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

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Prepared for
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Executive Summary

Air Improvement Resource, Inc. (AIR) reviewed the third 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

Based on comments from the public and CASAC, EPA has made significant revisions to the background ozone discussion in the third draft of the ISA. In particular, EPA has decided to consider U. S. background (USB) in addition to North American background (NAB), they have included the latest GEOS-Chem and CAMx modeling results, they agreed that the most relevant days to analyze are the days at the upper end of the ozone distribution, and they agreed that because of nonlinearities that further work is needed to determine the contribution of background sources of ozone to urban concentrations.

We support EPA's inclusion of USB in the background discussion. However, the Agency needs to do additional spatial and temporal analyses of USB to provide the same kind of detailed information that they provide for NAB in the ISA.

We support EPA's inclusion of the latest modeling results for GEOS-Chem and CAMx. In addition, we support EPA's inclusion of the days in the higher end of the MDA8 distribution in their analyses. Because CAMx's performance is better than GEOS-Chem at the higher end of the ozone concentration distribution, we recommend that the USB analyses also be performed using CAMx.

Finally, we agree with EPA that further work is needed to address the impact of the non-linearities in the estimation of the impact of USB on observed ozone concentrations. This work needs to be completed in time to inform the Policy Assessment.

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 biologically small and generally not statistically significant 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. The third 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 draft continues to inappropriately weigh the evidence from epidemiology with regard to ozone health effects.

While there is evidence of small acute FEV1 changes in the observational literature, 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 or mortality. 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. 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.

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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 third external review draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants[1] (ISA) in June 2012. 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] Finally, AIR and the Alliance provided public comments[3,4] on the first and second draft ISAs.[5,6]

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[1] U. S. Environmental Protection Agency, *Third External Review Draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants*, EPA/600/R-10/076c, June 2012.
[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] J. M. Heuss and G. 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.
[4] J. M. Heuss, G. T. Wolff, and D. F. Kahlbaum, 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," Air Improvement Resource, Inc. Report, Prepared for The Alliance of Automobile Manufacturers, November 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.

The following comments focus on the policy relevant background, 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.

The choice of the relevant measure of background 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[7] comments), the Alliance has been concerned that EPA underestimated the relevant background in the prior review. As discussed below, many of our concerns have been addressed in the third draft of the ISA, but EPA still need to provide some additional analyses.

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. 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 in order to judge the public health impact of these effects.

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.[8] However, the ISA continues to gloss over these issues and fails to address the concerns

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[6] 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, September 2011.

[7] 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.

[8] Alliance comments, supra note 3; Alliance comments, supra note 4; 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; American Petroleum Institute Comments on the U.S. EPA Integrated Science Assessment of Ozone and Related Photochemical Oxidants (Second External Review Draft), Docket ID EPA-HQ-ORD-2011-0050-0029; Comments of the Utility Air Regulatory Group on the Second External Review Draft, Docket ID No. EPA–HQ–ORD–2011–0050-0031.

and inconsistencies that have been raised in public comments on the first and second draft ISAs. As a result, the draft ISA continues to overstate the consistency and weight of evidence for ozone effects from epidemiologic studies.

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 a focus of AIR comments. Information from other chapters is discussed as it affects the interpretation and integration of the health effects data. Chapter 6 is organized by major health effect categories (e.g., respiratory, cardiovascular, 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. Background Ozone

Based on comments from the public and CASAC, EPA has made significant revisions to the background ozone discussion in the third draft of the ISA. In particular, EPA has decided to consider U. S. background (USB) in addition to North American background (NAB), they have included the latest GEOS-Chem and CAMx modeling results, they agreed that the most relevant days to analyze are the days at the upper end of the ozone distribution, and they agreed that because of nonlinearities that further work is needed to determine the contribution of background sources of ozone to urban concentrations.

A. Significant Revisions in Third Draft to Background Ozone

1. U.S. Background

Over the course of the three drafts of the ISA, there has been an evolution in EPA's treatment of background ozone. Continuing with the practice used in the previous ozone review,[9] EPA used policy relevant background (PRB) as their preferred measure for background ozone in the first draft of their ISA.[10] They defined PRB in the first draft:

> The background concentrations of O_3 that are useful for risk and policy assessments informing decisions about the NAAQS are

[9] U.S. EPA. 2006. *Air Quality Criteria for Ozone and Related Photochemical Oxidants.* EPA 600/R-05/004aF, Research Triangle Park, NC.

[10] ISA, supra note 5, at pp. 2-5.

> referred to as policy-relevant background (PRB) concentrations. PRB concentrations have historically been defined by EPA as those concentrations that would occur in the U.S. in the absence of anthropogenic emissions in continental North America (CNA) defined here as the U.S., Canada, and Mexico. For this document, PRB concentrations include contributions from natural sources everywhere in the world and from anthropogenic sources outside CNA.

The exclusion of emissions from Canada and Mexico was based on EPA's assumption that the U.S. could control emissions from Canada and Mexico by treaties and international agreements.

In the second draft of the ISA,[11] EPA stopped using the term PRB and switched to calling it North American background (NAB). EPA states: "For this document, we have focused on the sum of those background concentrations from natural sources everywhere in the world and from anthropogenic sources outside the U.S., Canada and Mexico, i.e., North American background." While they changed the term from PBR to NAB, they both had the same definition and NAB was still based on the controversial assumption that Canadian and Mexican emissions could be controlled by treaties or international agreements.

In AIR's comments[12] on the second draft of the ISA, we pointed out that their definition of NAB actually implied that Mexican and Canadian emissions could be eliminated by treaties or agreements and that this was not realistic. The way EPA used NAB resulted in their overestimating the risk reduction that would be achieved by lowering the NAAQS and it penalized the States because they would have to offset the Canadian and Mexican emissions in their State Implementation Plans. Instead of using NAB, AIR recommended that it was more appropriate to use a U.S. background (USB), which includes Canadian and Mexican emissions, for the risk assessments and for control strategy development.

In the third draft of the ISA[13], EPA has included three definitions of background ozone for consideration: NAB (as previously defined), USB and natural background. They define USB as the background that would exist in the absence of anthropogenic emissions from the U.S. Thus, ozone resulting from Canadian and Mexican emissions is included. EPA defines natural background as ozone "resulting from emissions from natural sources (e.g., stratospheric intrusion, wildfires, biogenic methane and more short-lived VOC emissions) throughout the globe." AIR supports EPA's inclusion of USB in their analyses.

2. Inclusion of the Latest Modeling Results

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[11] ISA, supra note 6, at pp. 1-4.
[12] Heuss et al., supra note 4, at pp. 7.
[13] ISA, supra note 1, at pp. 2-7.

In AIR's previous comments[14] on the second draft if the ISA, we also pointed out that the newest estimates of NAB from modeling studies were higher than the ones EPA had been using. The latest ISA now includes these estimates from both GEOS-Chem[15] and CAMx.[16]

3. The Most Relevant Days Are the Upper End of the Ozone Distribution

In the risk assessment conducted for the previous ozone review,[17] EPA used the monthly averaged diurnal ozone profiles of NAB. In the comments on the second ISA,[18] AIR said that this was inappropriate because it significantly underestimates the NAB on the highest ozone days which are the days of most concern to state regulators. In the third draft of the ISA, EPA acknowledges that the high ozone days need to be the focus. On page 3-32 they state: "An understanding of the sources and contributions of background O_3 to O_3 concentrations in the U.S. is potentially useful in reviewing the O_3 NAAQS, especially related to days at the upper end of the distribution of O_3 concentrations." In addition on p 3-45, they acknowledge that:
"background concentrations in many eastern areas tend to be higher on days when predicted total O_3 is >60 ppb."

Since the ozone NAAQS is an extreme value, the fourth highest daily maximum 8-hour concentration (MDA8) over three years, it is necessary to know what the concentrations of USB are on those high days. We support EPA's new focus on the days at the high end of the ozone distribution.

4. Additional Work is Needed to Determine the Contributions of Background Ozone to the Observed Concentrations

Three times (pages 2-10, 3-64 and 3-147) in the third draft of the ISA, EPA makes this cautionary statement:

> Note that the calculations of background concentrations presented in this chapter were formulated to answer the question, "what would O_3 concentrations be if there were no anthropogenic sources." This is different from asking, "how much of the O_3 measured or simulated in a given area is due to background

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[14] Heuss et al., supra note 4, at pp. 7.
[15] L. Zhang, D.J. Jacob, N.V. Downey, D.A. Wood, D. Blewitt, C.C. Carouge, A. Van donkelaar, D.B.A. Jones, L.T. Murray and Y. Wang, "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 (2011).
[16] C. Emery, J. Jung, N. Downey, J. Johnson, M. Jimenez, G. Yarwood and R. Morris"Regional and global modeling estimates of policy relevant background over the United States." *Atmos. Environ.,* 47:206-217 (2012).
[17] 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.
[18] Heuss et al., supra note 4, at p. 8.

> contributions." Because of potentially strong non-linearities—particularly in many urban areas—these estimates should not be used by themselves to answer the second question posed above. The extent of these non-linearities will generally depend on location and time, the strength of concentrated sources, and the nature of the chemical regime. Further work is needed on how these estimates of background concentrations can be used to help determine the contributions of background sources of O_3 to urban concentrations.

In previous comments by AIR,[19] which focused on background ozone in the first draft of the ISA, this issue was brought to EPA's attention. Aware of the non-linearities associated with ozone formation, AIR recommended:

> The contribution of natural sources and other PRB sources to North American cannot be realistically assessed in the absence of U.S. anthropogenic emissions. To realistically estimate the contribution of PRB sources, the PRB sources should be shut down in the presence of U.S. sources.

More will be said on this later.

B. Remaining Background Ozone Issues

1. USB

In the third draft of the ISA as well as in the first two drafts of the ISA, EPA presents comprehensive analyses showing the spatial and temporal distributions of the MDA8 (maximum daily 8-hour ozone) measurements and model projections for MDA8 and PRB (now NAB) across the entire country and in detailed time-series at the CASTNET sites. In addition, the third draft also contains some comparisons between the GEOS-Chem and CAMx modeling results for MDA8. These analyses provide the readers with a level of comfort that the estimates appear to be reasonable, at least on average, but that more analyses are needed to characterize model performance on the high ozone days of most concern. The same types of detailed analyses are also required for USB. Unfortunately, it does not appear that the USB estimates exist to do this. USB estimates only appear in four figures, Figures 2-2, 3-9, 3-10 and 3-15. Each of these graphs says these estimates are "adopted from Zhang et al. (2011)." However, Zhang et al. (2011) only contains an average nationwide estimate of USB. The only mention they make of USB is:

> We find that the US background is on average 1-3 ppbv higher than the North American background, reflecting anthropogenic sources in Canada and Mexico, with little variability except in

[19]G.T. Wolff, Comments on Policy Relevant Background Ozone As Discussed in EPA's Draft Integrated Science Assessment for Ozone and Related Photochemical Oxidants. Prepared for the Utility Air Regulatory Group, May 5, 2011.

> border regions. Our results for the US background are similar to those reported in the focused GEOS-Chem analysis of H. Wang et al. (2009)[20] and hence we do not discuss them further.

For the second draft of the ISA, EPA contracted ICF International[21] to conduct extensive GEOS-Chem modeling results with USB as an output and some of these results appeared in the second draft. Surprisingly, the third draft of the ISA does not even reference the ICF report.

Consequently, it is not clear where the USB estimates in the third draft of the ISA came. In any event, EPA needs to provide detailed and comprehensive analyses of USB.

2. Focus for USB Should Be On High Ozone Days

In addition to the analyses recommended above, EPA needs to show the spatial and temporal distributions of USB on the high MDA8 days because these are the days of most concern to the state and local regulatory agencies. In particular, EPA should include scatter plots of paired-in-time hourly USB and MDA8 predictions (similar to Figures 3 and 4 from AIR's comments[4] and Figures 11 and 12 from BP's comments[22] on the second ISA draft for hourly PRB and total ozone predictions). These plots clearly show a tendency for higher background concentrations on the higher ozone days throughout the country.

3. Models of Choice

According to the ISA, EPA agrees that CAMx performs better than GEOS-Chem in reproducing the higher concentrations at the higher end of the ozone distribution even though it too still underpredicts the highest days. This can be seen from Figures 11 and 12 from the BP comments cited above. For that reason, EPA should include CAMx modeling results in the analyses of the USB distributions.

4. Contributions of Background Ozone to Observed Ozone

As noted above, in three places in the text, EPA states that the ISA addresses the questions of what would the ozone concentrations in the U.S. be in the absence of U.S. or U.S. and North American anthropogenic emissions, rather than the questions of what are the contributions of USB or NAB to the *observed* concentrations at any given time and place. The answers to both set of questions would be the same if the system was linear.

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[20] Y.X. Wang, Y. Zhang, J. Hao andM. Luo, "Seasonal and spatial variability of surface ozone over China: contributions from background and domestic pollution." *Atmospheric Chemistry and Physics,* 11:3511–3525 (2011).

[21] ICF International, *Modeling for North American Background Concentrations,* Contract No. EP-C-09-009, October 28, 2011.

[22] N.D. Downey, D. Blewitt and D. Wood, Comments on EPA's Second Draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants EPA/600/R-10/076B Released September 2011. Prepared for BP America, December 29, 2011.

On a small spatial scale such as an urban area, it is known that it is highly non-linear. The best example of this is the so called weekend ozone effect where some urban areas experience higher ozone levels on weekends despite lower precursor emission levels.[23] On national or intercontinental scales the situation is not as clear. Wu et al. (2009)[24] found that on an intercontinental scale ozone responded linearly to changes in VOC emissions but for changes in NOx emissions, the response became more non-linear with increasing NOx reductions. Consequently, we agree with EPA that further work is needed.

We suggest two approaches that should be used. In the first, the USB should be set to zero. In other words, all non-U.S. anthropogenic emissions should be set to zero as well as all of the natural sources. The difference between that scenario and the base case scenario, where all sources and emissions are included, would provide an estimate of the contribution of USB to the base case ozone. In the second approach, a photochemical grid model with an embedded source apportionment module should be used. CAMx is one such modeling system with a source-apportionment module. With USB designated as a separate source category, the estimated contribution of USB to the base case ozone would be computed directly. A comparison of the USB contributions estimated from these two approaches with the estimates of USB derived from the approach described in the ISA, would provide information of the linearity or degree on non-linearity of the system.

Ideally, the analyses described in the preceding paragraph should be contained in the ISA. Nevertheless, the analyses need to be available to inform the Policy Assessment so that the risk reduction that can be achieved by reducing U.S. anthropogenic emissions can be estimated using the best scientific information.

C. Background Summary

1. We support EPA's inclusion of USB in the background discussion. However, the Agency needs to do additional spatial and temporal analyses of USB to provide the same kind of detailed information that they provide for NAB in the ISA.

2. We support EPA's inclusion of the latest modeling results for GEOS-Chem and CAMx. Because CAMx's performance is better than GEOS-Chem at the higher end of the ozone concentration distribution, we recommend that the USB analyses also be performed using CAMx.

3. We support EPA's inclusion of the days in the higher end of the MDA8 distribution in their analyses.

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[23] J.M. Heuss, D.F. Kahlbaum and G.T. Wolff, "Weekday/weekend ozone differences: What can we learn from them?" *J. Air & Waste Mgt. Assoc.* 53:772-788 (2003).

[24] S. Wu, B.N. Duncan, D.J. Jacob, A.M. Fiore and O. Wild,"Chemical nonlinearities in relating intercontinental ozone pollution to anthropogenic emissions," *Geophys. Res. Lett.*36:L05806, doi:10.1029/2008GL036607 (2009).

4. We agree that further work is needed to address the impact of the non-linearities in the estimation of the impact of USB on observed ozone concentrations. This work needs to be completed in time to inform the Policy Assessment.

II. Human Clinical Studies and Their Interpretation

A. Recent human clinical studies do not change what was known about ozone effects in the last review or provide evidence of clinically significant adverse effects below eight-hour exposures of 0.08 ppm.

As documented in the earlier Alliance comments, the recent human clinical studies do not change what was known or assumed in the previous review about the first effects of ozone. In response to CASAC's call for the ISA to "…provide a clear idea of whether new findings confirm or change the conclusions of the prior assessment…" the Summary and integrative sections in Chapters 1, 2, and 6 should clearly acknowledge this fact.

As indicated in the ISA,[25] 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. The protocol was developed to simulate someone carrying out heavy physical labor over a full workday. 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.[26] 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%. The draft ISA acknowledges that the group mean decrements are biologically small and generally do not attain statistical significance.[27] Importantly, respiratory symptoms were not affected by ozone exposure at the 0.060 ppm level.

B. The ISA still does not adequately discuss the public health significance of the first effects of ozone

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 still does not adequately lay the groundwork for answering

[25] ISA, supra note 1 at pp. 6-2.
[26] Literature referred to by author and date without a footnote are references included in the ISA.
[27] ISA, supra note 1, at pp. 6-18.

this question. The ISA refers to several publications regarding guidelines for determining clinically meaningful FEV1 changes. In Chapter 6, two 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 discussed in Chapter 6 are guidelines regarding what constitutes adverse air pollution effects. The 1999 Guidelines indicate:[28]

> 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.

The 1999 Guidelines were not included in the second draft ISA. The 1999 Guidelines are now referenced and discussed in the Preamble of the third draft.[29] However, the discussion in the Preamble omits the most relevant recommendations concerning lung function effectsthat are in the above quotation.

Based on the 1999 Guidelines, the ISA should evaluate the symptom results for the human clinical studies along with the FEV1 results to provide appropriate information to the reader. 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. This finding is at odds with the discussion in Section 6.2 where the ISA implies that 0.06 ppm tends to increases symptoms, although not in a statistically significant manner.

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[28] "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.

[29] ISA, supra note 1, at page lxxiv.

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 relying on the July 1999 ATS guidelines for adverse health effects of air pollution, the discussion in Chapter 6 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, noting that at 0.06 ppm "a considerable fraction of exposed individuals experience clinically meaningful decrements in lung function." 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 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. One of the CASAC panelists specifically commented on the difficulty the research and policy community has in accepting that this effect of ozone is entirely, or predominantly, due to triggering of airway receptors and neural responses.[30]

There are several problems with the ISA claim that 0.06 ppm with heavy exercise causes clinically meaningful decrements in lung function. First, as noted by public comments on the first draft ISA,[31] 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

[30] CASAC Review of the EPA's Integrated Science Assessment for Ozone and Related Photochemical Oxidants (Second External Review Draft – September 2011), March 13, 2012 J. Samet letter to Administrator Jackson, EPA-CASAC-12-004, at page A-79.
[31] Goodman Rpt., supra note 8.

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."[32] The second draft indicates "personal-ambient ratios are typically 0.1- 0.3"[33] 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.

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

[32] ISA, supra note 5 at pp. 4-8.
[33] ISA, supra note 1 at pp. 4-42.

2000 review by Mudway and Kelly[34] 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."[35] 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 daily 8-h maxima now range from about 0.060 to 0.080 as shown in Table 3-8 and Figure 3-48 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

[34] I. Mudway and F. Kelly, "Ozone and the Lung: A Sensitive Issue," *Mol. Aspect. Med.*, 21, 1-48 (2000).
[35] ISA, supra note 1, at pp. 2-11.

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 and Exposure 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 still deficient in this regard. CASAC has also called on EPA to include additional discussion of the implications of the human clinical studies. In particular, CASAC has called for more discussion of the severity of the key observed effects (especially spirometric changes, inflammatory changes, and symptoms) and discussion of the relationship of human clinical study protocols (including study participants, exposures, and activity patterns) to the real-world situation.[36]

C. Key factors, such as the distribution of ventilation rates, that influence the risk of pulmonary effects need to be covered in the ISA

In response to CASAC's call for more information of the activity patterns in the exposure studies, EPA added relevant tables in the third draft ISA in Chapters 4, 5, and 6. However, a missing piece of the puzzle in mapping the human clinical studies into human risk is the distribution of ventilation rates in the real world. 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.[37] The final ISA should address several of these concerns.

First, 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. During the previous review, Langstaff acknowledged that the "values produced by the ventilation rate algorithm may exhibit an excessive degree of variability."[38] The final sensitivity analysis for APEX included 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.[39] 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),[40] 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.

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[36] CASAC letter, supra note 30, at pp. 16.
[37] Alliance comments, supra note 2 at pp. 13-17.
[38] Draft Langstaff Memorandum at pp. 42.
[39] J. Langstaff, Technical Memorandum, *Analysis of Uncertainty in Ozone Population Exposure Modeling*, Jan. 31, 2007 at 52 (EPA-HQ-OAR-2005-0172-0174).
[40] 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).

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

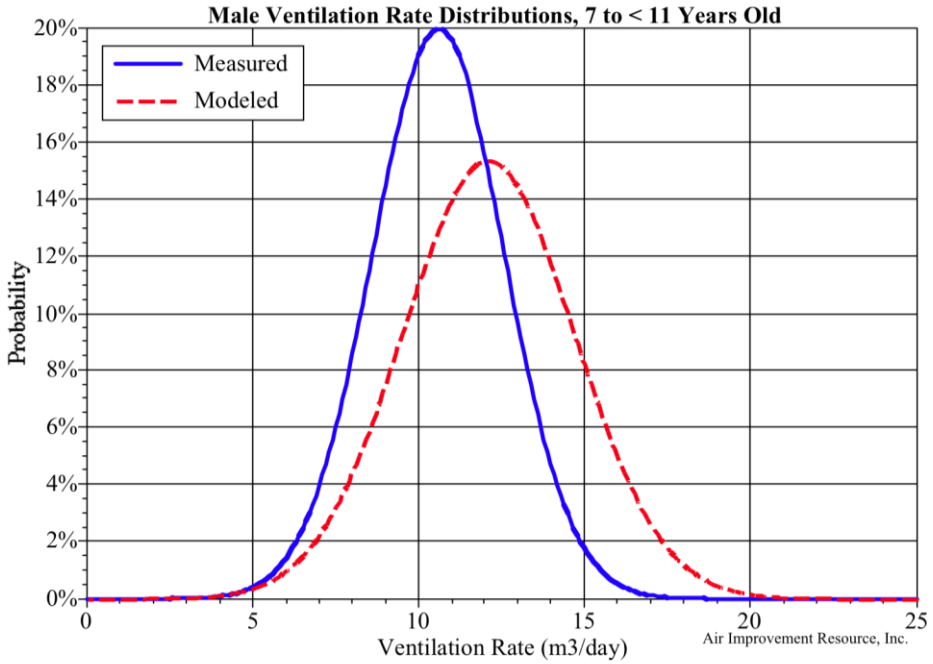

Figure 1: Comparison of measured vs. modeled daily ventilation rates for 7- to 10-year old boys.

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.

Second, 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)[41] measured the increment between ozone at 2 and 10 meters and 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.[42] 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.

Finally, the fact that the USB and NAB are now estimated to be higher than in the previous review needs to be factored into the integrative discussion. Background is important since it determines the lowest possible risk level that can be achieved by reducing U.S. anthropogenic emissions.

III. Epidemiological Studies and Their Interpretation

A. The ISA still overstates the consistency and coherence of ozone/health associations

As documented in the following, 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. Before one can weigh the evidence, the evidence must be presented and discussed. In the current draft, the evidence for health effects is presented but the evidence against interpreting the epidemiology as causal is ignored or downplayed. The current integrative synthesis ignores the issue of dose plausibility, leaves out consideration of

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[41] 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 Management Association, Nashville, TN, June 1996.

[42] 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, at pp. 7-46 and 7-47.

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.

1. There is substantial heterogeneity in the mortality and hospital admissions studies that is not consistent with ozone causing these associations

The ISA acknowledges that there is heterogeneity in the ozone/health associations. However, the discussion of possible reasons for the heterogeneity only discusses factors that could lead to varying degrees of positive association. In reality, especially for hospital admissions and mortality, the full pattern of associations in multi-city studies includes a substantial number of negative associations, a substantial number of null or near null associations, and a substantial number of positive associations. The full range of associations as shown in Figures 6-27, 6-28, and 6-30 varies between -5 to +10% change in daily mortality for a 10 ppb increase in ozone. Such a wide range, including both positive and negative associations is not consistent with ozone causing the health effects at issue. The individual-city associations in large multi-city studies cover a biologically implausible wide range from strongly negative to strongly positive, a finding which is readily apparent but not addressed in the ISA.

There are also temporal and spatial variations in the combined associations in multi-city studies that are not consistent with ozone causation. For example, in the regional analysis in Table 6-49, two of seven regions have positive and statistically significant ozone/mortality associations, two have small negative associations and the other three regions have positive but not statistically significant associations. In another 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. The combined associations for the two respiratory categories were positive in the 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.

There is also strong evidence for unrecognized stochastic variability in associations within a given city. Ito[43] 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 Ito's Figure 2, 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 plots shows that there are many negative

[43] K. Ito, "Revised Analyses of Time-Series Studies of Air Pollution and Health", *HEI Special Report*, pp. 143-156, May 5, 2003.

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.

It doesn't make sense if the ozone associations are causal that ozone would be dangerous in some cities and protective in others, or dangerous in some regions of the country and not dangerous in others, or dangerous in some seasons and not dangerous or actually protective in other seasons. 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 data presentation in the many figures in Chapter 6 provides a misleading impression of the overall patterns and consistency of the epidemiological data. By plotting only selected single-city associations and selected multi-city combined 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.

2. There is still substantial uncertainty in interpreting positive ozone associations as health effects caused by ozone particularly due to publication bias, potential confounding, and model specification issues

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 or correlated factor rather than evidence of an independent effect of that pollutant.

The ISA does not adequately discuss these methodological limitations and concerns. It discusses these issues in a general sense in the Preamble, but does not adequately consider these issues in the integrative or summary sections. The ISA 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."[44]

A 2006 paper by Keatinge and Donaldson,[45] that was brought to the Agency's attention but still is not included in the third draft 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)[46] (in another study brought to the Agency's attention but still 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 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

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[44] R. Henderson, CASAC Letter, EPA-CASAC-06-07, June 5, 2006 at pp. 3.
[45] W. Keatinge and G. Donaldson, "Heat acclimatization and sunshine cause false indications of mortality due to ozone," *Environmental Research*, 100, 387-393 (2006).
[46] 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).

weather, temporal or other unaccounted confounding factors, EPA cannot and should not draw conclusions on causality from these studies.

Despite detailed public comments from the Alliance[47] as well as from other parties,[48] that raised these methodological limitations and concerns with regard to the first and second draft ISAs, the third draft continues to over-rely on selected 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 third draft continues to inappropriately weigh the evidence from epidemiology with regard to ozone health effects.

3. Despite the ISA's claim to the contrary, a large multi-continent study demonstrates little consistent association of ozone with hospital admissions or mortality

In comments on the second draft ISA, the Alliance provided detailed information on the results of an HEI-sponsored multi-country epidemiologic study (APHENA) that evaluated the relation of ozone and particulate matter to daily mortality and hospital admissions. We pointed out that 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 addition, the Health Effects Institute provided comments noting that the ISA oversimplifies the APHENA findings, focuses on selected results, and draws stronger conclusions than would the investigators or the HEI Review Committee.[49] The HEI comments pointed out that this is especially true of the analyses of respiratory vs. cardiovascular mortality and the lack of coherence between the mortality and hospitalization analyses. After providing detailed comments supporting these general comments, HEI indicated:[50]

> We would suggest that, given that the APHENA study is the single major multi-city analysis of air pollution and mortality published since the last ISA, that NCEA carefully review – as described above – its treatment of APHENA, and especially the degree to which the relative lack of coherency between the mortality and hospitalization results affects the conclusions that NCEA can draw on causality.

Despite the detailed criticism in various public comments, the draft ISA continues to overstate the magnitude, consistency, and coherence of the APHENA findings.

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[47] Alliance ISA comments, supra note 4.
[48] ISA public comments, supra note 8.
[49] December 29, 2011 letter from D. Greenbaum to Drs Vandenberg and Samet, Health Effects Institute Comments on Docket EPA-HQ-ORD-2011-0050, Second Draft Integrated Science Assessment on Ozone, at page 2.
[50] Ibid., at pp. 6.

In October, 2009, the Health Effects Institute (HEI) published the results of the *Air Pollution and Health: A European and North American Approach (APHENA)*[51] 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 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

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

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 1 and 2, 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 1: 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 2: 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 ≥ 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, when the full pattern of the APHENA associations is evaluated, the results do not support EPA's claims of causal relationships between ozone and mortality or between ozone and hospital admissions. The HEI Review Committee also had reservations, noting "…it is remarkable how little coherence there is for the O_3 effects."

B. The ISA still overstates the case for 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 still 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.

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 first draft ISA noted 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.[52] It went 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. The third draft indicates only that "recent studies contributed less consistent evidence."[53] 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

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 and third drafts, the data from inflammatory marker studies was not shown in a Figure. In addition, a number of these studies were conducted in Los Angeles and Mexico City where the subjects are

[52] ISA, supra note 5, at page 6-17.
[53] ISA, supra note 1, at page 6-28.

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. In fact, CASAC noted with respect to the second draft ISA:[54]

> Newer multi-city studies of symptoms in asthmatic children, which should arguably carry the most weight, are not convincing or show no association. The conclusions regarding respiratory symptoms and medication use in asthmatic children can therefore be questioned.

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.

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[54] CASAC letter, supra note 30, at pp. 16.

3. The data on respiratory hospital admissions is less consistent that portrayed 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[55] 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: [56]

> 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).

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.[57]

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

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[55] S. Goodman, "The Methodologic Ozone Effect," *Epidemiology*, 16: 430-435 (2005).
[56] 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.
[57] 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).

individual-city results is considered in relation to Figure 6-18, it is clear that the current data presentation in Figure 6-18 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 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.

4. The ISA still 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.[58] The APHENA investigators indicated that, generally, there was little evidence of an effect of ozone on respiratory mortality in any center.[59] While the associations were generally higher in summer-only analyses, only 2 of 12 model combinations were statistically significant and, when controlled for PM_{10}, 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.

[58] APHENA report, supra note 52, at pp. 103.
[59] Ibid. at p. 50.

C. The evidence for cardiovascular effects from ozone 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 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 PM_{10}) 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, as acknowledged in the ISA.[60] 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 still not included in the ISA. Tank et al. (2011)[61] 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

[60] ISA, supra note 1 at pp. 6-218.

[61] J. Tank ,H. Biller, K. Heusser, O. Holz, A. Diedrich 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

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. The Alliance noted the Tank et al. (2011) study in comments on the second draft ISA. The third draft still does not include discussion of the study.

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 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 overall body of evidence across disciplines is suggestive of a causal relationship between relevant short-term exposures to O_3 and cardiovascular effects."[62] 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.[63] 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 shows no consistency. 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 <u>not</u> suggestive of a causal relationship between current short-term ozone exposures and cardiovascular effects.

D. Human clinical studies and the animal toxicology studies do not provide support for the ISA's claim that it is likely that ozone at current ambient concentrations causes excess mortality

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 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. Since premature mortality is one of the endpoints that is prominently discussed in the ISA, the arguments concerning the evidence for and against ozone causing death at or near current ambient concentrations need to be fully explored in the final ISA. The third draft is deficient in this regard.

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[62] ISA, supra note 1, at pp. 6-218.
[63] ISA, supra note 1, at pp. 6-214

CASAC comments on the second draft ISA also asked that the "findings from exposure studies should be integrated with discussions in other chapters of the ISA, as topics related to exposure error, confounding, and highly exposed populations are potentially important for the REA and PA" and that there needs to be better integration of the dosimetry and mode of action chapter with the other chapters of the document.[64]

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 for mortality effects is not fully discussed in the ISA.

With regard to this issue, Oberdorster et al. (2005)[65] 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 was acknowledged in the second draft ISA. For example, the second draft ISA indicated:[66]

> 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).

In the third draft, the first sentence was modified to indicate "A role for antioxidant defenses in modulating neural reflexes has been proposed given the delay in onset of O_3-induced pulmonary function responses that has been noted in numerous studies."[67]

The threshold nature is also evident in the studies of respiratory effects in 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

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[64] CASAC letter, supra note 30, at pp. 2.
[65] G. Oberdorster, et al., *Environ. Health Perspect*.,113: 823–839 (2005).
[66] ISA, supra note 6, at pp. 5-51.
[67] ISA, supra note 1, at pp. 5-34.

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)[68] discusses these issues in detail. Rhomberg et al. argue:

> The no-threshold proposal for noncancer toxicity is at variance with decades of experience in observing exposure-response relationships in pharmacology and toxicology, both within and below the usual experimental range for environmental chemicals.

They note:

> The no-threshold idea is also belied by our experience with medicines, poisons, foodstuffs, and many other kinds of exposure to agents that can have toxic effects if experienced in excess. With the possible exception of allergic reactions, within the range of low exposures, we do not observe slightly increased exposures to such agents somewhat increasing the probability that we will suffer the full effect of a toxic dose. In therapeutics, a small fraction of the therapeutic dose will not necessarily produce a moderate or full response in a diminished fraction of the treated population. It is only when the critical concentration is sustained at the site of action for the necessary period of time that an effect will be elicited. The experience of exposure thresholds for biological effects, including adverse effects, pervades daily life.

They also argue that the no-threshold proposal is at variance with basic tenets of homeostasis—the robust nature of living systems.

The toxicological studies of ozone also demonstrate both threshold behavior and the presence of effects that not only become less common with progressively lower doses, but they also become less severe. CASAC has noted:[69]

> As discussed in previous criteria documents, the toxicology data base is sufficiently strong to raise concerns about the range of effects that may occur in humans if exposures are sufficient.

The toxicological studies with elevated ozone levels, as noted by CASAC, raise concerns if and when exposures are sufficiently high. The concern arises when homeostasis and the defensive processes that keep organisms functioning normally even in the face of environmental fluctuation are overcome, with a gradation of more severe responses at higher exposures. Although there are toxicological studies showing effects from chronic ozone exposures, these studies utilize high ozone exposures compared to the day-to-day

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[68] L. Rhomberg, J. Goodman, L.Haber, M. Dourson, M. Andersen, J. Klaunig, B. Meek, P. Price,R. McClellan, and S. Cohen. "Linear low-dose extrapolation for noncancer health effects is the exception, not the rule." *Crit. Rev. Toxicol*. 41:1-19 (2011).

[69] CASAC letter, supra note 30, at pp. 15.

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 chronic personal exposures of the population which are typically one-quarter of the ozone measured at ambient monitors is not clear.

The ISA needs to include a 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.[70] At these low ambient concentrations, the personal exposures of the population are far 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.

Instead of fully discussing the dose-plausibility of low ozone causing mortality, the ISA depends on the epidemiology to support its causality determination. 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)[71] 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 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)[72] have shown, as others have previously shown, that measurement error can give a false linear result. Although the

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[70] 2007 SP, supra note 42, at Fig. 5-6.

[71] 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).

[72] L. R. Rhomberg, J. K. Chandalia, C. M. Long, and J. 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).

Rhomberg et al. study of the impact of measurement error in environmental epidemiology was cited in public comments on the second draft ISA, it is still ignored by the Agency. Despite these known problems, the ISA refers to continued evidence of a linear no-threshold C-R relationship for acute mortality. In fact the ISA concludes "the evaluation of the O_3-mortality C-R relationship did not find any evidence that supports a threshold in the relationship between short-term exposure to O_3 and mortality within the range of O_3 concentrations observed in the U.S."[73] This statement is much too strong and is contradicted by both several studies cited in the ISA and by Rhomberg et al. (2011).

The issue of the dose-response relationship at low concentrations of ozone and particulate matter has been a major issue for the Agency as each pollutant is reviewed. Although early drafts of the 2004 PM Criteria Document indicated that PM studies generally show linear concentration-response associations, the final CD specifically noted concerning dose-response that "In summary, the available evidence does not either support or refute the existence of thresholds for the effects of PM on mortality across the range of concentrations in the studies."[74] This change was made in response to a CASAC request in its October 4, 2004 letter to the Administrator. This view is consistent with points made by the Special Panel of the HEI Review Committee that raised several cautions in interpreting the NMMAPS concentration-response results. They pointed out that measurement error could obscure any threshold that might exist, that city-specific concentration-response curves exhibited a variety of shapes, and that the use of Akaike Information Criterion may not be an appropriate criterion for choosing between models. The HEI Panel cautioned that lack of evidence against a linear model should not be confused with evidence in favor of it.[75] Thus, the epidemiological studies cannot inform us as to whether there is or is not a biologic gradient for ambient ozone or PM at low concentrations or whether there is or is not a threshold. This is a very important point since it directly affects the assumptions made for the Risk and Exposure Assessment and the interpretation of the risk estimates in the Policy Assessment.

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 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.

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[73] ISA, supra note 1, at pp. 6-266.
[74] U.S. EPA. (2004). *Air Quality Criteria for Particulate Matter*. U.S. Environmental Protection Agency, Washington, D.C. EPA/600/P-99/002aF-bF, at pp. 9-44.
[75] Commentary in HEI Research Report Number 94, Part III, May 2004.