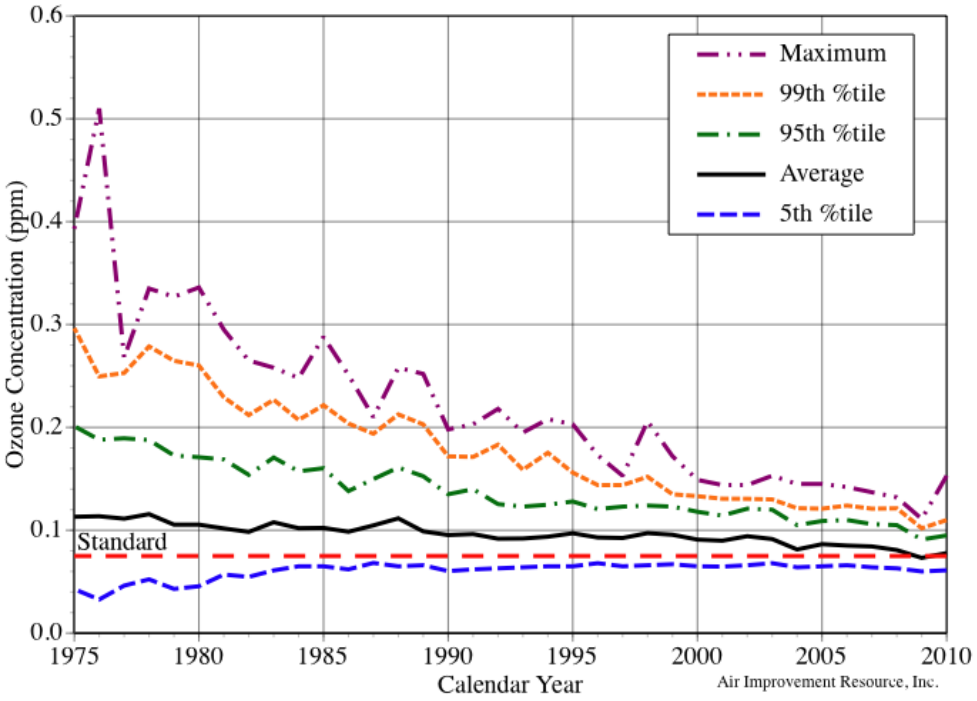

Figure 12: Highest annual 8-hour ozone concentrations for all US monitoring locations from 1975 to 2010.

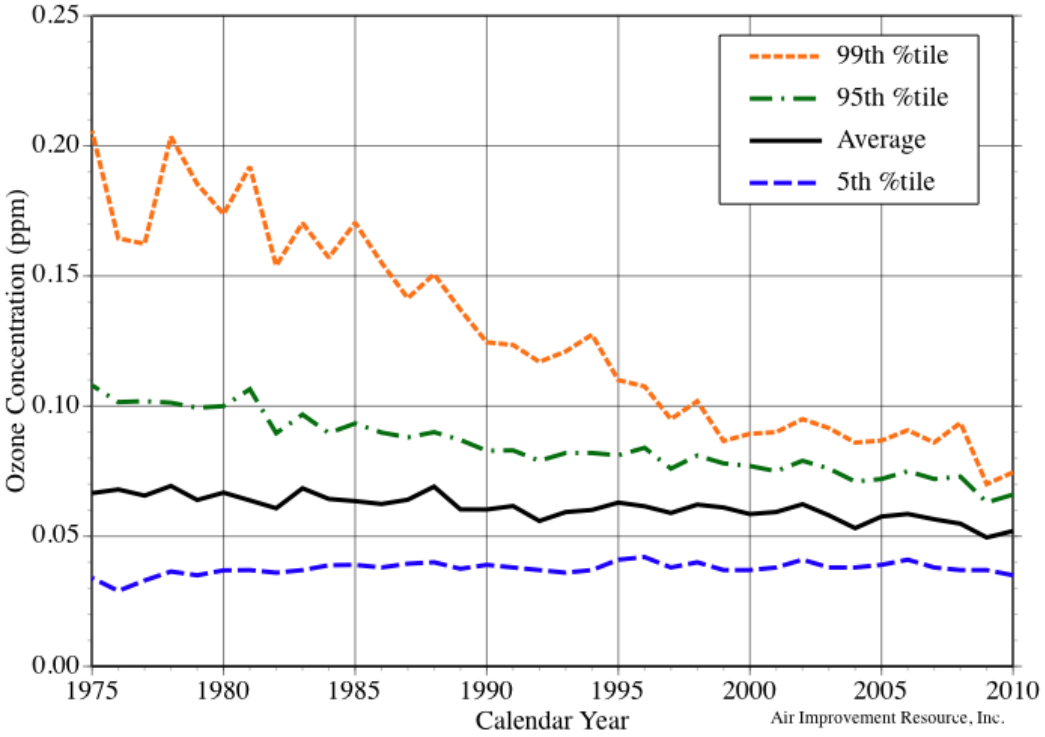

Figure 13: June - August average daily peak 1-hour ozone concentrations for all US monitoring locations from 1975 to 2010.

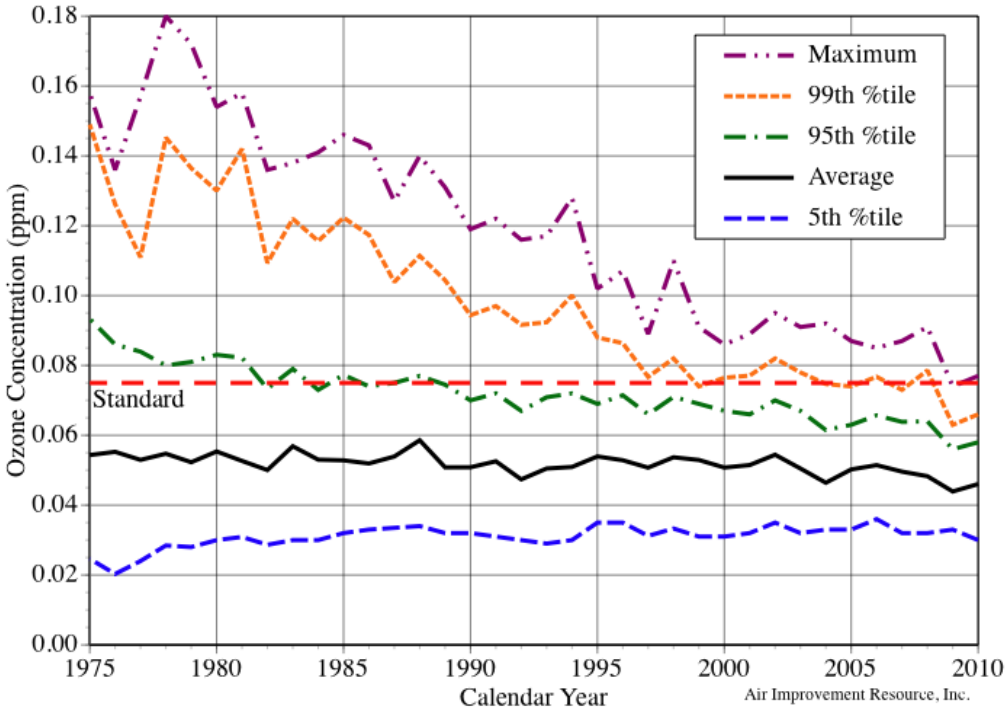

Figure 14: June - August average daily peak 8-hour ozone concentrations for all US monitoring locations from 1975 to 2010.

Although there are many small positive associations of ozone with changes in lung function in the literature, the data are less consistent than indicated in the ISA. A particular important study was carried out by the Health Effects Institute in the Los Angles Basin, the area of the country with the highest ambient ozone concentrations. Avol et al. (1998) concluded that the relationships between ozone and pulmonary function were erratic and difficult to reconcile with existing knowledge about the acute respiratory effects of air pollution. In addition, the small changes in lung function that have been reported, to the extent they may be caused by ozone, are not medically significant given the transient, reversible nature of ozone lung function changes.

The ISA notes that newer data on children attending camps, outdoor workers, and other healthy populations were limited, and across these studies, ambient O_3 exposure was associated with both decreases and increases in lung function.[59] It goes on to note that a large number of older studies comprise a majority of the supporting evidence from epidemiology regarding lung function test effects, whereas recent studies, which were far fewer in number, provide less compelling evidence. Whether this is due to reduced ozone exposures, differences in study design, or other factors should be discussed in the ISA and considered in the integrative sections.

2. The Data on Inflammatory Markers and Respiratory Symptoms Is Inconsistent -

[59] ISA, supra note 1 at pp. 6-17.

As with lung function measurements, observational studies of ozone association with the presence of inflammatory markers or respiratory symptoms suffer from limitations due to the presence of other pollutants and multiple comparisons. The ISA also notes that the clinical relevance of most biomarker changes is not clear. The text in the ISA notes several additional reasons why there may be inconsistencies in the data. On balance, there was little evidence of significant associations of ozone with inflammatory markers in Figures 6-10 and 6-11 of the first draft ISA. In the second draft, the data from inflammatory marker studies is not shown in a Figure. In addition, a number of these studies were conducted in Los Angeles and Mexico City where the subjects are exposed to high concentrations of both ozone and many other pollutants and report positive associations with various pollutants.

A particularly important study is described in the ISA as a well-designed panel study, Ferdinands et al. (2008). In this study, 16 adolescent long-distance runners in Atlanta, GA, were followed before and after exercise for 10 days in August 2004. Effect estimates for lags 0, 1, and 2 were positive, indicating O_3-associated decreases in airway inflammation. This study is important because the subjects, setting, and exercise level are just where one would expect to see ozone-induced inflammatory changes based on the clinical studies. Another study by Chimenti et al. (2009) measured some biological changes in adult male runners before and after races. However, the authors concluded that since no relationship was observed between neutrophil counts and inflammatory mediators 20 h after races, airways inflammation at this time point appears blunted in healthy runners and little affected by exposure to mild seasonal changes and airborne pollutants. Thus, under the situation with the greatest likelihood of inflammatory changes caused by ozone, there is little evidence of effects.

The lack of consistent increases in subclinical inflammatory markers is important information for the integrative synthesis. The lack of substantive effects in heavily exercising subjects suggests that there is even less likelihood of inflammatory changes due to ozone in the rest of the population as is goes about its daily activities. The findings in Adamkiewicz et al. (2004) of no inflammatory changes associated with ozone in elderly subjects including those with asthma and COPD confirm this view.

The evidence for respiratory symptoms associated with ozone in observational studies is mixed and inconsistent. For asthmatic children, the data appears somewhat consistent, but when one recognizes that similar data have been used by EPA to claim consistent effects on asthma from other pollutants, the reliance on single-pollutant studies is problematic. There are three multi-city studies that come to different conclusions with regard to individual pollutants. Therefore, the characterization of ozone having consistent effects on asthmatics cannot be supported. For children without asthma, the ISA acknowledges that the data are inconsistent.

The lack of consistent evidence implicating ozone as being associated with inflammation or respiratory symptoms in observational studies is an important finding that needs to be considered as the ISA evaluates the biological plausibility of even more severe effects such as hospital admissions and mortality.

3. A Large Multi-Country Study Demonstrates Little Association of Ozone with Hospital Admissions or Mortality - Before discussing the hospital admissions and mortality databases in the ISA, it is instructive to consider an important recent Health Effects Institute (HEI) study. HEI sponsored a large multi-country epidemiologic study to evaluate the relation of ozone and particulate matter to daily mortality and hospital admissions. The combined results of the large and comprehensive APHENA study are not consistent with ozone having a causal role in mortality or morbidity below the current standard. In October, 2009, the Health Effects Institute (HEI) published the results of the *Air Pollution and Health: A European and North American Approach (APHENA)*[60] study. The APHENA project was designed to take advantage of the largest databases available. These had been developed by the three groups of investigators for earlier studies: 1) the *Air Pollution and Health: A European Approach* Phase 2 (APHEA2) study involving 32 cities; 2) the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), conducted in the 90 largest US cities; and 3) multicity research on the health effects of air pollution in 12 Canadian cities. Each database included air pollution monitoring data for particulate matter and ozone, health outcome data in the form of daily mortality for all ages, for persons younger than 75 years, and for persons 75 years or older (from all nonaccidental causes [all cause]), cardiovascular disease, or respiratory disease) and daily hospital admissions for persons 65 years or older (for cardiovascular and respiratory disease). Other database variables used for APHENA included weather data and a number of socioeconomic and other variables known or suspected to influence mortality or hospital admissions.

In the original studies, each of the three groups used different modeling methodologies and entered different variables into their models. Although each group had reported positive and significant relationships between PM_{10}/O_3 and mortality and some morbidity endpoints, the magnitude of the relationships differed by geographic region. One goal of APHENA was to use common methodologies and variables and reanalyze their data sets. They intended to create a central repository for all three of the time-series databases and use a common quality assurance approach. In addition, they would conduct analyses on a combined, pooled dataset to study a variety of sensitivity issues including effect modification. They would then investigate the sensitivity of the estimates to a variety of smoothing methods and to the number of degrees of freedom. They also intended to explore reasons for the geographical heterogeneity of the effect estimates seen in their original studies. Another important goal of the program was to understand the extent of coherence between mortality and hospitalizations using data from cities in North America and Europe.

In the original analyses, all three groups used a two-stage approach. In the first stage, risks were estimated for the individual cities, and in the second stage, evidence across the cities were combined. Each group used different methods to perform both stages in the original analyses. In APHENA, the investigators wanted to identify a preferred way to do both stages and apply common methodologies to the three data sets. For the first

[60] Katsouyanni K. and Samet, J. (2009). "Air Pollution and Health: A European and North American Approach", (APHENA), *HEI Report* 142, Oct. 2009.

stage, they identified two smoothing techniques, natural splines (NS) and penalized splines (PS), and decided to use a number of degrees of freedom choices. They chose to use 3, 8 and 12 degrees of freedom and also the number of degrees of freedom chosen by minimizing the partial autocorrelation function (PACF).

For the second stage analyses, the two approaches used in original NMMAPS and the European studies represented the two major approaches used at the time to pool estimates. NMMAPS used Bayesian hierarchical regressions models while the Europeans used metaregression models. However, they could not determine the best method so they decided to use the models interchangeably.

Using the two smoothing techniques together with the four choices for the degrees of freedom and three choices of lags (0-1 day, 1 day and distributive lags which provided the cumulative effects of days 0 through 2) for each health outcome, the investigators ran a total of 24 different models for ozone. In addition, subsets of these choices were also used to examine the effects of controlling for PM_{10} and seasonal variations.
The results showed that the differences between the PS and the NS were very small in most cases and that the number of degrees of freedom tended to give similar results when greater than 6-8 degrees of freedom where used.

The overall modeling results for the mortality models and the morbidity models are summarized in Table 3 and 4, respectively. The denominator in the tables is the total number of different models that were run for each health effect outcome examined and

Cause of Death	**Canada**	**Europe**	**United States**
All Cause – all ages	24/24	15/24	12/24
≥ 75 yrs	23/24	2/24	6/24
< 75 yrs	18/24	22/24	10/24
All Cause PM controlled – all ages	4/8	8/16	0/16
≥ 75 yrs	0/8	3/16	0/16
< 75 yrs	5/8	14/16	0/16
All Cause – summer only	9/9	18/18 (4/12)*	18/18(0/12)*
Cardiovascular – ≥ 75 yrs	24/24	3/24	2/24
< 75 yrs	0/24	8/24	2/24
Cardiovascular –PM controlled ≥ 75yrs	0/8	0/16	0/16
< 75 yrs	0/8	5/16	2/16
Cardiovascular – summer only	0/6	8/12(0/8)*	11/12(0/8)*
Respiratory – all ages	0/24	0/24	0/24
≥ 75 yrs	0/24	0/24	0/24
Respiratory – PM controlled – all ages	0/8	0/16	0/16
≥ 75 yrs	0/8	0/16	0/16
Respiratory – summer only	6/6	4/12(0/8)*	2/12(0/8)*

*Denotes the PM controlled ratio

Table 3: APHENA modeling results for mortality. The numerators represent the number of models that showed a positive and statistically significant relationship between O_3 and mortality while the denominator is the total number of models run.

Type of Admission	Canada	Europe	United States
Respiratory	18/24	8/24	7/23
Respiratory – PM controlled	0/8	7/16	5/16
Respiratory – summer only	3/3	0/4	0/4
Cardiovascular	5/24	0/24	3/24
Cardiovascular – PM controlled	3/8	16/16	0/16
Cardiovascular – summer only	0/4	0/4	0/4

Table 4: APHENA modeling results for hospital admission for patients 65 years and older. The numerators represent the number of models that showed a positive and statistically significant relationship between O_3 and admissions while the denominator is the total number of models run.

the numerator is the number of models that resulted in a positive and statistically significant relationship between ozone and the health effect outcome. The way to interpret these tables is as follows. High ratios are suggestive of a robust and consistent relationship while low ratios are suggestive of no significant relationship. Intermediate values of the ratio suggest inconsistent and non-robust relationships that are dependent upon the model selected. Since there is no a priori way to determine the "correct" model, it is not possible to determine whether a small number (low ratio) of significant and positive relationships represents a real causal relationship or if they are false positives that can occur by chance or by confounding.

The all cause, all ages mortality results indicate a consistent relationship with ozone in Canada but somewhat less consistent relationships in Europe and the US. When the results for the two different age groups are examined, the interpretation of the results becomes even less clear. For $\geq$ 75 years of age, a consistent relationship still holds in Canada, but the European and US relationships become less consistent. When compared to the results for the < 75 years of age group, the results are implausible as they suggest that ozone is affecting the younger group more than the older group which goes against conventional wisdom. Controlling for PM makes the positive relationship for the older group disappear in all three locations, but the positive effect remains for the younger group except in the US where no relationship is evident. At all three locations a consistent summertime relationship is seen but vanishes in Europe and the US when PM

is controlled. PM controlled model results were not presented for the Canadian data. In any event, the results are not consistent with the existence of a causal relationship between ozone and all cause mortality.

The cardiovascular mortality/ozone modeling results are somewhat confusing. A clear positive relationship was found only in Canada and only for the ≥ 75 years of age group. Few significantly positive relationships were found for either age group for the other locations and no relationship was found in Canada for the younger age group. When PM is controlled for, few significant relationships remain. The summer only results suggest significant relationships in Europe and the US, but they vanish when PM is controlled. Taken altogether, these results do not support a causal relationship between ozone and cardiovascular mortality when the models are controlled for PM.

The cardiovascular hospital admissions/ozone results are also confusing. The annual results show a few significant model-dependent relationships in Canada and the US but none in Europe. When PM is controlled for, a few significant, model-dependent relationships remain in Canada, disappear in the US, but become consistently significant in Europe. The European results defy logic and were dismissed by the APHENA authors as a strong positive relationship was evident for respiratory hospital admissions and PM_{10}. The summer only results at all three locations show no significant relationships. Thus the weight of evidence from these results is consistent with the mortality results and does not suggest a causal relationship between ozone and cardiovascular hospital admissions.

In contrast to the cardiovascular mortality results, the respiratory mortality modeling results consistently show no relationship with one exception. None of the annual results at any location show any significant relationship between ozone and respiratory mortality. However for the summer, consistent significant results are found but only in Canada. Significant model-dependent results are seen in Europe and the US, but they disappear when controlled for PM. PM controlled results for Canada were not presented. Nevertheless, the weight of evidence of all the ozone/respiratory mortality model results does not support a causal relationship.

The respiratory hospital admissions show consistent significant relationships with ozone in Canada that disappears when PM is controlled. In the US and Europe, a few significant, model-dependent relationships are seen that persist when PM is controlled. However, during the summer when ozone is the highest and the strongest relationships would be expected, no significant relationships are found in either the US or in Europe. Consequently, the weight of evidence does not support a causal relationship between ozone and respiratory hospital admissions.

In summary, the APHENA results do not support EPA's claims of causal relationships between ozone and mortality or between ozone and hospital admissions.

4. The Data on Respiratory Hospital Admissions is less Consistent than Claimed in the ISA - In contrast to the summary of the APHENA study in the previous section, the

ISA uses selected APHENA results to suggest generally positive associations with respiratory hospital admissions even though many of the associations shown are not statistically significant. The ISA also discusses several other multi-city studies. However, the fact that those studies reported associations of other pollutants with respiratory hospital admissions is not acknowledged. For example, the Cakmak et al., 2006 study of respiratory hospital admissions in 10 large Canadian cities reported positive associations for the four gaseous pollutants evaluated in single-pollutant models. Cakmak et al. evaluated associations for daily lags from 0 to 5 days and chose the lag with the strongest positive association for each city to include in the combined associations they report. Goodman[61] cautions that this can lead to bias. He notes that investigators tend to report, if not believe, the analysis that produces the strongest signal; and in each single-site analysis, there are various model choices that affect the estimated strength of that signal.

Others have also pointed out the critical importance of model choice, particularly when effect estimates are small. For example, Smith et al. caution:

> 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).[62]

Smith et al. note that Lumley and Sheppard (2000) showed that the effect of choosing lags in this fashion has a bias which is of the same order of magnitude as the relative risk being estimated.[63]

The individual-city results were not reported by Cakmak et al. (2006). However, in studies that did report individual city results, the overall range among the cities was very wide. For example, the Medina-Ramon et al. (2006) study of 36 U. S. cities plotted the range of individual-city associations for the combined warm season ozone associations that they reported were statistically significant. The individual-city associations for COPD hospital admissions ranged from – 30 % to + 40 % for a 0.030 ppm increase in 8-hour ozone. The individual-city associations for pneumonia hospital admissions ranged from – 15 % to + 20 % for a 0.030 ppm increase in 8-hour ozone. When this wide range of individual-city results is considered in relation to Figure 6-19, it is clear that the current data presentation in Figure 6-19 is misleading. Thus, when all the individual-city results are considered, a very different pattern emerges making it very difficult to claim that there is a consistent ozone association with respiratory hospital admissions.

The combined associations for the two respiratory categories were positive in the

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[61] S. Goodman, "The Methodologic Ozone Effect," *Epidemiology*, 16: 430-435 (2005).

[62] R. Smith, P. Guttorp, L. Sheppard, T. Lumley and N. Ishikawa, "Comments on the Criteria Document for Particulate Matter Air Pollution," *Northwest Research Center for Statistics and the Environment Technical Report* , Series No. 66, July 2001.

[63] T. Lumley and L. Sheppard, "Assessing seasonal confounding and model selection bias in air pollution epidemiology using positive and negative control analyses," *Environmetrics*, 11, 705-717 (2000).

Medina-Ramon study in the warm season, but were negative in the cold season and not significant over all the year. It is difficult to rationalize this pattern as an effect of ozone. It is not plausible that ozone would cause hospital admissions in one season and protect against hospital admissions in another season. It is not plausible that ozone would have a strong effect on hospital admissions in some cities and have a strong protective effect against hospital admission in other cities. Given the stochastic variability and the similar pattern of associations for many pollutants, it is clear that time series analyses even with massive databases is a blunt tool that does not allow one to ascribe effects to individual pollutants.

The ISA also notes that studies that focused on respiratory-related outpatient or physician visits found no evidence of an association with short-term O_3 exposure. This finding is also not consistent with ozone having an effect on hospital admissions, since if ozone were causing exacerbations of respiratory problems there would be more instances of out-patient and physician visits associated with ozone than instances of hospital admissions associated with ozone. In contrast to the finding of no evidence for ozone associations, the studies reviewed in the ISA for this endpoint do implicate a range of other pollutants. Thus, the ISA practice of focusing on single-pollutant model results for ozone gives a misleading picture of the complexity of interpreting air pollution epidemiology with respect to individual pollutants.

5. The ISA Overstates the Case for Respiratory Mortality - The ISA in Section 6.2.8 notes that the data from the 2006 CD was inconsistent for an acute effect of ozone on respiratory mortality. The ISA goes on to indicate that the APHENA study found consistent positive associations for respiratory mortality in all-year analyses with stronger associations in analyses restricted to the summer. It also notes that respiratory mortality risk estimates were robust in the US dataset in summer season analyses. In contrast, the HEI Review Committee's commentary on the APHENA study indicates that in all-year analyses the associations between ozone and respiratory mortality were generally close to zero and were not significant in any region or in the combined estimate for all three regions.[64] The APHENA investigators indicated that, generally, there was little evidence of an effect of ozone on respiratory mortality in any center.[65] While the associations were generally higher in summer-only analyses, only 2 of 12 model combinations were statistically significant and, when controlled for PM10, none of the 8 model combinations presented in the APHENA report were statistically significant. Thus, the ISA overstates the case for an effect of ozone on respiratory mortality.

E. The Evidence for Cardiovascular Effects from Current Ambient Ozone Concentrations Is Weak and Inconsistent

The ISA notes that the cardiovascular morbidity data is inconsistent. Given the stochastic variability inherent in such studies, the many endpoints evaluated in even a single study, the complex mixtures involved, and the role of publication bias, it is not surprising that there would be some positive results for any endpoint. However, the overall pattern of

[64] APHENA report, supra note 32 at p. 103.
[65] Ibid. at p. 50.

ozone associations with cardiovascular morbidity endpoints is mixed and inconsistent. For example, the APHENA results for U. S. cardiovascular disease hospital admission associations with ozone (controlling for PM10) are essentially null. None of the 16 model combinations are statistically significant and 7 of the 16 model combinations actually have negative coefficients.

The ISA claims that there is a consistent cardiovascular mortality signal, but the overall spatial and temporal mortality pattern, as shown below, is not consistent with ozone causality. In addition, a mortality signal in the absence of a morbidity signal would be incoherent, not just weakly coherent as posited in the ISA.[66] Furthermore, the pattern of mortality associations for other criteria pollutants is remarkably similar to that for ozone in single-pollutant models.

The ISA also refers to toxicology studies showing ozone/cardiovascular effects. However, the animal studies cited used very high in vivo exposures where the respiratory defenses would be overwhelmed and in vitro exposures that the ISA acknowledges are speculative. In addition, the finding of increased aortic atherosclerotic lesion area in ApoE-/- mice reported in Chuang et al. (2009) is not unique to ozone. Similar findings have been reported in this sensitive animal model for elevated concentrations of both particles and other gaseous pollutants.

There is an important new controlled human exposure study that is not included in the ISA. Tank et al. (2011)[67] exposed healthy ozone responsive subjects to 0.25 ppm ozone for 3 hours, an exposure that elicits the FEV1 and mild inflammatory response, and evaluated several cardiovascular measurements, including ECG, finger blood pressure, brachial blood pressure, respiration, cardiac output, and muscle sympathetic nerve activity (MSNA). The study was conducted because of concern that pulmonary function changes implicate a neural mechanism and autonomic nervous system imbalance with raised sympathetic and attenuated parasympathetic activity may contribute to cardiovascular morbidity and mortality. There is also evidence in animals, that inflammation in the kidney or in gastrointestinal organs increases central sympathetic activity through afferent neural pathways. However, when compared to the clean air control exposure, none of the measures that are related to autonomic cardiovascular regulation were affected by the ozone exposure. The lack of any effect at 0.25 ppm ozone with exercise indicates that the lower doses associated with personal exposure to ozone from current ambient levels would not be expected to have cardiovascular effects. This would be consistent with the lack of a cardiovascular morbidity signal from epidemiology.

Thus, the overall evidence for cardiovascular effects from current ambient ozone concentrations is weak and inconsistent. The ISA weighs the results of what is described as a relatively strong body of toxicological studies and the claimed consistent

[66] ISA, supra note 1 at pp. 6-184.

[67] Tank J, Biller H, Heusser K, Holz O, Diedrich A, et al. (2011), "Effect of Acute Ozone Induced Airway Inflammation on Human Sympathetic Nerve Traffic: A Randomized, Placebo Controlled, Crossover Study", PLoS ONE 6(4): e18737. doi:10.1371/journal.pone.0018737

cardiovascular mortality effects against the against the lack of a consistent cardiovascular morbidity signal and weak evidence for biological plausibility for ozone-induced cardiovascular morbidity and concludes that "the generally limited body of evidence is suggestive of a causal relationship between relevant short-term exposures to O_3 and cardiovascular effects." The toxicological evidence indicates that elevated ozone levels can cause effects on the cardiovascular system but dose plausibility has not been demonstrated and, as noted in the ISA, it remains unclear if the mechanism is through a reflex response or due to O_3 reaction products.[68] With the addition of the Tank et al. (2011) study the human clinical database, although limited, does not support an effect of current ambient ozone on cardiovascular endpoints. In addition, the number of epidemiological studies of cardiovascular morbidity is now large and cannot be characterized as a generally limited body of evidence. Finally, the cardiovascular mortality data is less consistent than indicated in the ISA and indicates a spatial and temporal pattern that is not consistent with ozone causality. Thus, the overall evidence is not suggestive of a causal relationship between current short-term ozone exposures and cardiovascular effects.

A probable reason for the discordance between the cardiovascular morbidity and mortality results arises from the nature of the studies that make up the available database together with publication bias. For cardiovascular morbidity, the bulk of the studies either evaluated a suite of available pollutants or was focused on PM associations and included ozone in the analysis. In these studies, it is likely that null ozone results or negative ozone results would be included in the publications since positive associations with other pollutants would have been highlighted in the findings. In contrast, most of the mortality studies were designed as investigations of ozone-related mortality and either did not include other pollutants or may have considered PM as a potential confounder. In this case, it is much less likely that null or negative associations would be included in the published results. Over time, as multi-city studies appeared in the literature and then as studies that included regional and seasonal results appeared in the literature, the emphasis remained on highlighting the positive ozone-mortality associations. The existence of negative and null associations in various cities and regions is apparent in the detailed results of these studies, but not highlighted or discussed by the authors.

F. The Evidence for All-cause Mortality is Not Consistent with Ozone Causality

In addition to the discussion of respiratory and cardiovascular mortality in Sections 6.2.8 and 6.3.2.8, there is a major section on mortality that discusses all-cause mortality as well as specific causes of mortality. The ISA indicates that new multicontinent and multi-city studies reported consistent positive associations between short-term O_3 exposure and all-cause mortality in all-year analyses, with additional evidence for larger mortality risk estimates during the warm or summer months. It also indicates that these associations were reported across a range of ambient O_3 concentrations that were in some cases quite low. These statements overstate the case for consistent relationships. For example, the combined U. S. ozone associations for all-cause (and all-age) mortality in the APHENA multicontinent study are shown in Table 21 of the APHENA study. Of the 24 model

[68] ISA, supra note 1 at pp. 6-176 and 6-181.

combinations evaluated in single-pollutant models, 10 were not statistically significant and 7 were actually negative. More importantly, in the 16 model combinations presented that controlled for PM10, 4 were actually negative and none of the 16 were statistically significant. Thus, the APHENA ozone associations for all-cause mortality are not consistently positive.

The ISA supports the contention that there are consistent positive associations by referring to Figure 6-27. Figure 6-27 is misleading for several reasons. It includes only selected APHENA results. It includes three meta-analyses that are known to have substantial publication bias inflating the ozone/mortality association. It omits information on the full range of individual-city associations. Figure 6-29 of the ISA shows that the individual-city associations in the Franklin and Schwartz (2008) multi-city study range from -5 to +5 % for a 0.010 ppm ozone increase. That range translates into a - 10 % to + 10 % range for the scale of Figure 6-27, which is a 0.020 ppm increase in 24 –hour ozone. Similarly, the range in individual-city ozone associations in the Smith, Xu, and Switzer (2009) study shown in Figure 6-28 and in the Bell and Dominici (2008) study in Figure 6-31 translate into a range from roughly about – 10 % to + 10 % for the scale in Figure 6-27. Thus, if all the available data were shown on Figure 6-27, the perception of consistency would be dramatically altered.

The patterns in multi-city studies have spatial and temporal characteristics that are not consistent with causal relationships, demonstrating substantial stochastic variability. For example, the Smith, Xu, and Switzer[69] analysis of ozone mortality associations shows a wide range in individual-city associations as well as large regional differences in combined analyses that are not consistent with ozone causality. Figure 15 (Figure 1 from Smith, Xu, and Switzer) is shown below. A similar pattern of wide variations from negative to positive in individual-city associations is evident in all the multi-city studies for which the individual-city associations are reported or plotted. The pattern in multipollutant analyses is not as well established, but there is substantial evidence of unacknowledged stochastic variability in this case, too. The variability from city to city is too great to represent just heterogeneity due to different mixtures and exposures. Heterogeneity of response would imply varying positive associations. However, the pattern in multi-city studies is different. The associations either within a given city or among a group of cities range from positive to negative. The presence of many negative associations of ozone (or any other pollutant) with a health endpoint in the epidemiological literature is a fact that argues against interpreting selected positive associations as true health effects.

The spatial or regional patterns in ozone associations that are summarized in the ISA in Figures 6-32 and 6-33 and in Table 6-48 clearly are not consistent with the locations of highest man-made ozone in the monitoring data. The seasonal pattern with combined negative associations in colder months also raises a major issue with the claim of ozone causing mortality. The Schwartz (2005) multi-city study noted the negative association in winter and suggested that it may reflect the negative association between wintertime

[69] R. L. Smith, B. Xu, and P. Switzer, 'Reassessing the Relationship Between Ozone and Short-term Mortality in U.S. Urban Communities," *Inhalation Toxicology*, 29(S2), 37-61, 2009.

ozone and primary air pollutants. Schwartz went on then to ask "might not the positive association in the summer likewise reflect confounding with some other pollutant?" These and other possible explanations need to be rigorously considered by EPA.

In discussing the shape of the concentration-response function, the ISA points out that combined mortality effects for ozone have been found at concentrations well below the current standard and cite a multi-city study where high ozone days have been excluded, Bell et al. (2006). However, there is a follow-on study by Bell et al. (2007)[70] that illuminates this issue. When Bell et al. (2007) restricted the analysis to days with low ozone, in order to see if the small combined association persisted, the range in individual-community associations widened. For example, when the data was restricted to days with ozone less than 0.02 ppm, the range in individual city mortality associations for a 0.01 ppm increase in ozone was from – 20 % to + 30 %. It is inconceivable that such low ozone exposures would be causing a dramatic increase in mortality in one city and protecting against mortality in another. With such wide variation, the interpretation of a small combined association as a health effect is highly questionable, especially in light of the fact that ozone indoors, where people spend about 90 % of their time is

[70] M. L. Bell, J. Y. Kim, and F. Dominici, "Potential confounding of particulate matter on the short-term association between ozone and mortality in multisite time-series studies," *Environ Health Perspect*, 115, 1591-1595 (2007).

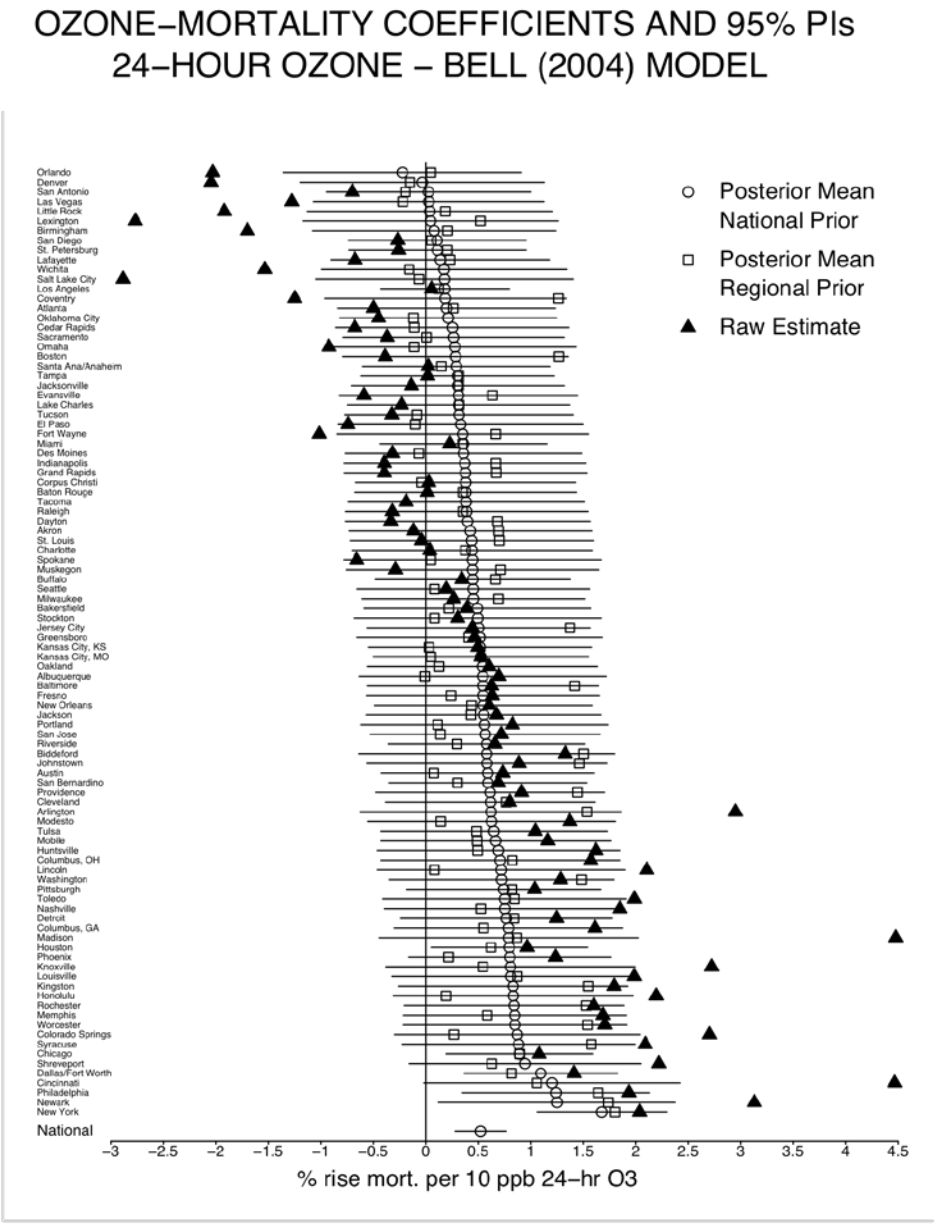

Figure 15: 95% posterior intervals for the ozone-mortality coefficients, all-year data, by the hierarchical Bayesian method as in Figure 2 of Bell et al. (2004). The Bayesian posterior estimates under the "national prior" (circles) are shown alongside those for the "regional prior" (squares) and the raw maximum likelihood estimates (triangles).

reduced about half or more by deposition to building surfaces.

In discussing the evidence for possible thresholds, the ISA downplays the findings of the Stylaniou and Nicolich (2009) study noting that given the city-to-city variation in risk estimates, combining the city-specific estimates into an overall estimate complicates the interpretation of a threshold. By the same reasoning, given the city-to-city variation in risk estimates, combining the city-specific estimates into an overall estimate complicates the interpretation that the multi-city time series studies show ozone as having a causal effect on mortality. In addition, Rhomberg et al. (2011)[71] have shown that measurement error can give a false linear result. Despite these known problems, the ISA refers to continued evidence of a linear no-threshold C-R relationship.

A 2006 paper by Keatinge and Donaldson,[72] that is not included in the ISA, provides important new insights into the issue of modeling weather effects in ozone studies. The authors evaluated whether mortality that is often attributed to ozone and other pollutants in hot weather results from confounding by neglected weather factors. Their analysis was restricted to days when the mean daily air temperatures exceeded 18 degrees C in Greater London from 1991 to 2002, and evaluated mortality counts at an age greater or equal to 65. The adjustment for acclimatization was based on the characteristic pattern that has been reported by various investigators that the rise in mortality on hot days is followed by a prolonged reduction in mortality lasting at least 14 days. When only current temperature (average of days 0 to –2) was considered in the model, significant mortality was attributed to ozone. When they allowed for cumulative exposure to heat throughout the summer and for sunshine (which contributes to heat stress at any given temperature), the ozone association was reduced by a factor of 10 and was no longer statistically significant. This study indicates that previously neglected weather factors may be confounding the mortality analyses relied on in the ISA. It was noted in the 2006 Ozone CD that variations in treatment of weather can change the results by a factor of 2 and that publication bias can inflate the perceived association by a factor of 3. The Keatinge and Donaldson analysis suggests that previously overlooked weather factors can reduce the association by a factor of 10.

With regard to uncertainty due to model selection, Koop and Tole (2004)[73] in another study not cited in the ISA conclude:

> Point estimates of the effect of numerous air pollutants all tend to be positive, albeit small. However, when model uncertainty is accounted for in the analysis, measures of uncertainty associated with these point estimates became very large. Indeed they became so large that the hypothesis that air pollution has no effect on

[71] Lorenz R. Rhomberg, Juhi K. Chandalia, Christopher M. Long, and Julie E. Goodman, "Measurement error in environmental epidemiology and the shape of exposure-response curves," *Critical Reviews in Toxicology*, Sept. 2011, Vol. 41, No. 8; pp. 651-671. (doi: 10.3109/10408444.2011.563420).

[72] W. Keatinge and G. Donaldson, "Heat acclimatization and sunshine cause false indications of mortality due to ozone," *Environmental Research*, 100, 387-393 (2006).

[73] G. Koop and L. Tole,"Measuring the Health Effects of Air Pollution: to What Extent Can We Really Say that People are Dying from Bad Air," *J. of Environmental Economics and Management*, 47, 30-54. (2004).

> mortality is not implausible. On the basis of these results, we recommend against the use of point estimates from time-series data to set regulatory standards for air pollution exposure.

The fact that the uncertainty due to model selection is much larger than the typical confidence limits on any given statistical association should be acknowledged in the ISA and considered in the interpretation of the epidemiological data. Given that the small positive results from time-series studies may reflect residual bias of the models due to weather, temporal or other unaccounted confounding factors, EPA cannot and should not draw conclusions on causality from these studies.

In addition, there is no discussion of the biological plausibility of ozone causing or contributing to excess deaths at very low ambient concentrations. The bulk of the ozone mortality estimated in the 2007 Risk Assessment accrued from ozone days with the ambient 8-hour maxima below 0.040 or 0.050 ppm.[74] At these low ambient concentrations, the personal exposures of the population are too low to experience any measurable effects in controlled exposure studies. Thus, it is inexplicable how such low ozone exposures could be causing the pattern of ozone/mortality associations in Bell et al. (2007), for the data restricted to low ozone days.

For all these reasons, the ozone mortality data is less consistent and persuasive than the ISA indicates and the conclusion that "there is likely to be a causal relationship between short-term O_3 exposure and all-cause mortality"[75] cannot be supported.

G. The Evidence for Other Acute Endpoints is Weak and Inconsistent

There are a variety of other acute endpoints discussed in Chapter 6 of the ISA. However, the data are cited as being suggestive, inconsistent, and/or inadequate. Because of the issues of stochastic variability, publication bias, model selection uncertainty, and potential confounding, it is not surprising that there would be some positive associations of ozone with any endpoint evaluated even in the absence of a causal relationship.

H. The Evidence for Chronic Ozone Effects is Overstated in Chapter 7

Chapter 7 on chronic effects draws the conclusion that there is now substantial evidence for effects associated with chronic exposure. However, the evidence is less certain than indicated in the ISA. The data on lung function growth is mixed and inconsistent as indicated in the ISA, making it difficult to determine independent effects of ozone or other pollutants. What is described as the strongest new evidence is (1) one new chronic mortality study and (2) several studies implicating ozone in new onset asthma. All these studies are weaker than they appear because they rely on ambient ozone measurements to characterize the exposures. In reality, personal exposure is the proximate cause of any chronic effects and total personal exposure is the metric that should be considered.

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[74] 2007 SP, supra note 8 at Fig. 5-6.
[75] ISA, supra note 1 at pp. 6-233.

For new onset asthma, the studies involve analyses of data from the Southern California Children's Health Study. Studies of effects in Los Angeles or Mexico City, areas with high historic levels of ozone and other pollutants, are not relevant to effects at or below the current standard. Another major concern with these studies is that the many other variables that are known to affect asthma are not fully considered. For example, differences in living conditions in the indoor environment (or changes in living conditions in the indoor environment due to energy conservation) may play a role by increasing exposure to common household allergens such as mold, dust mites and animal dander.

With regard to asthma and chronic ozone, Dockery et al. (1996)[76] evaluated asthma prevalence and respiratory symptoms in a group of 13,369 8 to 12 year old children in 24 communities and reported that the prevalence of asthma or asthmatic symptoms was not associated with chronic exposure to ozone. The Dockery et al. (1996) study is not included in the ISA. In addition, McConnell et al. (2002) followed 3,535 children with no history of asthma from 12 communities in Southern California, as part of the Children's Health study. The risk for developing asthma was not greater in high ozone communities compared to low ozone communities. Although there has been an increase in asthma in both developed and developing nations in the past 20 or 30 years, outdoor air pollution, in general (and ozone, in particular), has been decreasing. Outdoor air pollution cannot be the cause of the increase in asthma.

With regard to chronic mortality, the ISA summarizes several studies showing no effect but focuses on the Jerrett et al. (2009) study as showing a chronic respiratory mortality signal for ozone. However, the respiratory mortality signal is present only for females in spite of the fact that males would be expected to receive higher ozone doses by being outside exercising more than females. In addition, the regional results reported by Jerrett et al. show no respiratory mortality effect in Southern California, the Northeast, or the Industrial Midwest, the regions of the country with the highest historic man-made ozone exposures. Finally, the presence of a chronic respiratory mortality signal is not coherent with the lack of an acute respiratory mortality signal in APHENA. For these reasons, the evidence for a chronic ozone mortality effect is much weaker than indicated in the ISA.

Although there are toxicological studies showing effects from chronic ozone exposures, these studies utilize high ozone exposures compared to the day-to-day personal ozone exposures of the population. At high chronic exposures, effects due to repeated lung injury and repair cycles are apparent. However, the relevance of these studies to the personal exposures of the population which are typically one-quarter of the ozone measured at ambient monitors is not clear.

I. As a Result of the Aforementioned Errors, the ISA Overstates the Case for Ozone Causality

[76] D. Dockery, J. Cunningham, A. Damokosh, L. Neas, J. Spengler, P. Koutrakis, J. Ware, M. Raizenne and F. Speizer, "Health Effects of Acid Aerosols on North American Children: Respiratory Symptoms," *Environmental Health Perspectives*, 104: 500-505, 1996.

The ISA overstates the consistency and coherence of the available data with regard to respiratory morbidity and mortality and all-cause mortality. There are now numerous multi-city studies that all exhibit a wide range of individual-city associations between ozone measured at central city monitors and daily health statistics for mortality and morbidity. The overall patterns in the associations are not consistent with ozone causality. The individual city associations vary widely from positive to negative, a finding that is not addressed sufficiently in the ISA. It is not plausible that ozone would cause effects in some cities and protect from effects in other cities.

The seasonal variability in associations is also not consistent with causality. Combined associations in multi-city studies are generally negative in winter and positive in summer. The differences in ozone exposure between summer and winter are not that large as shown in the many graphs in Section 3.10.4 that they can explain the negative combined associations in winter. The correlations of ozone with other pollutants are very different between winter and summer as shown in Figure 3-47. This suggests that ozone is acting as an indicator of the air pollution mix in summer but is anti-correlated with the air pollution mixture in winter. The strong possibility that ozone is only showing associations because it is an indicator and not an independent causal factor needs to be acknowledged and fully discussed in the ISA.

The spatial variability of combined ozone associations in acute multi-city studies is also not consistent with ozone causality. Studies by Bell et al. and Smith et al. show that there are positive combined ozone associations in some regions but not in others. In fact, the spatial pattern of positive ozone associations is similar to that for particulate matter (PM) and is not consistent with the locations of highest man-made ozone exposure. These facts need to be acknowledged and discussed in the ISA.

Finally, the multicontinent APHENA study demonstrates an inconsistent and incoherent pattern of combined mortality and hospital admission associations. The HEI Review Committee's commentary, for example, indicated that it is remarkable how little coherence there is for the O_3 effects.[77] Even with a massive database, APHENA modeling shows few statistically significant combined effects. Although the APHENA study did not report all the individual-city associations, the small subset that is included in the report shows, in agreement with other multi-city studies, that the combined associations result from a mix of individual-city associations that include cities with strong positive ozone associations, cities with strong negative associations, and cities with no ozone association. The overall pattern in APHENA is not consistent with ozone causing respiratory or cardiovascular mortality and morbidity. Rather the pattern of combined associations probably represents residual confounding.

With regard to chronic mortality, the ISA focuses on the Jerrett et al. (2009) study as showing a chronic respiratory mortality signal for ozone. However, the respiratory mortality signal is present only for females in spite of the fact that males would be expected to receive higher ozone doses by being outside exercising more than females. In addition, the regional results reported by Jerrett et al. show no respiratory mortality

[77] APHENA report, supra footnote 59 at p. 109.

effect in Southern California, the Northeast, or the Industrial Midwest, the regions of the country with the highest historic man-made ozone exposures. Finally, the presence of a chronic respiratory mortality signal is not coherent with the lack of an acute respiratory mortality signal in APHENA. For these reasons, the evidence for a chronic ozone mortality effect is much weaker than indicated in the ISA.