Review and Critique of EPA November, 2013 "Integrated Science Assessment for Oxides of Nitrogen– Health Criteria: First External Review Draft"

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Prepared for
The Alliance of Automobile Manufacturers
January 21, 2014

Synopsis

- While there are many more epidemiological studies reporting associations of NO_2 with health endpoints since the last review, AIR, Inc. concludes that there are numerous issues with the epidemiological studies that limit their usefulness in the current review. For example, it is now well established that model selection uncertainty, confounding, and publication bias hinder the interpretation of air pollution epidemiological studies. In systematic analyses of multiple cities, there is a biologically implausible wide range in individual city associations (from positive to negative) for mortality, hospital admissions, and other health endpoints. Although there may be somewhat more positive associations than negative associations, there is significant noise or variability in the data. Therefore, it is beyond the capability of current methods to identify which positive associations may be real, independent health effects of NO_2 and which are not. Because of these issues, the epidemiological data are not particularly useful in establishing NO_2 health effects.
- In contrast, the understanding of NO_2 health effects based on controlled exposures of humans and animals has not changed substantively since the last review.
- The current "single pollutant" approach used in this ISA leads to artificial limits being placed on the evaluation of pollutant confounding and overstate the consistency, coherence, and biological plausibility of NO_2 health effects. Since the current NOx review will be completed in the 2015/2016 time frame, considering the NO_2 epidemiology in a multipollutant framework should be a major consideration in the NOx ISA.
- Based on the comments and analysis in this critique, the evidence for long-term respiratory health effects from ambient NO_2 is similar to that in the last review and does not merit a change in the causality determination.

Executive Summary

Under the Clean Air Act, the U. S. Environmental Protection Agency (EPA) is charg$_e$d with periodically reviewing and revising, if necessary, the air quality standards for pollutants which may reasonably be anticipated to endanger public health and welfare and which result from diverse mobile or stationary sources. The EPA is in the process of reviewing the National Ambient Air Quality Standards (NAAQS) for the oxides of nitrogen (NO_x). Although there are several oxides of nitrogen and several other nitrogen-containing products that arise from the oxidation of NO_x species in the atmosphere, it is acknowledged in the draft ISA and in the prior reviews that the oxide of nitrogen of primary concern for human health is nitrogen dioxide (NO_2).

In November 2013, EPA released the First External Review Draft of the NO_x Integrated Science Assessment (ISA) for review and comment by the public and the Clean Air Scientific Advisory Committee (CASAC). EPA completed the prior review when, in the February 9, 2010 Final Rule, the Administrator retained the nitrogen dioxide (NO_2) annual primary standard of 53 ppb and supplemented that standard by establishing a new short-term NO_2 standard of 100 ppb based on the 3-year average of the 98th percentile of 1-hour daily maximum concentrations. EPA also established requirements for an NO_2 monitoring network that will include monitors within 50 meters of major roadways.

A key issue in the current review is the extent to which new information materially changes our understanding of the health effects of NO_2. As documented in these comments, the understanding of NO_2 health effects based on controlled exposures of humans and animals has not changed substantively since the last review. However, there are many more epidemiological studies published since the last review that include reports of associations of NO_2 with health endpoints.

Air Improvement Resource, Inc. (AIR) has reviewed the draft ISA focusing on the new information since the 2008 ISA, paying particular attention to the consistency and the interpretation of the epidemiological evidence, to the coherence or lack of coherence between the levels of NO_2 that cause effects in controlled studies compared to the levels implicated by epidemiological associations, and to the way traffic and near-roadway exposures are described in the document.

The First Draft ISA uses the new epidemiological studies to strengthen the claims for NO_2 causing health effects for each category of effects for which causal determinations were made in the 2008 NOx ISA. For total mortality, the evidence that was “Suggestive but not Sufficient to Infer a Causal Relationship” in 2008 is upgraded to “Likely to be a Causal Relationship” in the 2013 Draft. The reason for this upgrade is EPA's claim that "Recent multicity studies evaluated since the completion of the 2008 ISA for Oxides of Nitrogen continue to provide consistent evidence of positive associations between short-term NO_2 exposures and total mortality."

Of the eight recent papers that EPA cites as the reason for the upgrade, two of them should not be used because they found inconsistent and mostly nonsignificant

associations between NO_2 and mortality, and neither produced any support of an independent effect of NO_2 on mortality. Another paper should not be used to support an independent NO_2-mortality effect because the authors stress they are using indicators of air pollution to determine the health impact of the total "air pollution mix."

The remaining five epidemiology studies do suggest consistent NO_2-mortality relationships. However, caution needs to be exercised when extrapolating the results of the four non-U.S. studies to the U.S. for reasons articulated by EPA in the ISA:

> Although these studies are informative in evaluation of the relationship between oxides of nitrogen and mortality, the broad implications of these studies in the context of results from studies conducted in the U.S., Canada, and Western Europe are limited. This is because studies conducted in Asia encompass cities with meteorological (Tsai et al., 2010; Wong et al., 2008b), outdoor air pollution (e.g., concentrations, mixtures, and transport of pollutants), and sociodemographic (e.g., disease patterns, age structure, and socioeconomic variables) (Kan et al., 2010) characteristics that differ from cities in North America and Europe, potentially limiting the generalizability of results from these studies to other cities.

This is especially true for the Asian studies where the concentrations of PM and NO_2 are much higher than those currently experienced in the U.S. However, there is another reason why the results of these studies should be viewed with caution: the authors of these studies did not conduct sensitivity analyses to determine if their results were sensitive to their choice of statistical approach.

The sensitivity of the results to the choice of the statistical approach or model selection was underscored by the analyses contained in the eighth paper by Moolgavkar et al. (2013). The purpose of this paper was to reanalyze the rich National Morbidity, Mortality, and Air Pollution Study (NMMAPS) database using a different modeling approach to see if the NMMAPS results were model dependent. Moolgavkar et al. do not conclude that NO_2 is causing mortality, but only that the strength of the relationship is dependent on the modeling approach that is used. This important conclusion applies not only to the mortality studies, but also to the epidemiology studies that examine other health endpoints.

The conclusion that the evidence for respiratory effects which was “Sufficient to Infer a Likely Causal Relationship” in the 2008 ISA has been upgraded to a “Causal Relationship” in the 2013 Draft ISA. EPA arrives at this conclusion " based on the consistency, coherence, and biological plausibility of evidence integrated across epidemiologic, controlled human exposure, and animal toxicological studies indicating increases in asthma exacerbations.

EPA cites six references to support their claim that epidemiology studies consistently demonstrate associations between increases in ambient NO_2 concentrations and increases in hospital admissions and ED visits. As shown in this critique, this claim is not valid. In fact, in one very large study involving 400,000 ED visits in 14 Canadian hospitals in 7 cities, there were no statistically significant positive associations of NO_2 with asthma or with the other categories of respiratory visits.

EPA provides four references to support its claims of coherence. These studies, however, suffer from the same limitations regarding causality as do the ED and hospital admissions studies. They all evaluated multiple pollutants and report associations for many different pollutants, including NO_2, so the studies do not implicate NO_2 over other pollutants. In fact, the ISA notes the epidemiologic findings specifically for respiratory symptoms are only weakly supported by findings from controlled human exposure studies.

The ISA indicates that key biological plausibility for NO_2-associated asthma morbidity is provided by findings of NO_2-induced increases in airway hyperresponsiveness (AHR) in controlled human exposure studies of adults with asthma. In the discussion of the AHR studies, the ISA indicates "statistically significant effects on responsiveness to nonspecific challenge were reported following exposures as low as 100 ppb NO_2, although most studies showing significant effects were in the range of 300 ppb NO_2 or greater.

This conclusion conflicts with an extensive review of NO_2 health effects by Hesterberg et al. (2009) who conclude: "available human clinical results do not establish a mechanistic pathway leading to adverse health impacts for short-term NO_2 exposures at levels typical of maximum 1-hour concentrations in the present-day ambient environment (*i.e.*, below 0.2 ppm)."

The EPA analysis relies heavily on the Orehek, et al. (1976) study of airway responsiveness that has never been replicated. Ironically, the Orehek study was fully evaluated and considered by EPA during previous NO_2 reviews and discounted because it has never been replicated.

Regarding respiratory effects, the 2013 ISA also upgraded the 2008 ISA's conclusion that long-term exposure to NO_2 is "Suggestive but not Sufficient to Infer a Causal Relationship" to "Likely to be a Causal Relationship." Based on the comments and analysis in this critique, the evidence for long-term respiratory health effects from ambient NO_2 is similar to that in the last review and does not merit a change in the causality determination.

Although EPA repeatedly overstates the need for near-road monitoring in the ISA, an analysis of existing 1-hour NO_2 Design Values and road-side measurements indicates that some of the 100 or so near-road monitors required by 2017 are likely to trigger an exceedance of the 1-hour NAAQS. Despite this EPA has still not articulated what will be done with the data, especially as it pertains to nonattainment designations and the State Implementation Plan process. Past inquiries by CASAC, industry groups as well by state

and local agencies have been largely ignored. In addition, EPA has not adequately responded to the concern that the lack of a requirement that the monitoring sites represent population exposure means that any violations found will reflect the consequences of locating monitors where no-one lives or works.

I. Introduction

Under the Clean Air Act, the U. S. Environmental Protection Agency (EPA) is charged with periodically reviewing and revising, if necessary, the air quality standards for pollutants which may reasonably be anticipated to endanger public health and welfare and which result from diverse mobile or stationary sources. The Clean Air Act charges the EPA Administrator, after reviewing the science, to establish national primary air quality standards requisite to protect the public health with an adequate margin of safety and national secondary standards to protect the public welfare from any known or anticipated adverse effects associated with the presence of the pollutant in the ambient air.

The EPA is in the process of reviewing the national air quality standards for the oxides of nitrogen (NOx). In November 2013, EPA released the First External Review Draft of the NOx Integrated Science Assessment (ISA)[1] for review and comment by the public and the Clean Air Scientific Advisory Committee (CASAC). EPA completed the prior review when, in the February 9, 2010 Final Rule,[2] the Administrator retained the nitrogen dioxide (NO_2) annual primary standard of 53 ppb and supplemented that standard by establishing a new short-term NO_2 standard of 100 ppb based on the 3-year average of the 98th percentile of 1-hour daily maximum concentrations. EPA also established requirements for an NO_2 monitoring network that will include monitors within 50 meters of major roadways.

Although there are several oxides of nitrogen and several other nitrogen-containing products that arise from the oxidation of NOx species in the atmosphere, it is acknowledged in the draft ISA and in the prior reviews that the oxide of nitrogen of primary concern for human health is nitrogen dioxide (NO_2).

A key issue in the current review is the extent to which new information materially changes our understanding of the health effects of NO_2. As documented below, the understanding of NO_2 health effects based on controlled exposures of humans and animals has not changed substantively since the last review. Although there are many more epidemiological studies published since the last review that include reports of associations of NO_2 with health endpoints, there are numerous issues with the epidemiological studies that limit their usefulness in the current review.

The First Draft ISA uses the new epidemiological studies to strengthen the claims for NO_2 causing respiratory and cardiovascular health effects for each category of effects for which causal determinations were made in the 2008 NOx ISA.[3] For example, the conclusion that the evidence for respiratory effects which was "Sufficient to Infer a Likely Causal Relationship" in the 2008 ISA is upgraded to a "Causal Relationship" in the 2013 Draft. For cardiovascular effects, the evidence that was "Inadequate to Infer the

[1] U. S. EPA (2013). First External Review Draft Integrated science assessment for oxides of nitrogen: Health criteria (EPA/600/R-13/202). Research Triangle Park, NC.
[2] 75 Federal Register 6474, February 9, 2010.
[3] ISA, supra note 1, at lxxiii.

Presence or Absence of a Causal Relationship" in 2008 is upgraded to "Likely to be a Causal Relationship" in the 2013 Draft. For total mortality, the evidence that was "Suggestive but not Sufficient to Infer a Causal Relationship" in 2008 is upgraded to "Likely to be a Causal Relationship" in the 2013 Draft.

Air Improvement Resource, Inc. (AIR) has reviewed the draft ISA focusing on the new information since the 2008 ISA, paying particular attention to the consistency and the interpretation of the epidemiological evidence, to the coherence or lack of coherence between the levels of NO_2 that cause effects in controlled studies compared to the levels implicated by epidemiological associations, and to the way traffic and near-roadway exposures are described in the document.

While there are many more epidemiological studies reporting associations of NO_2 with health endpoints since the last review, AIR concludes that there are numerous issues with the epidemiological studies that limit their usefulness in the current review. For example, it is now well established that model selection uncertainty, confounding, and publication bias hinder the interpretation of air pollution epidemiological studies. In systematic analyses of multiple cities, there is a biologically implausible wide range in individual city associations (from positive to negative) for mortality, hospital admissions, and other health endpoints. Although there may be somewhat more positive associations than negative associations, there is significant noise or variability in the data. Therefore, it is beyond the capability of current methods to identify which positive associations may be real, independent health effects of NO_2 and which are not. Because of these issues, the epidemiological data are not particularly useful in establishing NO_2 health effects.

The NOx ISA is the first of a new round of NAAQS reviews for the major air pollutants.[4] As such it will provide the template for how the next round of reviews for the other pollutants will be conducted. Of particular interest is the shift in focus from controlled studies where cause and effect can be established to epidemiological studies where correlation need not imply causation. In recent years there has been an outpouring of epidemiological studies implicating <u>all</u> the major pollutants as potential causes of health effects. As each pollutant is reviewed, in turn, EPA compiles all the epidemiological associations for that pollutant in single pollutant analyses in the ISA, evaluates confounding in a limited way, and then tends to claim that the pollutant under review has independent effects on health. This constitutes a major flaw in the procedures EPA is using to review the various National Ambient Air Quality Standards. We show in both general comments and in comments on the database for specific health endpoints how the current procedures and methods the Agency is using overstate the consistency, coherence, and biological plausibility of NO_2 health effects.

II. General Comments

The ISA acknowledges that:

[4] The ozone review is the only NAAQS review that has not been concluded in recent years. The Ozone ISA was completed in February 2013 but the Agency has not issued second drafts of the Risk and Exposure Analysis or the Policy Assessment as yet.

> Associations between NO_2 and health effects observed in epidemiologic studies may represent an independent effect of NO_2 or the effect of another air pollutant or mixture that is related to both the health effect being examined and NO_2 concentrations.[5]

and that:

> In the 2008 ISA for Oxides of Nitrogen, a major uncertainty noted for the relationships between NO_2 exposure and several health effect categories was the difficulty in distinguishing whether the epidemiologic associations observed with ambient NO_2 concentrations were independent of the effects of another traffic-related air pollutant or mixture.[6]

The quandary as to whether ambient NO_2 is a causal agent or is an indicator of either traffic-related air pollution or the urban air pollution mix in general is a central issue in the NOx review. It arises because the exposures in observational studies are to complex mixtures of gases and particles from both natural and man-made sources. Another complexity arises because people spend 90 % of their time indoors and the typical observational study uses data from central monitoring sites or other outdoor sites to estimate exposure to the pollutants of interest.

EPA has begun to recognize this complexity and held a workshop in February 2011 to get input on a multipollutant focus.[7] Since the 2004 National Research Council report on air quality management in the U. S. recommended that EPA address multiple pollutants in the NAAQS review and standard setting process, there have been several papers/reviews discussing how to do this.[8] An EPA presentation at the workshop indicated that EPA planned to develop a Multipollutant Science Assessment (MSA) in parallel with the current ISAs for individual pollutants. EPA indicated the MSA would be developed over several years with a final MSA available in the 2015/2016 time frame. The Agency further indicated that the MSA will evaluate the health effects of exposure to combinations of pollutants as well as to single pollutants in a multipollutant context so that the MSA will inform the NAAQS decisions for single pollutants in that time frame.

Since the current NOx review will be completed in the 2015/2016 time frame,

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[5] ISA, supra note 1, at lxx.
[6] Ibid., at lxxi
[7] February 22-24, 2011 Workshop on Multipollutant Science and Risk Analysis in Chapel Hill, NC, co-sponsored by the Health Effects Institute and U. S. EPA.
[8] Dominici et al. (2010) Protecting human health from air pollution: Shifting from a single-pollutant to a multipollutant approach. *Epidemiology*, 21: 187-194; Greenbaum and Shaikh (2010). First steps toward multipollutant science for air quality decisions. *Epidemiology*, 21: 195-197; Hidy and Pennell (2010). Multipollutant air quality management. *J Air Waste Manage Assoc*, 60: 645-674; Mauderly et al. (2010) Is the air pollution health research community prepared to support a multipollutant air quality management framework? *Inhal Toxicol*, 22(S1), 1-19; Vedal and Kaufman (2011) What does multi-pollutant air pollution research mean? *Am J Respir Care Med*, 183: 4-6; National Research Council (2004) *Air Quality Management in the United States*. National Academies Press Washington DC.

considering the NO_2 epidemiology in a multipollutant framework should be a major consideration in the NOx ISA. As we demonstrate in the specific comments, this is not the case for the first draft. In almost all cases, investigators evaluated a number of different pollutants, report positive associations with one or more pollutants, and often refer to NO_2 as a surrogate or tracer for traffic-related pollutants.

It has been known for a long time that there are severe limitations to the use of epidemiology to try and tease out interactions and to evaluate causality. A meta-analysis by Steib et al. (2002, 2003)[9] evaluated 109 acute mortality studies from around the world. They reported that there are positive associations with mortality (with a wide range in the individual cities) for all the major pollutants in single pollutant models and that for each, when other pollutants are included, the association with the first pollutant, on average, is decreased. In fact, the patterns in single-pollutant epidemiological studies were remarkably similar for all the criteria pollutants.

The studies evaluated by Steib et al. are all subject to publication bias. To avoid publication bias that would inflate the apparent association, investigators have carried out large multi-city analyses. In fact, the patterns in single-pollutant associations in multi-city epidemiological studies are also very similar for all the criteria pollutants. The individual-city associations in large multi-city studies, such as NMMAPS, cover a biologically implausible wide range from strongly negative to strongly positive at each lag evaluated, a finding which is readily apparent but seldom discussed.[10]

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. 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."[11]

There is also strong evidence for unrecognized stochastic variability in associations within a given city. In 2003, Ito[12] re-analyzed the 1220 separate air pollution mortality

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[9] Steib, DM; Judek, S; Burnett, RT. (2002) "Meta-analysis of time series studies of air pollution and mortality: Effects of gases and particles and the influence of cause of death, age, and season," *J. Air & Waste Manage. Assoc*., **52:** 470-484 and Stieb, DM et al. (2003) *J. Air & Waste Management Association*, **53:** 258- 261.

[10] When the individual city data for the NMMAPS re-analysis were posted on the Johns Hopkins website, the data showed a remarkable similarity in that there was a biologically impossible wide range of associations from positive to negative for each pollutant for each lag that was evaluated. This data was provided to EPA and CASAC during the PM review process; J. Heuss, Comments on the 4th Draft Criteria Document for Particulate Matter, AIR, Inc. comments prepared for the Alliance of Automobile Manufacturers, August 20, 2003.

[11] Henderson, R. (2006) CASAC Letter, EPA-CASAC-06-07, June 5, 2006 at page 3.

[12] Ito, K. (2003) in HEI Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health, May 5, 2003 at pages 143-156.

and morbidity associations that were included in the original Lippmann et al. 2000 HEI study of Detroit. As shown in Figure 1, there was a wide range of negative and positive risks in Detroit when all pollutants, lags, and endpoints were considered. Ito shows 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 positive associations, Ito's plots shows that there are many negative associations in the data. Although there may be somewhat more positive associations than negative associations, there is so much noise or variability in the data, that identifying which positive associations may be health effects and which are not is beyond the capability of current methods.

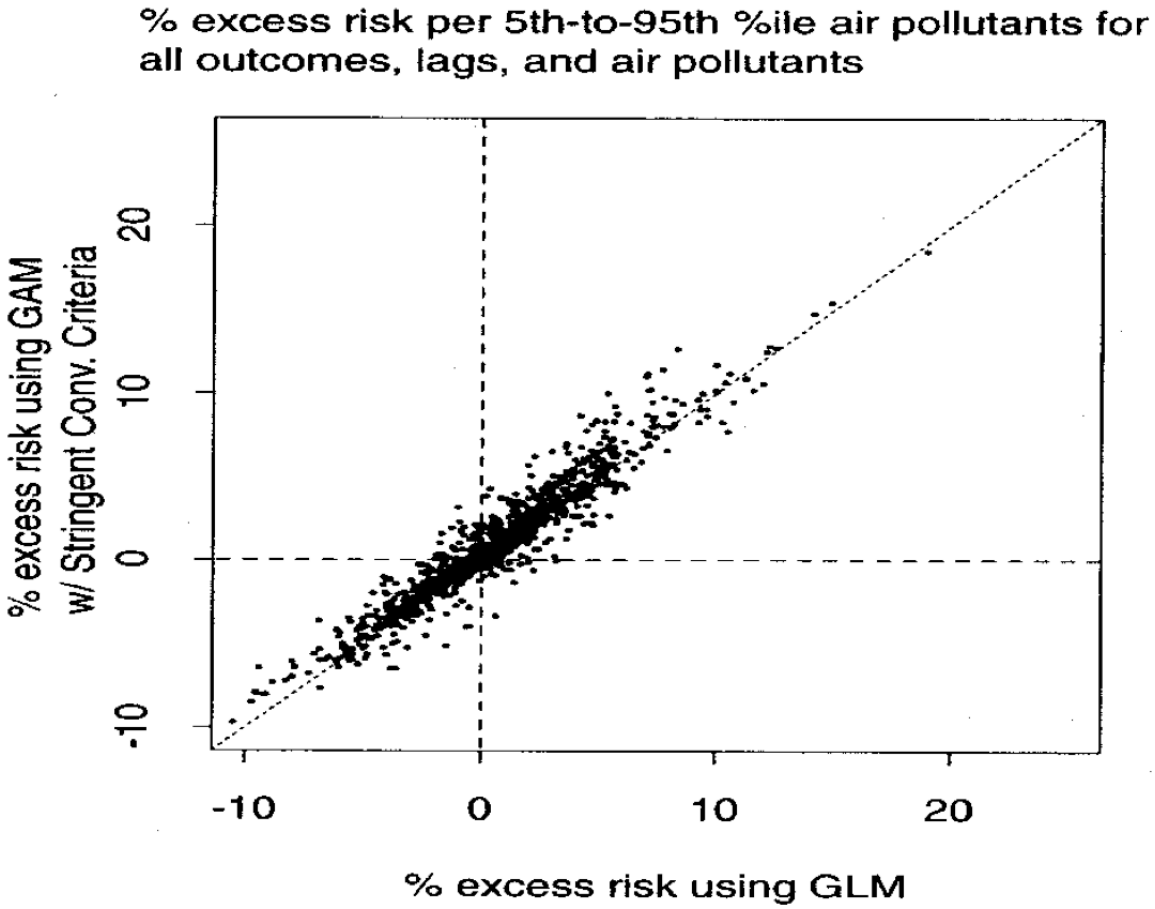

Figure 1: Percent Excess Risk for all pollutants, lags, and outcomes in Generalized Additive Models versus Generalized linear Models.

Additional evidence for substantial stochastic variation comes from an HEI study[13] that evaluated coherence between the time-series associations of mortality and hospital admissions in 14 cities. That study found little or no coherence between the PM_{10} mortality and morbidity associations and, importantly, found little or no correlation between the time series of health event counts (mortality and hospital admissions) in the

[13] Dominici, F et al. (2005) HEI Research Report 94, Part IV Health Effects Institute.

various cities. As in other multi-city studies, the individual associations for mortality and morbidity covered a wide range from positive to negative.

Multipollutant statistical analyses add a layer of complexity to the issues known in single-pollutant models. For example, the 2004 PM CD points out that there are at least five different interpretations of PM associations in multi-pollutant models that differ in their attribution of causality to PM.[14] Thus, single-pollutant models may give erroneous results because of potential confounding, and multi-pollutant models may give erroneous results for a variety of reasons, including differential measurement error. Because of these limitations, relying on multi-pollutant models to answer questions of confounding is not sufficient.

Inferring causation from observational (epidemiologic) associations involves consideration of a range of factors, including the strength of association, consistency, coherence, temporality, biologic plausibility, etc. The framework used in the ISA of judging the overall weight of evidence and putting various types of potential health effects into one of five categories, with different descriptors ranging from "sufficient to infer causation" to "suggestive of no causal relation," is based on similar frameworks developed for other regulatory situations.

While the use of such a framework is to be commended, there are several issues with the effort. First, EPA has included the category "sufficient to infer a likely causal relationship (i.e., more likely than not)" between the categories " sufficient to infer a causal relationship" and "suggestive but not sufficient to infer a causal relationship." The main difference in the ISA elaboration between the "sufficient to infer a likely" and "suggestive, but not sufficient" categories is that chance, bias, and confounding are "minimized" in the first instance and "cannot be ruled out" in the second. Given the many problems with interpreting the epidemiology, as noted above, this distinction is too subtle and too subjective. Second, even though the framework is generally applied throughout the ISA, its application is not as rigorous or complete as it should be. In particular, the way consistency is evaluated in the discussion of epidemiology is less than scientifically rigorous or sound.

Since ambient NO_2 occurs in conjunction with other common air pollutants, issues of confounding and surrogacy plague the interpretation of the epidemiological literature. Goodman et al. (2013)[15] provide a critique of the EPA Causality Framework and conclude:

> The framework claims to rely heavily on the criterion of consistency across studies in its categorization scheme, but, in practice, it does not fully evaluate consistency or incorporate other

[14] U.S. Environmental Protection Agency (2004) "Air Quality Criteria for Particulate Matter" EPA 600/P99/002aF October 2004, at page 8-246.
[15] Goodman, JE; Prueitt, RL; Sax, SN; Bailey, LA; Rhomberg, LR. (2013) Evaluation of the causal framework used for setting National Ambient Air Quality Standards. Crit Rev Toxicol, 43(10): 829–849.

> criteria such as coherence, biological plausibility, biological gradient or strength of association.

Furthermore, Goodman et al. point out:

> EPA states that evidence is sufficient to conclude a causal relationship if ''chance, bias, and confounding [can] be ruled out with reasonable confidence'' (US EPA, 2013a), yet there is no guidance on what constitutes ''reasonable confidence''. Based on the current framework, EPA cannot make that determination reliably because there is no guidance for assessing chance, bias, or confounding in a consistent manner. Although such an assessment is inevitably a scientific judgment, the basis for coming to and justifying the judgment should be included in the evaluation. Moreover, an evaluation of how confident one is in ruling out chance, bias and confounding should include an examination of the evidence for or against competing explanations of the results being evaluated.

Goodman et al. provide specific recommendations to improve the causality framework to make it thorough, transparent, and scientifically sound. They also present specific examples of the problems with the framework and its application from the recent Ozone ISA review.

As AIR has reviewed the ISA, two major issues with regard to integrating the results from controlled exposures and observational studies are apparent. First, there is a major disconnect between the results of controlled human or animal studies of NO_2 and the current interpretation of the epidemiological results that is not acknowledged in the ISA. The disconnect is blurred in the ISA because biologic plausibility is discussed without sufficient regard to dose plausibility. Biologic plausibility involves consideration of the kinds of effects a toxicant can generate as well as the doses that are required to elicit the effect. Dose plausibility is of particular importance in the ISA because the final choice of the air quality standard (as to level, averaging time, and statistical form) is the choice of a dose metric that should not be exceeded in order to protect the public health. Therefore, it is important for the ISA to provide the scientific underpinning concerning dose that will inform the policy choices the Administrator of EPA makes elsewhere in the NAAQS review.

The 2008 ISA, in discussing the strengths and limitations of controlled human studies, indicated that they are limited, for ethical and practical reasons, to concentrations expected to produce only mild and transient responses.[16] Since concentrations as high as 4,000 ppb have been used in human clinical studies, it is clear that the investigators did not think that acute exposures in the ppm range would cause anything other than mild and

[16] U. S. EPA (2008) Integrated science assessment for oxides of nitrogen: Health criteria (EPA/600/R-08/071). Research Triangle Park, NC. NOx ISA Annexes at page 5-2.

transient responses much less premature mortality or respiratory hospital admissions, or the other serious health effects that are implicated by some epidemiological studies as occurring at extremely low concentrations.

Second, as EPA reviews the various criteria pollutants, very similar mechanisms and modes of action are posited in the ISAs for the various pollutants. For example, activation of neural reflexes, inflammation, etc. are discussed for ozone, SO_2, and PM as well as for NO_2. Even though there are many associations with these other pollutants for the same categories of health endpoints in the literature (and highlighted in the other ISAs) there is no discussion of the clinical and toxicological findings for the full range of ambient pollutants as they relate to the potential causal agents with regard to asthma exacerbation, markers of inflammation, emergency room visits, hospital admissions, etc. This omission is important because it limits the discussion of and consideration of alternative explanations for positive associations in the NO_2 literature.

With these general comments in mind, in the following sections, we review the evidence for the most serious health endpoints and the endpoints for which the ISA claims the most consistency. We also include a section on roadway and traffic-related exposures and a short section on the other health endpoints evaluated in the ISA.

III. Specific Comments

A. Short-Term Mortality

In the previous ISA, EPA concluded that the epidemiology studies at that time were "suggestive but not sufficient to infer a causal relationship" between NO_2 and total mortality. In the present ISA, EPA strengthens that conclusion to "likely be a causal relationship." They state:

> Recent multicity studies evaluated since the completion of the 2008 ISA for Oxides of Nitrogen continue to provide consistent evidence of positive associations between short-term NO_2 exposures and total mortality. This collective evidence indicates that there is likely to be a causal relationship between short-term NO_2 exposures and total mortality. This conclusion represents a change from the 2008 ISA for Oxides of Nitrogen that concluded the evidence "was suggestive but not sufficient to infer a causal relationship" (U.S. EPA, 2008c). The recent multi-city studies evaluated inform key uncertainties and limitations in the NO_2-mortality relationship identified in the 2008 ISA for Oxides of Nitrogen including confounding, modification of the NO_2-mortality relationship, potential seasonal differences in NO_2-mortality associations, and the shape of the NO_2-mortality C-R relationship.[17]

[17] ISA, supra note 1, at 4-281 - 4-282.

The recent multi-city, short-term mortality studies[18] that EPA identifies are: 1) Moolgavkar et al. (2013),[19] 2) Stieb et al. (2008),[20] 3) Bellini et al. (2007),[21] 4) Wong et al. (2008),[22] 5) Cakmak et al. (2011),[23] 6) Chen et al. (2012),[24] 7) Chiusolo et al. (2011),[25] and 8) Berglind et al. (2009).[26] Each of these studies will be examined to evaluate the results to determine if they support EPA's claims of consistent evidence.

1. Moolgavkar et al. (2013)

EPA cites this paper to show that the NO_2/total mortality relationship was robust in a copollutant analysis with PM_{10}.[27] In addition, EPA claims that Moolgavkar et al.'s concentration-response relationship is linear even though the authors say the data "suggest non-linearity and threshold like behavior."[28] These claims by EPA, however, miss the main point of the Moolgavkar et al. paper which was to illustrate that "different statistical approaches to multicity analyses can yield disparate results."[29]

The purpose of this paper was to reanalyze the rich NMMAPS[30] database using a different modeling approach to see if the NMMAPS results were model dependent. In the original NMMAPS, the authors used a two-stage Bayesian hierarchical approach which assumed city-specific risk estimates are normally distributed around a national

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[18] Ibid,, at 4-263.
[19] Moolgavkar, SH; McClellan, RO; Dewanji, A; Turim, J; Luebeck, EG; Edwards, M. (2013). Time-series analyses of air pollution and mortality in the United States: a subsampling approach. Environ Health Perspect., 121: 73-78.
[20] Stieb, DM; Burnett, RT; Smith-Doiron, M; Brion, O; Shin, HH; Economou, V. (2008). A new multipollutant, no-threshold air quality health index based on short-term associations observed in daily time-series analyses. J. Air Waste Management Assoc., 58: 435-450.
[21] Bellini, P; Baccini, M; Biggeri, A; Terracini, B. (2007). The meta-analysis of the Italian studies on short-term effects of air pollution (MISA): Old and new issues on the interpretation of the statistical evidences. Environmetrics, 18: 219-229.
[22] Wong, CM; Vichit-Vadakan, N; Kan, H; Qian, Z. (2008). Public Health and Air Pollution in Asia (PAPA): A multicity study of short-term effects of air pollution on mortality. Environ. Health Perspect., 116: 1195-1202.
[23] Cakmak, S; Dales, RE; Angelica Rubio, M; Blanco Vidal, C. (2011). The risk of dying on days of higher air pollution among the socially disadvantaged elderly. Environ. Res., 111: 388-393.
[24] Chen, R; Samoli, E; Wong, CM; Huang, W; Wang, Z; Chen, B; Kan, H. (2012). Associations between short-term exposure to nitrogen dioxide and mortality in 17 Chinese cities: The China Air Pollution and Health Effects Study (CAPES). Environ. Int., 45: 32-38.
[25] Chiusolo, M; Cadum, E; Stafoggia, M; Galassi, C; Berti, G; Faustini, A; Bisanti, L; Vigotti, MA; Dessì, MP; Cernigliaro, A; Mallone, S; Pacelli, B; Minerba, S; Simonato, L; Forastiere, F. (2011). Short term effects of nitrogen dioxide on mortality and susceptibility factors in 10 Italian cities: The EpiAir Study. Environ. Health Perspect., 119: 1233-1238.
[26] Berglind, N; Bellander, T; Forastiere, F; von Klot, S; Aalto, P; Elosua, R; Kulmala, M; Lanki, T; Löwel, H; Peters, A; Picciotto, S; Salomaa, V; Stafoggia, M; Sunyer, J; Nyberg, F. (2009). Ambient air pollution and daily mortality among survivors of myocardial infarction. Epidemiology, 20: 110-118.
[27] EPA (2013), supra note 1 at p. 4-267.
[28] Ibid, p. 4-277.
[29] Moolgavkar et al. (2013), supra note 19 at p. 77.
[30] Dominici, F; McDermott, A; Daniels, M; Zeger, SL; Samet, JM. (2003). Mortality among residents of 90 cities. In Revised analyses of time-series studies of air pollution and health (pp. 9-24). Boston, MA: Health Effects Institute.

mean. Moolgavkar et al. used a subsampling approach where a random sample of 4 cities was removed from the 108 cities over 5,000 bootstrap cycles to examine associations between short-term air pollution concentrations and mortality. In the original NMMAPS, single pollutant models with NO_2, SO_2 or CO exhibited statistically significant positive relationships with mortality at lag one, but the relationships became insignificant in any two-pollutant model. In contrast, Moolgavkar et al. found that using the subsampling approach, the relationship of NO_2 and SO_2 with mortality remained positive and statistically significant in two- and three-pollutant models. Moolgavkar et al. do not conclude that NO_2 is causing mortality, but only that the strength of the relationship is dependent on the modeling approach that is used. In their closing comments, they state:

> Previous publications have reported that the results of time-series analyses of air pollution data in individual cities can be highly sensitive to choice of statistical model (e.g., Clyde 2000; Koop and Tole 2004; Moolgavkar 2003). While our analyses are based on the most recent data available to us (which are not identical to the data used in previous analyses), our results suggest that different statistical approaches to multicity analyses can yield disparate results.[31]

2. Stieb et al. (2008)

In citing this paper, EPA says that Stieb et al.'s analysis "indicate that the NO_2-mortality relationship remains robust when adjusted for other pollutants (quantitative results not presented)."[32] First of all, quantitative results for the multipollutant results are shown in Stieb et al.'s Figure 3 and it clearly shows that not all of the multipollutant models for NO_2 and mortality are robust. Further, Stieb et al. say that there is evidence of confounding among NO_2, O_3 and PM. They also conclude that the effects seen cannot be attributable to any one pollutant. They state:

> This is not meant to imply that the observed effects are necessarily singularly attributable to each individual pollutant. Rather, the premise is that by using the AQHI to guide their exposure to outdoor air pollution, individuals will be able to reduce their exposure to whatever elements of the air pollution mix are actually responsible for adverse health effects. Whether the effects of these pollutants are best represented based on the results from single or multipollutant models is unclear.[33]

Other results presented by Stieb et al. are not consistent with a direct effect due to NO_2. First, the authors examine the effects of the pollutants for two different time periods: 1981 to 1990 and 1991 to 2000. Although the concentrations of NO_2 were about 12% higher in the 1981 to 1990 period, the estimated risk of mortality from NO_2 was 100%

[31] Moolgavkar et al. (2013), supra note 19 at p. 77.
[32] EPA (2013), supra note 1, at p. 4-267.
[33] Stieb et al. (2008), supra note 20 at p. 441.

higher in the 1991 to 2000 time period. This is not plausible. In addition, although peak NO_2 concentrations were observed in the winter, larger associations between NO_2 and mortality were observed in the warm season.

In addition, the authors make the following comments:

> In the case of NO_2 and SO_2 (CO was not included in the review), the existence of independent effects was considered less certain.[34]

and,

> At this point it remains unclear whether NO_2 is independently associated with mortality or other effects at typical concentrations in Canadian cities, or is in fact a marker for traffic, or more generally, combustion. Increasing attention is being paid to traffic-related air pollution as a particularly important element of the air pollution mix. NO_2 could potentially be an indicator for local source, primary $PM_{2.5}$ and it has been suggested that at least in some locations, health effects associated with gaseous pollutants may in fact be attributable to PM exposure, by virtue of the correlation of ambient concentrations of gases with personal exposure to ambient source PM.[35]

Thus the authors of this paper do not support EPA's claims of an independent mortality effect of NO_2.

3. Bellini et al. (2007)

In this study the authors find a statistically significant positive correlation between total mortality and 24-hour average NO_2 concentrations using single-pollutant models in 15 Italian cities, which EPA uses to support their arguments that NO_2 is likely a cause of mortality. In addition, EPA also uses this paper in support of their overall evidence that NO_2 causes respiratory and cardiovascular health effects even though Bellini et al. does not find statistically significant effects with NO_2 and these endpoints.

Although Bellini et al. do find a significant relationship between NO_2 and all natural caused mortality, there are a certain details about their findings that raise flags concerning the causal nature and robustness of this finding. First of all, as with Stieb et al., the relationship between NO_2 and mortality is larger in the summer when the NO_2 is the lowest. For example, in Milan, the NO_2 levels are 3 times higher in the winter than in the summer,[36] but the NO_2/mortality risk is 7.2 times higher in the summer than the winter. This large seasonal difference leads the authors to conclude: "The huge seasonal

[34] Ibid, p. 447.
[35] Ibid, p. 448.
[36] Ordonez, C; Richter, A; Steinbacher M; Zellweger C; Nub H; Burrows JP; Prevot ASH. (2006). Comparison of 7 years of satellite-borne and ground-based tropospheric NO_2 measurements around Milan, Italy. J. Geophys. Res., 111: D05310, doi:101029/2005JD006305.

differences shown in Table 2 cast some doubts on the fairness of the attribution of all of the effects to any specific pollutant."[37] Second, the overall pooled estimate of the risk from the 15 different Italian cities is only marginally significant. However, for the individual cities, the risk is positive and statistically significant in only one city and 5 cities have a negative risk. Thus, this study does not demonstrate a consistent statistically significant relationship between NO_2 and mortality. In addition, the authors do not claim there is an independent effect of NO_2. Here is what the authors stated:

> *2.4. Specificity*
>
> This criterion is established when a single putative cause produces a specific effect. This is not the case for the associations under study. There is an agreement that for the time being all pollutants which have been investigated should be considered as no more than indicators of exposure. Also the investigated effects are far from being specific (i.e. exclusive and constant).[38]

4. Wong et al. (2008)

This study identifies small but positive, statistically significant relationships between mortality and NO_2, SO_2, PM_{10} and O_3 in Bangkok, Hong Kong, Shanghai and Wuhan. However, because the concentrations of these air pollutants are so much higher in Asia than in Europe or North America and for other reasons, EPA cautions:

> Although these studies are informative in evaluation of the relationship between oxides of nitrogen and mortality, the broad implications of these studies in the context of results from studies conducted in the U.S., Canada, and Western Europe are limited. This is because studies conducted in Asia encompass cities with meteorological (Tsai et al., 2010; Wong et al., 2008b), outdoor air pollution (e.g., concentrations, mixtures, and transport of pollutants), and sociodemographic (e.g., disease patterns, age structure, and socioeconomic variables) (Kan et al., 2010) characteristics that differ from cities in North America and Europe, potentially limiting the generalizability of results from these studies to other cities.[39]

These cautions, however, do not deter EPA from listing this paper as part of their weight of evidence for a likely causal effect for NO_2 and mortality at the low concentrations that currently exist in the U.S.

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[37] Bellini et al. (2007), supra note 21 at p. 227.
[38] Ibid, p. 224.
[39] EPA (2013), supra note 1 at p. 4-259.

The Wong et al. study was part of the Public Health and Air Pollution in Asia (PAPA) study[40] conducted by the Health Effects Institute (HEI). In their review of the Wong et al. study, the HEI review committee noted:

> The potential for residual confounding and other biases also suggests caution in the interpretation of the more complex patterns found in these studies, including the apparent linearity of relationship between estimated effects and concentrations, up to high concentrations, and apparent dominance of NO_2 over PM_{10} in most cities. The evidence on these questions should be considered as suggestive rather than strong.[41]

Consequently, the HEI review committee is less certain than EPA about a NO_2-mortality link.

5. Cakmak et al. (2011)

Cakmak et al. presented the pooled results of optimized single pollutant models for 7 cities in Chile. They found statistically significant positive relationships between mortality and CO, O_3, SO_2, NO_2, $PM_{2.5}$, PM_{10}, elemental carbon (EC) and organic carbon (OC). Unfortunately the authors failed to present the single city results so the heterogeneity of the results could not be assessed. In addition, since only single-pollutant models were used, the robustness of the observed relationships could not be determined. As with the Wong et al. results, the applicability of the results to the U.S. is problematic because of much higher concentrations of PM and NO_2 concentrations in the Chilean cities compared to the U.S. Lastly, the authors make no attempt to determine the relative culpability of any of the individual pollutant species included in their analyses.

6. Chen et al. (2012)

The purpose of this study was to find a relationship between mortality and NO_2 using a single-pollutant model for 17 Chinese cities and then pool the results to develop a nationwide risk estimate. The statistically significant pooled estimate was 1.63% percent increase in mortality per 10 $\mu g/m^3$ increase in NO_2. In two-pollutant models, the estimate was attenuated to 1.28 with the addition of PM_{10} and to 1.36 with the addition of SO_2. Results for a three-pollutant model were not given. Because the estimates with the two-pollutant models remained statistically significant, the authors claim they are observing an independent effect of NO_2. This claim is on very weak grounds considering the limited number of multi-pollutant models they examined.

This study should also be considered to have very little relevance to the U.S. for the same reasons cited above for the Wong et al. study.

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[40] HEI (2010). Public health and air pollution in Asia (PAPA): Coordinated studies of short-term exposure to air pollution and daily mortality in four cities, Executive Summary. Research Report 154, Boston, MA, Health Effects Institute.

[41] Ibid, p. 13.

7. Chiusolo et al. (2011)

The authors present the pooled results for single-pollutant models relating NO_2 to mortality in 10 Italian cities. The pooled result is positive and statistically significant.[42] Although they do not present the individual city results, they mentioned that they were heterogeneous across the cities and that some of the city results were unrealistic as they were statistically significant, but negative (protective effect). On the basis of the results of one two-pollutant model with PM_{10}, which they did not show, they argue that they are seeing an independent effect of NO_2. Their evidence to support this claim is even weaker than Chen et al.'s evidence. Like Bellini et al., the estimated risk from NO_2 is 4 times higher in the warm season than in the colder half of the year despite lower warm season NO_2 concentrations. This is an argument against an independent effect of NO_2. Finally, the concentrations reported for NO_2, O_3 and PM_{10} in the Italian cities are sufficiently higher than in most U.S. cities to question the applicability of the results to the U.S.

8. Berglind et al. (2009)

EPA uses the Berglind et al. results to support its overall claim of a causal mortality NO_2 association as well as to provide evidence that individuals with pre-existing conditions (in Berglind et al.'s case, the subjects were all survivors of myocardial infarctions) increased the risk of NO_2-related mortality. In their analysis, Berglind et al. examined single pollution models for particle number concentration (PNC), PM_{10}, CO, NO_2, SO_2, and O_3 in 5 European cities and then pooled the results to determine overall average results. Although most of the relationships they observe in the individual city models between mortality and the air pollutants are positive, most of them are not statistically significant. For example for NO_2, they examined three different lags (0 - 1, 0 - 4, and 0 -14 days) for each of the 5 cities for a total of 15 modeling runs. Of the 15 results, only 2 (both 0 - 1 lags in 2 different cities) were statistically significant. The pooled results fared no better. For NO_2, the 0 - 4 day lag was barely significant while the 0 - 1 and 0 - 14 results were not significant. In the pooled results for NO_2 stratified into different age groups, none of the 8 model results found a statistically significant relationship. In light of these results, the authors could only conclude:

> In summary, our results suggest that exposure to traffic-related air pollution is associated with all-cause daily mortality in MI survivors, with a stronger positive effects for longer averaging times. The effect estimates from this study are in general substantially higher than those for the general population.[43]

[42] It should be noted that in Figure 4-17 of the ISA, EPA reports about an 8% increase in total mortality/20 ppb increase in NO_2 from Chiusolo et al. (2011). This number is in error as the number that is reported in Chiusolo et al. is 2.09%.

[43] Berglind et al. (2009), supra note 10 at p. 117.

The basis for these conclusions was not their largely insignificant results for NO_2, but rather the somewhat stronger mortality relationships observed with other traffic-related pollutants such as PNC, PM_{10} and CO.

9. Summary of Recent Short-Term Mortality Studies

Of the 8 recent papers that EPA claims "continue to provide consistent evidence of positive associations between short-term NO_2 exposures and total mortality," two of them, Bellini et al. (2007) and Berglind et al. (2008) should be dismissed immediately because they found inconsistent and mostly nonsignificant associations between NO_2 and mortality, and neither produced any support of an independent effect of NO_2 on mortality. Of the 6 remaining papers, Stieb et al. (2008) should not be used to support an independent NO_2-mortality effect because the authors stress they are using indicators of air pollution to determine the health impact of the total "air pollution mix."

The remaining 5 epidemiology studies do suggest consistent NO_2-mortality relationships. However, caution needs to be exercised when extrapolation the results of the non-U.S. studies to the U.S. for all the reasons articulated by EPA in the ISA which we have quoted above in section III.A.4. This is especially true for the Asian studies where the concentrations of PM and NO_2 are much higher than those currently experienced in the U.S. However, there is another reason why the results of these studies should be viewed with caution: the authors of these studies did not conduct sensitivity analyses to determine if their results were sensitive to their choice of statistical approach.

The sensitivity of the results to the choice of the statistical approach or model selection was underscored by the analyses of Moolgavkar et al. (2013) and warrants a further discussion of model selection bias.

Selecting an appropriate statistical model for epidemiology analyses of air pollution data is an extremely important process that can affect the outcome of the study in a very significant way. It can make the difference between finding a positive association, a negative association or no association. It involves making a number of choices for which there is little biological knowledge to inform these choices.

In a commentary on the challenges of air pollution epidemiology, Lumley and Sheppard (2003) point out:

> Estimation of very weak associations in the presence of measurement error and strong confounding is inherently challenging. In this situation, prudent epidemiologists should recognize that residual bias[44] can dominate their results. Because the possible mechanisms of action and their latencies are uncertain, *the biologically correct models are unknown*. This model selection problem is exacerbated by the common practice of screening

[44] Residual bias is the bias that may remain by chance after all known sources of bias have been controlled.

> multiple analyses and *then selectively reporting only a few important results* (emphasis added).[45]

Many others have made similar comments regarding the critical importance of model choice, particularly when effect estimates are small, which they are in air pollution epidemiology studies. For example, in comments on a draft PM CD submitted to the EPA, Smith, et al. (2001), state:

> 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). As has been demonstrated in Lumley and Sheppard (2000),[46] the effect of choosing lags for PM in this fashion has a bias which is of the same order of magnitude as the relative risk being estimated (emphasis added).[47]

From the descriptions of the methodologies used by Cakmak et al., Chiusolo et al., Chen et al., and Wong et al., it appears that these investigators chose a model that optimized the NO_2-mortality relationships.

Koop and Tole have been especially outspoken in their concerns over model selection bias. Koop and Tole (2004) state:

> The main empirical finding of [our] paper is that standard deviations for air pollution-mortality impacts become very large when model uncertainty is incorporated into the analysis. *Indeed they become so large as to question the plausibility of the previously measured links between air pollution and mortality* (emphasis added).[48]

The main conclusion from their paper was that when model uncertainty was considered, there was little evidence of an air pollution association with mortality at recent concentrations observed in the U.S. and Canada.

A single event was responsible for raising the appreciation of the model selection bias issue more than any one single paper. That event occurred in May of 2002. Most time

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[45] Lumley T; Sheppard L. (2003). Time series analyses of air pollution and health: straining at gnats and swallowing camels? Epidemiology, 14: 13-14.

[46] Lumley T; Sheppard L. (2000). Assessing seasonal confounding and model selection bias in air pollution epidemiology using positive and negative control analysis. Environmetrics, 11: 705-717.

[47] Smith R; Guttorp P; Sheppard l; Lumley T; Ishikawa N. (2001). Comments on the Criteria Document for Particulate Matter Air Pollution, NRSCE Technical Report Series #66. Available:http://www.nrcse.washington.edu/research/reports.html (as of 1-2-2014).

[48] Koop G; Tole L. (2004). Measuring the health effects of air pollution: to what extent can we really say that people are dying from bad air? J. Environ Econ and Management, 47: 30-54.

series studies of air pollution had used the Generalized Additive Models (GAM) for analyses of data. The most widely used software for fitting these models is a statistical package called S-plus. In May of 2002, the NMMAPS investigators discovered that the implementation of GAM in S-plus was flawed and could yield misleading results.[49] EPA, which was in the process of preparing a revised PM CD, halted work on the CD and asked investigators to re-analyze a number of studies that EPA had identified as key studies. These re-analyses were carried out under the auspices of the Health Effects Institute and published in 2003[50] with commentaries by the expert panel[51] convened by HEI to serve as a peer review panel for the revised analyses.

The revised analyses necessitated by the S-plus problems clearly indicate that methods used for controlling temporal trends and weather can have profound effects on the results of time-series analyses of air pollution data, as the HEI expert panel noted.[52] Moreover, there appears to be no objective statistical test to determine whether these factors have been adequately controlled in any analysis. The HEI Expert Panel for the re-analyses stated:

> Ritov and Bickel (1990)[53] have shown, however, that for any continuous variable, no strictly data-based (*i.e.*, statistical) method can exist by which to choose a sufficient number of degrees of freedom to insure that the amount of residual confounding due to that variable is small. This means that no matter what statistical method one uses to select the degrees of freedom, *it is always logically possible that even if the true effect of pollution is null, the estimated effect is far from null due to confounding bias* (emphasis added).[54]

In other words, even if the true effect of pollution is zero, the estimated effect may be positive because it is impossible to control temporal trends or weather without accurate information from external sources that do not exist. The HEI expert panel comments further, *"Neither the appropriate degree of control for time, nor the appropriate specification of the effects of weather, has been determined for time-series analyses"* (emphasis added).[55]

The HEI Special Review Committee noted that "In the few studies in which investigators performed further sensitivity analyses, some showed marked sensitivity of the PM effect

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[49] Health Effects Institute. (2003). Revised Analyses of Time-Series Studies of Air Pollution and Health. HEI Special Report. 291pp.
[50] Ibid.
[51] Special Panel of the Health Review Committee. (2003). Commentary on Revised Analyses of selected studies. In: Revised Analyses of Time-Series Studies of Air Pollution and Health, HEI Special Report, pp. 255-291.
[52] Ibid, p. 227-269.
[53] Ritov Y. and P. Bickel. (1990). Achieving information bounds in non- and semi-parametric models. Ann. Stat., 18:925–938.
[54] Special Panel of the Health Review Committee (2003), supra note 51 at p. 267.
[55] Ibid, p. 269.

estimate to the degree of smoothing and/or the specification of weather."[56] One of the re-analysis participants tested the impact of model selection by running over a thousand possible models. Ito (2003)[57] carried out a systematic re-analysis of the air pollution associations in the Detroit area and re-analyzed the 1220 separate air pollution mortality and morbidity associations that were included in the original Lippmann et al. (2000)[58] study of Detroit. As shown in Figure 1 of his report, there was a wide range of negative and positive risks in Detroit when all pollutants, lags, and endpoints were considered. Ito showed that the wide range of associations occurred for each pollutant. Although the focus in the original Lippmann et al. study, as it is in almost all the published literature, was on the positive associations, Ito's plot showed that there are many negative associations in the data. Although there may be somewhat more positive associations than negative associations, there is so much variability in the risk estimates, that identifying which positive associations may be real health effects and which are not appears beyond the capability of current methods. Moreover, in the Ito re-analysis, the overall pattern for each pollutant is similar so that one pollutant or one PM indicator is not implicated over any of the others.

A final paper on model selection bias that deserves attention is another contribution from Koop and Tole. Koop et al. (2010)[59] underscores many of the issues raised in the preceding paragraphs and adds additional insights as to the reasons why the real relationships between health effects and air pollution at relevant exposures are small and insignificant. In this study, the authors conduct a comprehensive analysis of air pollution morbidity relationships for eleven Canadian cities over a long record from 1974 to 1994. As a result, they have a unique data set that allowed the examination of both spatial and temporal variations. In addition to including the five criteria pollutants, CO, PM, SO_2, NO_2 and O_3, they also controlled for socioeconomic factors, smoking and meteorology. Much shorter subsets of this data set have been analyzed without the socioeconomic and smoking variables by a number of research groups to demonstrate significant relationships with a number of health outcomes and individual pollutants. The long data set enabled the present investigators to explore the impact of significantly lower air pollution concentrations at the end of the data set compared to the beginning. Koop et al. also employed the two major methods used to formulate the statistical models in time-series studies, model selection by the use of some statistical criteria and Bayesian Model Averaging (BMA), to address the all-important issue of model selection uncertainty.

As Koop et al. noted for air pollution/mortality or morbidity epidemiology results in general, the results are conflicted. In other words, the results range from positive to

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[56] Ibid, p. 267.

[57] Ito, K. (2003). Associations of particulate matter components with daily mortality and morbidity in Detroit, MI. In: Revised Analyses of Time-Series Studies of Air Pollution and Health, HEI Special Report., pp. 143-156.

[58] Lippmann M., K. Ito, A. Nádas and R.T. Burnett RT. (2000). *Association of Particulate Matter Components with Daily Mortality and Morbidity in Urban Populations.* Research Report 95, Health Effects Institute, Cambridge MA.

[59] Koop, G., R. McKitrick, and L. Tole. (2010). Air pollution, economic activity and respiratory illness: Evidence from Canadian cities, 1974-1994. Environ. Model. Softw. 25:873-885.

negative and from significant to insignificant for all pollutants and for all health endpoints. Koop et al. state:

> One of the reasons for this profusion of apparently contradictory results is model uncertainty. With very few exceptions (e.g. Clyde, 2000; Clyde and DeSimone-Sasinowska, 1997 and Koop and Tole, 2004, 2006),[60,61,62,63] previous studies on air pollution-health effects have used model selection methods, i.e. choosing one or a few regression specifications and reporting point estimates and their associated variances conditional on that being the true model. However, the estimation exercise is inherently opportunistic. Many plausible covariates could be included, but the choice is not dictated by theory so much as by data availability. Hence there is not only uncertainty about regression slope coefficients conditional on the model selection, but about the model specification itself.

Compounding the issue of selecting the true model is the large number of potential explanatory variables and possible forms that will influence the model results. As Koop et al. articulate:

> However, the number of potential confounding variables implies that a huge number of models could be used to explain health effects. The number of potential models is on the order of $2k$ where k is the number of potential explanatory variables, including lags. Since results can be sensitive to the particular regression specification, and since the number of potential models is so large, model uncertainty has been shown to be an important issue in this literature (Clyde, 2000; Koop and Tole, 2004).

To address the model uncertainties, Koop and Tole use BMA. This method includes information from every potential model. The BMA results are weighted averages of the estimates from each model. The weights are proportional to the support the data give each model.

The results of the BMA analyses show that the health outcomes are explained by the smoking and the socioeconomic variables and that none of the air pollutants showed a statistically positive relationship with health. In fact most pollutant relationships were slightly negative, but not robust. With this particular data set the BMA results were largely similar (except NO_2 showed an effect in a single model) to the results obtained by

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[60] Clyde, M. (2000). Model uncertainty and health effect studies for particulate matter. Environmetrics 11:745–764.
[61] Clyde, M; DeSimone-Sasinowska, H. (1997). Accounting for Model Uncertainty in Poisson Regression Models: Particulate Matter and Mortality in Birmingham, Alabama. Institute of Statistics and Decisions Sciences, Duke University Discussion Paper 97-06.
[62] Koop and Tole (2004), supra note 48.
[63] Koop, G; Tole L. (2006). An Investigation of thresholds in air pollution mortality effects. Environmental Modelling & Software. 21:1662–1673.

selecting a single model. This is in contrast to their earlier results in Koop and Tole (2004)[64] for Toronto which found many relationships when a single model was used. In the earlier paper, a shorter data record was used and the smoking and socioeconomic variables were not included. This may explain the differences and underscores the importance of including these variables in a longer time-series in these types of studies.

In summary, this study demonstrates the importance of: 1) incorporating smoking and socioeconomic variables into the models, 2) using a longer time series that has significantly different pollutant concentrations at the beginning and end of the study, 3) using the BMA approach which minimizes model selection uncertainties and finds insignificant health impacts. Such an approach would likely change the conclusions of the Cakmak et al., Chiusolo et al., Chen et al., and Wong et al. papers.

The preceding discussions apply not only to the recent 8 epidemiology studies EPA claims support an NO_2-mortality relationship, but to all the epidemiology studies EPA uses to make claims for any NO_2-health endpoint relationship. Until there is coherence between the epidemiology studies and the NO_2 toxicology studies so plausible biological mechanisms are established, the epidemiological studies should not be used to determine the level of any of the NAAQS.

B. Respiratory Effects

1. Short-term

With regard to short-term exposures the ISA indicates:

> **The strongest evidence is for respiratory effects, and it indicates that there is a causal relationship with short-term NO_2 exposure** (Section 4.2.9). This conclusion is based on the consistency, coherence, and biological plausibility of evidence integrated across epidemiologic, controlled human exposure, and animal toxicological studies indicating increases in asthma exacerbations. Epidemiologic studies consistently show associations between short-term increases in ambient NO_2 concentration and increases in hospital admissions and emergency department (ED) visits for asthma. Associations also are found with respiratory symptoms, pulmonary inflammation, and decreases in lung function in children with asthma. Epidemiologic associations are demonstrated in studies conducted in diverse geographical locations and using varied designs, including multicity analyses. Evidence from controlled human exposure and animal toxicological studies for NO_2-induced increases in airway responsiveness in adults with asthma and increases in allergic inflammation and oxidative stress demonstrate that the effects of

[64] Koop and Tole (2004), supra note 48.

NO_2 exposure on asthma exacerbations are biologically plausible.[65]

Thus, the ISA indicates that asthma-related effects are the strongest evidence for short-term NO_2 health effects. For short-term effects, Section 4.29 from pages 4-181 to 4-186 and the accompanying Table 4-23 provide the rationale for the EPA causality determination. In the following, the relevant data is discussed with regard to consistency, coherence, and biologic plausibility.

Consistency Section 4.2.9 claims that epidemiologic studies consistently demonstrate associations between increases in ambient NO_2 concentration and increases in asthma hospital admissions and ED visits, providing six references. Table 4.23 includes these six studies along with a Canadian multi-city study, Stieb et al. (2009),[66] that is indicated as showing no association. A careful reading of these references provides a more complex view of the situation than the consistency claimed in the ISA.

First, the Stieb et al. (2009) study evaluated a database of about 400,000 emergency department visits from 14 hospitals in seven Canadian cities. Stieb et al. evaluated associations for six pollutants, including NO_2, with three categories of respiratory visits, asthma, COPD, and respiratory infections, as well as three categories of cardiovascular visits at three lags. With this large database, there were no statistically significant positive associations of NO_2 with asthma or the other respiratory categories at any of the lags investigated. There were some positive associations for pollutants with respiratory categories as well as some positive associations with cardiovascular categories. However in each positive association case, the authors show the individual city results which indicate a mix of positive, null and negative findings. With regard to asthma visits, the results implicate possibly ozone and particulate matter, but not NO_2.

The Ito et al. (2007)[67] study in New York City may include a NO_2 association, but the paper highlights (in the abstract, title, and conclusions) an association of coarse PM ($PM_{10-2.5}$) that was found in the warm season but not the cold season. The authors point out that coarse particles preferentially deposit in the upper respiratory tract, and therefore may contribute to asthma exacerbation. Ito et al. is the only group that highlighted coarse particles, per se, with respect to ED visits although other studies evaluated coarse PM, $PM_{2.5}$, and/or PM_{10}.

Strickland et al. (2010)[68] evaluated the association of a wide range of pollutants with pediatric asthma ED visits for a number of different lags. They reported positive

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[65] ISA, supra note 1, at lxxiv-lxxv.

[66] Stieb, DM; Szyszkowicz, M; Rowe, BH; Leech, JA. (2009). Air pollution and emergency department visits for cardiac and respiratory conditions: A multi-city time-series analysis. Environ Health Global Access Sci Source 8: 25.

[67] Ito, K; Thurston, GD; Silverman, RA. (2007). Association between coarse particles and asthma emergency department (ED) visits in New York City. American Thoracic Society International Conference 2007, San Francisco, CA.

[68] Strickland, MJ; Darrow, LA; Klein, M; Flanders, WD; Sarnat, JA; Waller, LA; Sarnat, SE; Mulholland, JA; Tolbert, PE. (2010). Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. Am J Respir Crit Care Med 182: 307-316.

associations for 10 of 11 pollutant measures in the warm season, including NO_2, and only one positive association in the cold season, coarse PM. Strickland et al. implicate ozone and primary pollutants from traffic as having the most consistent associations.

Villeneuve et al. (2007)[69] evaluated asthma ED visits associated with six pollutants, four lag combinations, and six different age groups for year round, warm, and cold seasons in Edmonton, Canada. They reported that five of the six pollutants had positive associations in the warm season for all age asthma, but only one, ozone, was positive in the cold season.

Li et al. (2011)[70] evaluated the association of four pollutants with pediatric asthma ED visits and hospitalizations for a wide range of lags in Detroit. The authors implicate SO_2 and $PM_{2.5}$ as having the most consistent associations.

Son et al. (2013)[71] report positive associations with PM_{10}, NO_2, SO_2, and ozone in a study of hospital admissions in eight cities in Korea. The authors conclude that ambient air pollution is associated with hospital admissions in Korea. Ko et al. (2007)[72] report on the association of five pollutants with emergency hospital admissions in Hong Kong. They report that four of the five pollutants evaluated showed association.

It is clear that all the studies EPA relies on to claim consistency with regard to NO_2 evaluated multiple pollutants, multiple lags, and, often, different seasons. In many cases, a given study evaluated a hundred or more potential associations. None of the studies implicated NO_2 as a causal agent, per se. Typically, NO_2 is discussed as part of the air pollution mix or as a surrogate for traffic emissions.

In addition to the studies EPA highlights in Table 4-23, other new asthma ED studies report similar findings of associations with multiple pollutants. For example, Jalaludin et al. (2008)[73] report the strongest positive associations in Sydney, Australia with the six pollutants evaluated at lag 0. In contrast, Li et al. reported no associations with the various pollutants evaluated at lag 0 in Detroit.

As the EPA discussion proceeds from a summary of ED visits on page 4-176 to the summary Section 4.2.9, to the Integrated Summary in Chapter 1, and to the Executive Summary, important qualifiers keep dropping out. The NO_2 results are initially described as "generally provide evidence of consistent associations" with associations "primarily

[69] Villeneuve, PJ; Chen, L; Rowe, BH; Coates, F. (2007). Outdoor air pollution and emergency department visits for asthma among children and adults: A case-crossover study in northern Alberta, Canada.
[70] Li, S; Batterman, S; Wasilevich, E; Wahl, R; Wirth, J; Su, FC; Mukherjee, B. (2011). Association of daily asthma emergency department visits and hospital admissions with ambient air pollutants among the pediatric Medicaid population in Detroit: Time-series and time-stratified case-crossover analyses with threshold effects. Environ Res 111: 1137-1147.
[71] Son, JY; Lee, JT; Park, YH; Bell, ML. (2013). Short-term effects of air pollution on hospital admissions in Korea. Epidemiology 24: 545-554.
[72] Ko, FWS; Tam, W; Wong, TW; Lai, CKW. (2007). Effects of air pollution on asthma hospitalization rates in different age groups in Hong Kong. Clin Exp Allergy 37: 1312-1319.
[73] Jalaludin, B; Khalaj, B; Sheppeard, V; Morgan, G. (2008). Air pollution and ED visits for asthma in Australian children: A case-crossover analysis. Int Arch Occup Environ Health 81: 967-974.

observed at lags from 0-2 days." With respect to confounding, it is stated that in the "majority of studies" NO_2 was not found to be highly correlated with other combustion-related pollutants. Each of these important qualifications disappears as the data gets summarized and the causal determination gets made. Thus, there is less consistency than EPA indicates.

The Stieb et al. (2009) multi-city study that shows no asthma ED visit association with NO_2 appears to be given no weight in the discussion of causality. The fact that some associations are observed only in the warm season is not fully discussed. If ambient NO_2 is causing health effects, they should be observed throughout the year and especially in seasons when the NO_2 concentrations are highest. These inconsistencies argue against causality.

The EPA practice of plotting selected NO_2 associations from single pollutant models for each health endpoint is known to overestimate the strength of association due to publication bias. The ISA acknowledges this elsewhere in the document,[74] but the implications of the finding are not considered in the causality determination. Since bias is an important consideration in the EPA causality framework, this is an important omission.

There is also inadequate discussion of chance in explaining the total pattern of air pollution associations. Both the extent of stochastic variability in the data and the implications of investigating literally hundreds or thousands of potential associations need to be fully vetted in the ISA.

Potential confounding is another key factor that needs to be fully evaluated. It is clear the authors of almost all the studies relied on by EPA have evaluated multiple air pollutants and report associations with some or all of the candidate pollutants. The EPA practice of evaluating selected two pollutant or multipollutant models is not a sufficient way to rule for or against confounding. In fact the ISA acknowledges:

> The interpretation of copollutant models can be limited and methods to adjust for multiple copollutants simultaneously are not reliable." Thus, the potential for residual confounding is recognized.[75]

Coherence. The next argument EPA makes is the observations regarding ED visits and hospitalization are supported by evidence in children and adults with asthma for increases in respiratory symptoms, providing four references to support the claim. These studies, however, suffer from the same limitations regarding causality as do the ED and hospital admissions studies. They all evaluated multiple pollutants and report associations for many different pollutants, including NO_2, so the studies do not implicate NO_2 over other pollutants. In fact, the ISA notes the epidemiologic findings specifically for respiratory symptoms are only weakly supported by findings from controlled human

[74] ISA, supra note 1, at xliii.
[75] Ibid., at 4-184.

exposure studies.[76]

Biological Plausibility The ISA indicates that key biological plausibility for NO_2-associated asthma morbidity is provided by findings of NO_2-induced increases in airway hyperresponsiveness (AHR) in controlled human exposure studies of adults with asthma. In the discussion of the AHR studies, the ISA indicates "statistically significant effects on responsiveness to nonspecific challenge were reported following exposures as low as 100 ppb NO_2, although most studies showing significant effects were in the range of 300 ppb NO_2 or greater.[77]

The interpretation of the AHR studies are important because it is the only effect might be occurring near ambient levels based on controlled exposure studies. For example, Hesterberg et al. (2009)[78] reviewed the human clinical studies and report:

> We examined more than 50 experimental studies of humans inhaling NO_2, finding that such clinical data on short-term exposure allowed discrimination of NO_2 no-effect levels *versus* lowest-adverse-effects levels. Our conclusions are summarized by these six points: *For lung immune responses and inflammation*: (1) healthy subjects exposed to NO_2 below 1 ppm do not show pulmonary inflammation; (2) at 2 ppm for 4 hours, neutrophils and cytokines in lung-lavage fluid can increase, but these changes do not necessarily correlate with significant or sustained changes in lung function; (3) there is no consistent evidence that NO_2 concentrations below 2 ppm increase susceptibility to viral infection; (4) for asthmatics and individuals having chronic obstructive pulmonary disease (COPD), NO_2-induced lung inflammation is not expected below 0.6 ppm, although one research group reported enhancement of proinflammatory processes at 0.26 ppm. *With regard to NO_2-induced AHR*: (5) studies of responses to specific or nonspecific airway challenges (*e.g.*, ragweed, methacholine) suggest that asthmatic individuals were not affected by NO_2 up to about 0.6 ppm, although some sensitive subsets may respond to levels as low as 0.2 ppm. *And finally, for extra-pulmonary effects*: (6) such effects (*e.g.*, changes in blood chemistry) generally required NO_2 concentrations above 1 ppm to 2 ppm.

Their review led Hesterberg et al. to conclude:

> The available human clinical results do not establish a mechanistic pathway leading to adverse health impacts for short-term NO_2 exposures at levels typical of maximum 1-hour concentrations in the present-day ambient environment (*i.e.*, below 0.2 ppm).

Because of the importance of the AHR results for establishing the first effects of NO_2 and

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[76] Ibid., at 4-182.
[77] IIbid., at 4-25.
[78] Hesterberg, TW; Bunn, WB; McClellan, RO; Hamade, AK; Long, CM; Valberg, PA. (2009). Critical review of the human data on short-term nitrogen dioxide (NO_2) exposures: Evidence for NO_2 no-effect levels. Crit Rev Toxicol 39: 743-781.

for evaluating biologic plausibility, the ISA spends considerable space in Section 4.2.2 presenting and discussing the relevant studies. While there is considerable discussion of statistical significance with regard to the AHR studies, there is little or no discussion of the medical significance.

The airway hyperresponsiveness identified in the human clinical studies of allergen and nonspecific bronchial challenges in asthmatics needs to be put into perspective in the ISA to properly weigh the results in the causality determination. The ISA acknowledges that transient increases in airway responsiveness have the potential to increase symptoms and worsen asthma control. However in the 2008 Review, the Agency noted that the allergen-induced effects were not accompanied by any changes in pulmonary function or subjective symptoms. The authors of these studies note that these are subclinical effects from repeated short-term exposures that might be of clinical importance (Barck et al. (2002) and Barck et al. (2005a)). The most recent California review of that state's NO_2 air quality standard noted that these are subclinical effects, that the various endpoints were not consistently seen across studies with very similar protocols, and that dose-response information is lacking. The Administrator's June 2009 proposal to set a new 1-hour standard recognized that the clinical significance of the responses is not known.[79]

Furthermore, Folinsbee (1992)[80] noted that the NO_2 exposures in the 25 studies in his meta-analysis did not lead to clinical asthma exacerbation. Folinsbee noted that the health implications of an acute increase in nonspecific airway responsiveness are unclear. He further noted that it could potentially lead to a temporary exacerbation of asthma symptoms and possibly increased medication use but he also noted that, in the studies he evaluated, there was no reported incidence of increased medication usage following NO_2 exposure. The lack of clinically important responses in the now numerous human exposure studies needs to be considered in the causality determination.

The ISA discusses three meta-analyses of the AHR studies, Folinsbee's 1992 analysis of 25 studies of NO_2 and airway responsiveness conducted between 1976 and 1991, an update to that analysis that was conducted by EPA during the prior review, and a new meta-analysis by Goodman et al. (2009).[81] Folinsbee reported that, on balance, there were more asthmatic subjects that had increased airway reactivity than had decreased airway reactivity when exposed to NO_2 (in the range of 0.1 to 0.3 ppm) as compared to clean air. (For healthy subjects, an increase in airway responsiveness was seen only at concentrations above 1.0 ppm.) The effect in asthmatics was evident only in exposures conducted at rest, which he described as puzzling, since the subjects received higher doses when exercising. It is still puzzling since the "at rest" studies, where the effect was seen, were of shorter duration than the "with exercise" studies. Folinsbee posited several possible explanations and the ISA discusses several possibilities, but to date none have been identified as the cause.

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[79] 74 Federal Register 34404, at 34437.

[80] Folinsbee, LJ. (1992). Does nitrogen dioxide exposure increase airways responsiveness? Toxicol Ind Health 8: 273-283.

[81] Goodman, JE; Chandalia, JK; Thakali, S; Seeley, M. (2009). Meta-analysis of nitrogen dioxide exposure and airway hyper-responsiveness in asthmatics. Crit Rev Toxicol 39: 719-742.

EPA relied on the Agency's update of the Folinsbee analysis in setting the new 1-hour standard. The ISA shows this analysis in Tables 4-3 and 4-4. The most important issue with the EPA analysis is that it relies heavily on the Orehek, et al. (1976)[82] study of airway responsiveness that has never been replicated. The large effect reported by Orehek et al. is the reason there is a significant effect at 0.10 ppm is reported in the analysis. However, the Orehek study was fully evaluated and considered during previous NO_2 reviews and discounted because it has never been replicated. For example, the 1995 Staff Paper explicitly concluded "Several controlled exposure studies (Ahmed et al., 1983a,b; Bylin et al., 1985; Hazucha et al., 1982, 1983; Koenig et al., 1985; Orehek et al., 1981) of asthmatics showed no significant effect on responsiveness at very low NO_2 concentrations of 0.1 to 0.12 ppm."[83]

Goodman et al. (2009) reported that although several effect estimates from their meta-analyses are statistically significant, they are all so small that they are not likely to be clinically relevant. More importantly, they point out that there are no exposure-response associations for any effect estimate.

Hesterberg et al. (2009) discusses the differences among these meta-analyses and point out the small magnitude of NO_2-induced pulmonary changes (for the most part, only 2-7 % different from baseline or control exposures) and the transient nature of these changes in the absence of symptoms. These factors, together with the lack of a dose-response diminish the biologic plausibility of a causal explanation for the adverse-health respiratory outcomes reported by epidemiology studies.

2. Long-term

With regard to long-term exposure the ISA indicates:

> A broad range of health effects has been evaluated for relationships with long-term NO_2 exposure. **The strongest evidence is for respiratory effects, and it indicates that there is likely to be a causal relationship with long-term NO_2 exposure** (Section 5.2.17)**.** The key supporting evidence includes consistent recent epidemiologic findings for associations between long-term ambient NO_2 concentrations and asthma incidence in children.[84]

Thus, the ISA indicates that asthma-related effects are also the strongest evidence for long-term NO_2 health effects. For long-term effects, Section 5.2.17 from 5-73 to 5-76

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[82] Orehek, J; Massari, JP; Gayrard, P; Grimaud, C; Charpin, J. (1976). Effect of short-term, low-level nitrogen dioxide exposure on bronchial sensitivity of asthmatic patients. J Clin Invest 57: 301-307.
[83] U. S. Environmental Protection Agency (1995) "Review of the National Ambient Air Quality Standards for Nitrogen Dioxide: Assessment of Scientific and Technical Information," OAQPS Staff Paper, EPA-452/R-95-005, September 1995, at page 37.
[84] ISA, supra note 1, at lxxviii.

and Table 5-9 present the EPA rationale. The relevant data are discussed in the following.

a. Asthma incidence

Section 5.2.17 indicates:

> The strongest evidence is provided by recent studies of asthma incidence in children where previous evidence was inconsistent. Multiple longitudinal, prospective studies (Table 5-9) have demonstrated associations between higher ambient NO_2 concentrations measured in the first year of life, in the year of diagnosis, or over a lifetime and asthma incidence in children.[85]

It also indicates (1) the 2008 ISA had primarily cross-sectional studies available to consider, (2) the high correlations among traffic-related pollutants which made it difficult to accurately estimate the independent effects of long-term NO_2 exposures was a key uncertainty that remains, and (3) recent meta-analyses of asthma incidence informs the evidence base.

The Gowers et al. (2012) review[86] is particularly relevant. It provides a summary of the evidence that the United Kingdom Committee on the Medical Effects of Air Pollutants (COMEAP) considered in developing its statement in response to the question, 'Does outdoor air pollution cause asthma?' Among the sources of information that Gowers et al. review are two meta-analyses by Anderson, Favarato, and Atkinson. One is a meta-analysis of cohort studies[87] and the other is a meta-analysis of multi-community or cross-sectional studies.[88] The multi-community study found no evidence of an association between community levels of air pollution (NO_2, SO_2, ozone, and PM_{10}) and asthma prevalence.

The cohort study, on the other hand, did find positive associations for several pollutants. The authors identified 17 cohorts (eight birth cohorts and nine child/adult cohorts) with a total of 99 population-based risk estimates. They report that most studies were based on within-community exposure contrasts dominated by traffic pollution. Twelve of the cohorts reported at least one positive statistically significant association between air pollution and a measure of incidence. Of the total of 99 estimates, only a minority (29) were positive and statistically significant. The meta-analysis indicated positive

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[85] Ibid., at 5-73.

[86] Gowers, AM; Cullinan, P; Ayres, JG; Anderson, HR; Strachan, DP; Holgate, ST; Mills, IC; Maynard, RL. (2012). Does outdoor air pollution induce new cases of asthma? Biological plausibility and evidence; a review. Respirology 17: 887-898.

[87] Anderson, HR; Favarato, G; Atkinson, RW. (2013). Long-term exposure to air pollution and the incidence of asthma: Meta-analysis of cohort studies. Air Qual Atmos Health 6: 47-56.

[88] Anderson HR, Favarato G, Atkinson RW. (2013) Long-term exposure to outdoor air pollution and the prevalence of asthma: meta-analysis of multi-community prevalence studies. Air Qual. Atmos. Health 6: 57-68.

associations for several pollutants, including NO_2. The authors concluded that the results are consistent with an effect of outdoor air pollution on asthma incidence.

Gowers et al. point out that the results of these two meta-analyses appear contradictory. If higher concentrations of outdoor air pollutants are associated with increased asthma incidence, it would be expected that they would also be associated with higher prevalence, because incidence is an important determinant of prevalence. While Gowers et al. discuss several possible explanations, they are all speculative in nature.

For the purposes of the ISA, the contradiction is important and needs to be presented and discussed. If NO_2 is causing new cases of asthma, the effect should be seen wherever a contrast in exposure occurs. That it is not seen in multi-community studies is a strong argument against causality.

The Agency's bias toward highlighting the evidence supportive of effects and downplaying or ignoring evidence against effects is demonstrated by the inclusion of the Anderson et al. cohort meta-analysis in the references of the ISA along with the omission of the Anderson et al. multi-community meta-analysis by the same authors.

The Gowers et al. review also includes a systematic review of 97 studies of the association between exposure to traffic-related pollution and asthma, including some of the cohort studies included in the meta-analysis.

Based on the quantitative analyses and the narrative review of 97 studies, the UK Advisory Committee reached the following conclusions:

> 1. Evidence from studies comparing communities (i.e. at a city or administrative area level) suggests that the induction of asthma does not appear to be associated, at a population level, with levels of air pollutants.
>
> 2. Evidence from studies on traffic-related air pollution suggests that it is possible that air pollution plays a part in the induction of asthma in some individuals who live near busy roads, particularly roads carrying high numbers of heavy goods vehicles.
>
> 3. Examination of the mechanistic evidence bearing on the possible interaction between exposure to air pollutants and the induction of asthma leads the Committee to think that a causal explanation for conclusion (2) is plausible.
>
> 4. The contribution of exposure to air pollutants to the induction of asthma in those in whom it plays a part is likely to be small in comparison with those from other contributory factors. The proportion of the population so affected is also likely to be small.

Gowers et al. indicate that their findings are broadly consistent with the 2010 Health

Effects Institute Panel's[89] conclusion that living close to busy roads was an independent risk factor for the onset of childhood asthma. The HEI Panel regarded the evidence for a causal relationship to be between 'sufficient' and 'suggestive but not sufficient', the main difference between these classifications being whether chance, bias and confounding could be ruled out with reasonable confidence.

For the purposes of the ISA, the health effects signal identified by the UK Committee and the HEI Panel is something specific to heavily travelled roads with a high density of trucks. Since NO_2 is much more broadly distributed in urban communities than other roadway emissions because of the photochemical oxidation of NO to NO_2, it is not likely that NO_2 is causing the weak health effects signal.

Coarse particles from re-suspended road dust are a much more likely candidate than NO_2. Vehicles, especially larger vehicles, re-suspend substantial paved road dust that contains biological particles along with crustal material and previously deposited man-made particles.[90,91] Allergens from over 20 different source materials have been identified in paved road dust.[92] Coarse particles re-suspended from roadways deposit closer to the road than fine particles and have been associated with acute asthma-related effects as noted above. Coarse particles, therefore, should be added to the list of alternative explanations for the data that should be discussed in the ISA.

In the cohort studies on asthma-related endpoints as well as in the other observational studies evaluated in Chapter 5, investigators typically evaluated a number of pollutants and, where there were positive associations, the investigators concluded that air pollution or traffic-related air pollution was associated with the health effect studied. Because of the way the data is presented, however, the casual reader of the ISA would get the impression that all these studies did was evaluate NO_2 and in some cases NO_2 together with another pollutant. This is very misleading. In order to evaluate consistency, chance, and the possibility of confounding, one has to look at the total pattern of results not just focus on NO_2 and consider the total number of outcomes evaluated.

With regard to the causality determination, the reliance on single pollutant model results weakens the case for causality. The uncertainty as to whether NO_2 is acting as a surrogate for another pollutant(s) or the mix of pollutants generally also weakens the case for causality. In addition, the Agency uses a weak definition of consistency and coherence. For example, the 2008 ISA noted that:[93]

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[89] HEI (Health Effects Institute). (2010). Traffic-related air pollution: A critical review of the literature on emissions, exposure, and health effects [HEI]. (Special Report 17). Boston, MA.

[90] McDonald, JD; Chow, JC; Peccia, J; Liu, Y; Chand, R; Hidy, GM; Mauderly, JL. (2013) Influence of collection region and site type on the composition of paved road dust. Air Quality, Atmosphere & Health 6: 615-628.

[91] Bozlaker, A; Spada, NJ; Fraser, MP; Chellam, S. (2014) Elemental Characterization of $PM_{2.5}$ and PM_{10} Emitted from Light Duty Vehicles in the Washburn Tunnel of Houston, Texas: Release of Rhodium, Palladium, And Platinum. *Environ. Sci. Technol.*48: 54–62.

[92] Miguel, A; Cass, G; Glovsky, M; Weiss, J. (1999) Allergens in Paved Road Dust and Airborne Particles. *Environ. Sci. Technol.* 33: 4159–4168.

[93] NOx ISA, supra note 16, at 5-6.

> "The epidemiologic evidence for respiratory effects can be characterized as consistent, in that associations are reported in studies conducted in numerous locations with a variety of methodological approaches. The findings are coherent in the sense that the studies report associations with respiratory health outcomes that are logically linked together."

The arguments made in Chapters 4 and 5 use these same broad generalizations. The weak definition of consistency and coherence is akin to the counting of studies that EPA previously argued is not credible:

> "A tallying of studies reporting statistically significant or nonsignificant results does not point toward credible conclusions about the relative weight of the evidence and the likelihood of causality."[94]

b. Respiratory Symptoms in Asthmatics Related to Indoor NO_2 Exposure

Table 5-9 indicates that several studies indicate increases in respiratory symptoms related to indoor NO_2 exposure, referencing Belanger et al. (2013) and Hansel et al. (2008). In addition to the studies noted in the ISA, there is a substantial literature addressing the issue of health effects from indoor NO_2 exposures. Much of the work revolves around the fact that gas appliances, such as gas stoves and unvented gas heaters, are an indoor source of NO_2. This literature is relevant to the question of an ambient NO_2 standard because (1) people spend about 90 % of their time indoors, with much of that time at home, and (2) the NO_2 exposures from gas appliances have fewer potential confounders present than the typical ambient exposure, and (3) levels indoors can be much higher than outdoors in the presence of an indoor source.

Over the years there have been several reviews or meta-analyses of this database. Basu and Samet (1999)[95] reviewed 45 studies of the health effects from the emissions of gas stoves and concluded that the findings were not consistent across all studies. They concluded that the evidence does not support a causal relationship between exposure to NO_2 or use of a gas stove and increased risk for respiratory morbidity. They acknowledged that some studies did show increased risk and cautioned that the evidence doesn't support a conclusion that such exposures are risk free.

More recently Lin et al. (2013)[96] conducted a meta-analysis on 41 population studies of the association between indoor NO_2 (and gas cooking) and childhood asthma and

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[94] Ibid., at 1-8.

[95] Basu, R; Samet, JM. (1999) A review of the epidemiological evidence on health effects of nitrogen dioxide exposure from gas stoves. Journal of Environmental Medicine 1:173–187.

[96] Lin, W; Brunekreef, B; Gehring, U. (2013) Meta-analysis of the effects of indoor nitrogen dioxide and gas cooking on asthma and wheeze in children. International Journal of Epidemiology 42:1724–1737.

wheeze. The meta-analyses found no increase in the risk of asthma in relation to indoor NO_2 exposure but there was an increase in the risk of wheeze.

Hansel et al. (2008)[97] monitored indoor NO_2 in the bedrooms of inner city pre-school children who had asthma. The presence of a gas stove and the use of a space heater or oven/stove for heat were independently associated with higher NO_2 concentrations. While NO_2 was associated with small increases in some asthma symptoms, NO_2 was not associated with increased health care utilization. Hansel et al. also report minimal correlation between indoor and ambient NO_2. In the discussion Hansel et al. point out that (1) current evidence has not yet convincingly demonstrated that high indoor NO_2 concentrations contribute to the risk of developing asthma, because NO_2 concentrations are similar in homes of children with and without asthma, and (2) studies done in subjects with asthma have suggested that higher indoor NO_2 concentrations lead to increased asthma symptoms; however, results have not been consistent.

Belanger et al. (2013)[98] monitored NO_2 for monthly periods in bedrooms and dayrooms (the rooms where the children spent the most of their waking hours) for a cohort of school age children with asthma and reported associations of NO_2 with asthma symptoms and with rescue medication use.

There are two important issues in evaluating the indoor NO_2 studies with respect to an ambient standard. The first is that the distribution of exposures in the presence of an indoor source is different, with many repeat peaks compared to the ambient distribution. This difference is important because peak levels of exposure are more toxic than long-term average exposures in animal studies.[99]

For the studies that do report associations with respiratory symptoms from indoor sources, we do not know what aspect of the exposure may be responsible. For example, Franklin et al. (2006)[100] point out that most health studies measuring indoor NO_2 concentrations have used long-term passive monitors, that may not provide adequate information on short-term peaks, which may be important when examining health effects of this pollutant. Therefore, they investigated the relationship between short-term peak and long-term average NO_2 concentrations in kitchens and the effect of gas cookers on the relationship. They report that average NO_2 concentrations do not adequately identify exposure to short-term peaks of NO_2 that may be caused by gas cookers.

The second issue is that while there are fewer potential confounders in gas appliance studies, confounding is still an important consideration. It is well known that gas cooking

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[97] Hansel, NN; Breysse, PN; McCormack, MC; Matsui, EC; Curtin-Brosnan, J; Williams, DAL; Moore, JL; Cuhran, JL; Diette, GB. (2008). A longitudinal study of indoor nitrogen dioxide levels and respiratory symptoms in inner-city children with asthma. Environ Health Perspect 116: 1428-1432.

[98] Belanger, K; Holford, TR; Gent, JF; Hill, ME; Kezik, JM; Leaderer, BP. (2013). Household levels of nitrogen dioxide and pediatric asthma severity. Epidemiology 24: 320-330.

[99] Miller G, Graham JA, Raub JA, Illing JW. (1987) Evaluating the toxicity of urban patterns of oxidant gases. II. Effects in mice from chronic exposure to nitrogen dioxide. J Toxicol Environ Health 21: 99-112.

[100] Franklin, P; Runnion, T; Farrar, D; Dingle, P. (2006) Comparison of peak and average nitrogen dioxide concentrations inside homes. Atmospheric Environment 40:7449–7454.

produces NO_2 and other pollutants such as ultrafine particles. Seaton and Dennekamp (2003)[101] have proposed that the associations of NO_2 with illness in observational studies may be a result of confounding by ultrafine particles. Also, Breysse et al.(2010)[102] report that both indoor fine and indoor coarse PM are associated with increased respiratory symptoms in asthmatic inner-city children.

c. Summary for long-term respiratory effects

Based on the comments and analysis in this critique, the evidence for long-term respiratory health effects from ambient NO_2 is similar to that in the last review and does not merit a change in the causality determination.

[101] Seaton, A; Dennekamp, M. (2003) Hypothesis: Ill health associated with low concentrations of nitrogen dioxide—an effect of ultrafine particles? Thorax 58:1012-1015.
[102] Breysse, PN; Diette, GB; Matsui, EC; Butz, AT; Hansel, NN; McCormack, MC. (2010) Indoor Air Pollution and Asthma in Children. Proc Am Thorac Soc 7:102–106.

C. Roadway and Traffic-Related Exposures

AIR reviewed the ISA with regard to how the document portrays roadway and near-roadway exposures. The draft ISA misstates the magnitude of the exposures, the potential health implications of the exposures, and the usefulness of the near-road monitoring program in aiding in the conduct of health effects studies and the resolution of existing uncertainties.

There is a major error/omission in Chapter 2 that affects the understanding of the spatial variability in ambient NO_2 and the relative importance of near- versus far-roadway exposures. The ISA indicates:

> A major chemical transformation in the air is the reaction of NO and ozone (O_3) to form NO_2 (Section 2.2, Figure 2-1). Rather than direct emissions, this reaction is the main source of the ambient air NO_2 concentrations measured in most urban locations.[103]

While the reaction of NO with ozone is important, Figure 2-1 clearly shows another pathway. The photolysis of NO_2 produces NO plus an O atom that reacts with O_2 to form O_3. The reactions of HO_2 and RO_2 radicals oxidizing NO to NO_2 provide a pathway to produce NO_2 without using up ozone. This pathway allows ozone to build up in the atmosphere and is the primary source of NO_2 downwind of sources. Therefore, maximum NO_2 concentrations need not occur near the source.

In the following subsections, we describe the near-road monitoring program, review the available near-road and in-vehicles studies of NO_2 exposure, demonstrate how the ISA overstates the magnitude and importance of near-roadway exposures, and show how the near-road monitoring program will results in measurements of NO_2 and other pollutants that are not indicative of the maximum exposures of either near-by residents or commuters. As such, the near-road measurements will not be useful in future health studies.

1. The Near-Road Monitoring Program

In the 2010 Final Rules concerning the National Ambient Air Quality Standards (NAAQS) for nitrogen dioxide (NO_2),[104] the Environmental Protection Agency (EPA) added requirements for near-roadway monitoring. This was a significant change to the nation's air monitoring strategy. Prior monitoring strategies focused on identifying maximum air pollutant exposures in populated areas where people live and work. The new strategy requires the placement of NO_2 (and $PM_{2.5}$ and CO) monitors alongside (within 50 meters) of the heaviest traveled interstate highways and freeways and encourages placement in the right-of-way (ROW) where the public has no access let

[103] ISA, supra note 1, at lxviii and 2-2.
[104] 75 Federal Register 6474, February 9, 2010.

alone lives. For NO_2, all urban areas with a population of 500,000 or more must establish one roadside monitoring site while those with more than 2.5 million must situate two sites. In addition, a second site is required in any urban area that has a road segment that exceeds 250,000 vehicles per day. In all, there will be over 100 NO_2 roadside monitoring sites across the country.

EPA required that the NO_2 roadside monitoring begin January 1, 2014. Subsequent to the 2010 rulemaking, the EPA revised the deadlines by which the near-road monitors are to be operational in order to implement a phased deployment approach.[105] The near-road NO_2 monitors will become operational between January 1, 2014 and January 1, 2017.

The CO and $PM_{2.5}$ Final Rules indicate that the near-roadway monitors for these pollutants should be co-located with the new near-roadway NO_2 monitors, although exceptions can be approved by an EPA Regional Administrator. EPA has issued a Technical Assistance Document (TAD) to provide guidance to the states for selecting the near-roadway NO_2 sites.[106] This guidance, therefore, also applies to the siting of near-roadway CO and $PM_{2.5}$ monitors.

Three years of data must be collected before attainment/nonattainment designations can be made. However, some state and local agencies have been deploying the roadside sites ahead of EPA's schedule. For example, in Michigan, the MDEQ began collecting roadside CO and NO_2 data in Detroit in October of 2011. In any event, it will be a few years before 3-years worth of data have been collected at most sites.

2. Synthesis of Near-Road Measurements

A comprehensive review of near-road pollutant measurements is contained in a paper by Karner et al. (2010).[107] The authors synthesized the results from 41 roadway studies conducted from 1978 to 2008. It should be noted that these sites were primarily research studies of short duration under site conditions chosen to minimize background concentrations so the impact of the roadways could be observed. To compare the results of the different studies they performed two data normalization procedures: 1) for studies that measured upwind or background measurements, they normalized the data to the background concentrations and plotted them as a function of distance from the roadway, and 2) for all of the studies, they performed an edge-of-road normalization of the data. Since some studies made upwind or background measurements, while others did not, by performing edge-of-road normalization, they were able to compare all the data sets and infer the background concentration by determining at what distance downwind the pollutant achieved a stable concentration. In concept, stability is indicative of near-road concentrations approaching or reaching upwind background values. They had 125 data sets for NO_2.

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[105] 78 Federal Register 16184, March 14, 2013

[106] U.S. Environmental Protection Agency. (2012). Near-road NO_2 Monitoring Technical Assistance Document, EPA-454/B-12-002.

[107] Karner, AA; Eisinger, DS; Niemeier, DA. (2010). Near-roadway air quality: synthesizing the findings from real-world data. Environ. Sci. Technol., 44: 5334-5344.

The data sets that were normalized to background are shown in Figure 2. A loess smoother was fitted to each pollutant to generate the regression curves. The point at which the curves reach or approach the horizontal line indicates the distance from the roadway the pollutant returns to upwind or background concentration. As Figure 1 shows, NO_2 reaches background at about 400 m.

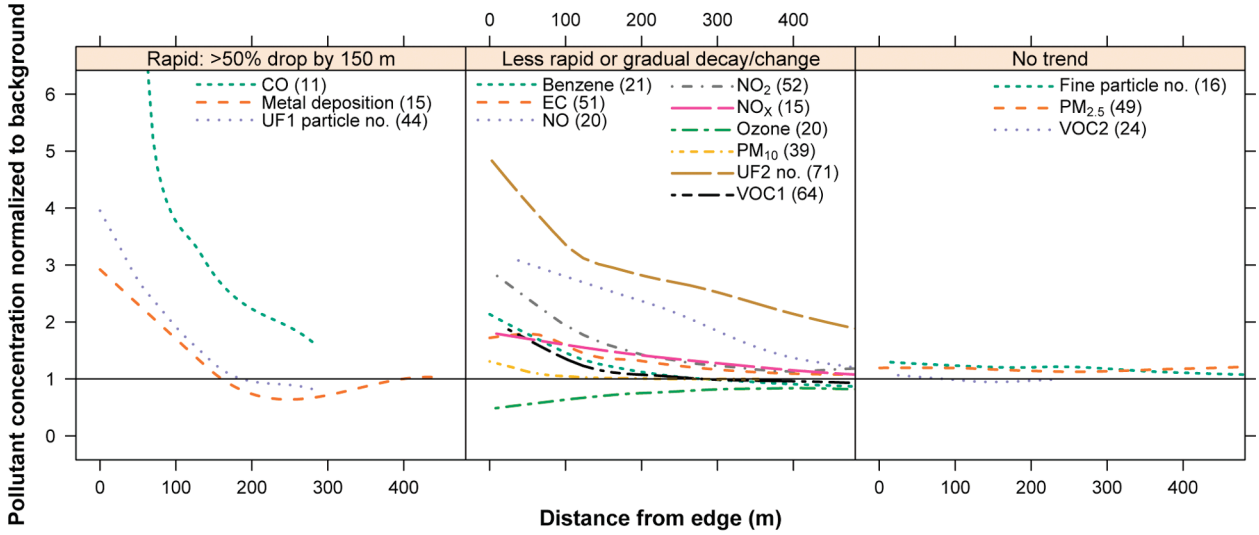

Figure 2: Pollutant concentrations normalized to background concentrations as a function of downwind distance from the road. The regression sample size is given in parentheses after each pollutant. The horizontal line indicates the background concentration. From Karner et al. (2010).

The edge-of-road normalized graphs for NO_2 from Karner et al. were digitized and the regression curve was reproduced for closer examination. This is shown in Figure 3. Karner et al. classify these decay curves into two categories: rapid decay (more than a 50% drop in concentration by 100-150 m) and gradual decline. The NO_2 curve falls into the second category of a gradual decline. The slower decay pattern associated with NO_2 is indicative of a pollutant with small roadway emissions relative to background and/or of secondary pollutants that are formed downwind from roadway emissions. For NO_2, both of these conditions appear to apply. Figure 2 indicates that the increase in NO_2 concentrations relative to background is less than 2-fold. There is both theoretical and observational evidence that roadway NO emissions are converted downwind by O_3 to additional NO_2.

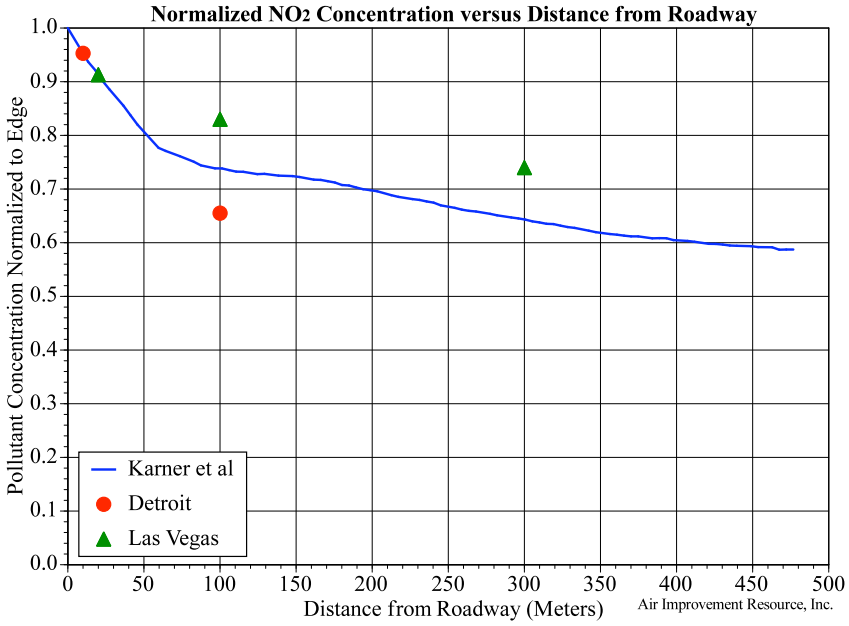

Figure 3: Edge-of-road normalized NO_2 data from Karner et al. (2010). The Las Vegas and Detroit data are from recent near-road measurements cited in the text.

Also shown on Figure 3 are edge-of-road normalized data points from near-road sites next to I-15 in Las Vegas[108] and next to I-96 in Detroit.[109] To normalize the data, it was assumed that the points closest to the roadway (10 m in Detroit and 20 m in Las Vegas) fell on the decay curves. The Detroit data points at 100 m and the Las Vegas data points at 100 m and 300 m are reasonably close to the regression curves, which suggest that the shapes of the Detroit and Las Vegas decay curves are explained by the same factors that control the shapes of the Karner et al. curves.

Based on the roadway profiles observed in Karner et al. and at the I-15 and I-96 sites in Las Vegas and Detroit, the maximum roadway impact on concentrations of NO_2 will be observed at the monitoring site closest to the road. This was the case except on rare occasions when additional NO_2 was formed further downwind from the roadway in Las Vegas. This rare occasion occurred less than 10% of the time.

As discussed above, the edge-of-road normalized regression curve, shown in Figure 2, provides an estimate of the background or upwind concentration at the distance where the concentration becomes stabilized. A visual examination indicates that a stable concentration is reached at a distance of approximately 400 m for NO_2. By 50 m, the NO_2 roadway contribution has decayed to about 50% and to 25% by 200 m.

[108] Rutter, AP; Hafner, HR. (2012). Assessment of Near-Roadway NO_2 Concentrations, CRC Report A-79, Coordinating Research Council, Alpharetta, GA.
[109] Air Quality Division. (2012). Michigan's 2013 Ambient Air Monitoring Network Review, Michigan Department of Environmental Quality, Lansing, MI.

Based on the above, the maximum concentrations for NO_2 is, except on rare occasions, most likely to be measured at a site closest to the road. For practical and safety considerations, 10 m is probably the closest a near-road monitor would be placed. Based on the regression curves generated by Karner et al., a site at 10 m from the road should capture about 95% of the maximum roadway NO_2 concentration that would be measured if a monitor was on the roadway. By the time the roadway emissions decay to a stable concentration, which is assumed to be background, the NO_2 concentration has decayed according to Karner et al. curves to about 60% of the expected roadway maximum.

The ratio of the value at 10 m to the background concentration provides an estimate of the factor a 10 m site would be elevated above regional background or above the upwind background. For NO_2 the factor is 95%/60% = 1.58.

For the purposes of this discussion, we will make a "worst case" assumption to be on the conservative side. We shall assume that the current Design Value (DV) for each U.S. county for NO_2 is representative of the upwind roadway background for a near-road monitoring site in that county. We can then multiply the DV by the 1.58 to estimate how much it would increase if a 10 m near-road monitor was installed. The 2012 DVs were obtained from EPA.[110]

For NO_2, with a factor of 1.58, an annual DV of greater than 33 ppb would be at risk of exceeding the annual NAAQS of 53 ppb. The two highest annual DVs are found in Maricopa, AZ, 26 ppb and Denver, 25 ppb. Consequently, exceedances of the annual NAAQS for NO_2 are unlikely.

For the new 1-hour NO_2 NAAQS of 100 ppb, however, the situation is different. A site with a DV of 64 ppb or higher would be at risk. At present there are 4 counties in California as well as Philadelphia, Union County, NJ, Sedgwick, KS and Maricopa, AZ that have DVs between 64 and 74 ppb. In addition, 5 additional counties have DVs between 60 and 63. Consequently, the odds of one or more of these counties finding a near-road NAAQS violation are high.

Using the latest version of MOVES (version 2010b),[111] U.S. emissions from highway vehicles were projected for the years 2012 to 2030 for NO_x. These emission estimates were then normalized to the 2012 emissions so that the fractional emission reductions could be examined. The normalized plot is shown in Figure 4.

[110] U.S. EPA. (2012). Design Value Reports. http://www.epa.gov/airtrends/values.html (accessed January 6, 2014).
[111] U.S. EPA. 2013. MOVES (Motor Vehicle Emission Simulator). http://www.epa.gov/otaq/models/moves/. (accessed October 23, 2013).

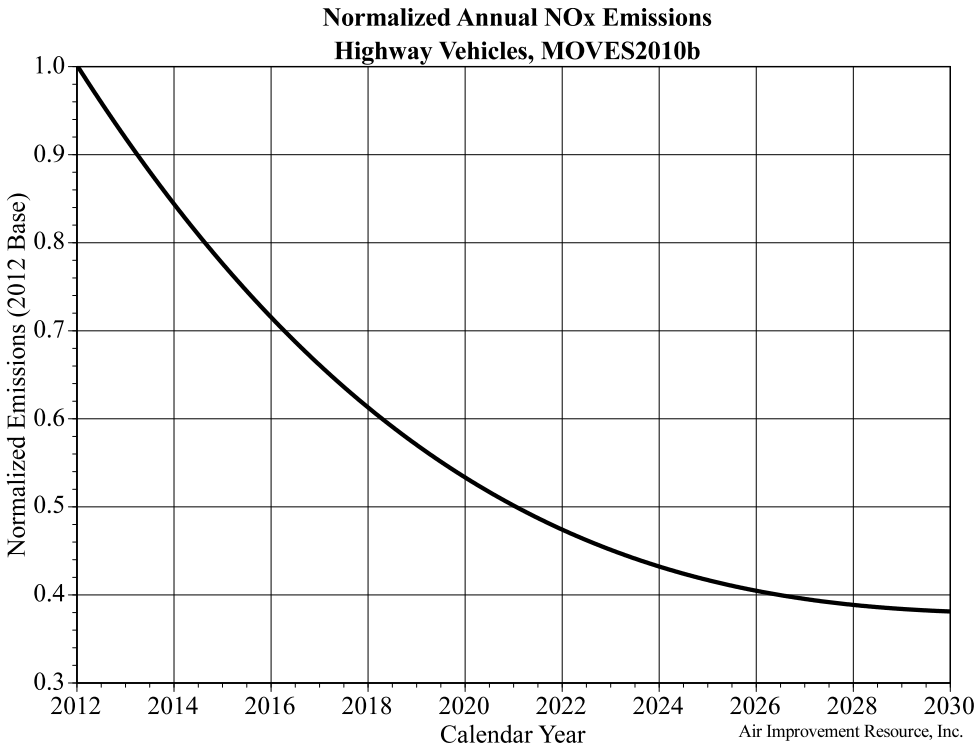

Figure 4: MOVES emission estimates for NO_x normalized to the 2012 estimates.

The initial decline in NO_x emissions to 2015 is 4.33%/year, which is identical to the rate of decline in recent highway vehicle estimates for NO_x emissions of 4.33%/year,[112] but higher than the observed changes in nationwide ambient NO_2 concentrations of 2.42%/year.[113] The likely reason for this discrepancy is the non-linear relationship between NO_x emissions and NO_2 concentrations. The decline in NO_x emissions from highway vehicles continues through 2030. By 2030, it has declined by 62% from 2012.

Because future emissions of NO_x are expected to continue to decline another 62% by 2030 relative to 2012, the factor of 1.58 will decline in the future. Since it appears a 1% reduction in NO_2 occurs for about a 2% reduction in NO_x emissions, the factor of 1.58 should decline towards about 1.4. At this value, sites with a DV of 71 ppb of higher would be at risk. At present, only three California counties have a DV exceeding 71 ppb.

As shown above, a near-road violation of the annual NO_2 NAAQS should not occur under normal conditions. Surely if one did occur, it would have to have been caused by temporary highly unusual conditions and should qualify for a waiver. However, near-road exceedances at 10 m of the 1-hour NO_2 NAAQS will not require unusual conditions and can be expected in a number of areas around the U.S. However, they will be only be

[112] U.S. EPA. 2013. National Emissions Inventory (NEI) Air Pollution Emissions Trend Data. http://www.epa.gov/ttn/chief/trends/index.html. (accessed October 25, 2013).
[113] U.S. EPA. 2013. National Trends in NO_2 Levels. http://www.epa.gov/airtrends/nitrogen.html. (accessed October 24, 2013).

representative of exposures within 10 m of the road and not be representative of exposures further than 10 m away.

3. In-vehicle NO_2 Concentrations

EPA's rationale for near-road monitoring is, in part, due to the Agency's concern for on-road and in-vehicle exposures. For example, in the NO_2 Final Rule:

> EPA notes that the intent of the revised primary NO_2 NAAQS is to protect against the maximum allowable NO_2 concentration anywhere in an area, which includes ambient air on and around roads.[114]

Further, EPA notes "traffic-related exposures can dominate personal exposures to NO_2" and "While driving, personal exposure concentrations in the cabin of a vehicle could be substantially higher than ambient concentrations measured nearby."[115]

Because of the EPA concern, the available data concerning on-road and in-vehicle exposures to NO_2 with a focus on the concentrations and exposures on heavily traveled expressways is briefly reviewed. A distinction is made between "on-road measurements" and "in-vehicle measurements" because pollutants can interact with the surfaces in the passenger compartment and in the vehicle's ventilation system generally producing lower "in-vehicle" concentrations than "on-road" concentrations.

The 2008 NO_2 Integrated Science Assessment indicated:

> NO_2 concentrations in heavy traffic or on freeways have been observed in the range of 40 to 70 ppb and can be more than twice the residential outdoor or residential/arterial road level (Lee et al., 2000; Westerdahl et al., 2005).[116]

The Westerdahl et al. 2005[117] study of on-road concentrations in the Los Angeles Basin does report measurements of NO_2 and other pollutants in an instrumented electric vehicle driving on freeways in Los Angeles with greater than 200,000 vehicles per day that had between 1 and 18 % diesel trucks in the vehicle mix. The vehicle was driven on a freeway-dominated loop that took approximately two hours. The median NO_2 concentrations reported by Westerdahl et al. range from 31 to 55 ppb, with a peak instantaneous concentration of 200 ppb. Westerdahl et al. specifically report that roadway NO_2 was usually no more than twice the ambient concentration. This study, conducted in 2003 on major freeways (including freeways with a high percentage of diesel trucks) in the Los Angeles Basin, the area with both the historic highest NO_2

[114] NO_2 Final Rule, supra note 2, at page 6512.
[115] Ibid., at page 6479.
[116] 2008 ISA, supra note 16, at page 4-9.
[117] Westerdahl, D; Fruin, S; Sax, T; Fine, PM; Sioutas, C. (2005). Mobile platform measurements of ultrafine particles and associated pollutant concentrations on freeways and residential streets in Los Angeles. Atmos. Environ. 39: 3597-3610.

concentrations and the highest traffic density, demonstrates the magnitude of on-roadway exposures in worst-case driving situations. The Fujita et al. study conducted in 2004 did not report NO_2 concentrations although both NO and NO_x concentrations are reported. Since NO_2 concentrations are determined by difference, presumably there was a mismatch between the response time of the instrument (one minute) and the rapidly varying concentrations in high-speed heavy traffic. Nevertheless, the mean differences between NO and NO_x reported by Fujita et al. are the same order of magnitude as reported by Westerdahl et al. who modified the response time of their instrument to avoid the issue. Since the California and federal motor vehicle control programs are continuing to reduce vehicle NO_x emissions, current and future on-road exposures will be even lower.

The Lee et al., 2000[118] reference in the 2008 NO_2 ISA did not include actual measurements of NO_2 during commuting but does include an estimate of NO_2 exposures during transportation derived from an analysis of personal NO_2 exposure data compared to indoor home, indoor workplace, and outdoor home levels for 57 office workers in Brisbane, Australia.

The 2008 ISA also indicates that sometimes exposure in traffic can dominate personal exposure to NO_2 referencing the Lee et al., 2000 paper and Son et al., 2004.[119] As noted above, the Lee et al. paper does not include actual in-vehicle exposure measurements. The Son et al. paper does; however the measurements are of occupational exposures to Korean taxi drivers. The mean personal exposure of the Korean taxi drivers was 30 ppb. The Son et al. study concludes that some subpopulations, such as professional drivers, might be exposed to high NO_2 levels because they drive diesel taxies outdoors in Korea, a finding that is not particularly relevant to expressway exposures of commuters in the United States.

The one high on-road NO_2 concentration noted in the 2008 ISA is a maximum concentration of 0.548 ppm reported in the Riediker et al., (2003)[120] study of in-vehicle exposures of NO_2 and other pollutants in patrol cars operating in and around Raleigh, NC. However, the 548 ppb data point is noted in three places in the Riediker et al. study as being an obvious outlier/flawed measurement since it was six standard deviations above the mean of the other measurements and since none of the other pollutants were elevated during the shift in which the high NO_2 sample (on a passive filter badge) was obtained. In fact Riediker et al. specifically comment that NO_2 inside the cars was always low, and report the average in-vehicle concentration (without the outlier) was 31 ppb

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[118] Lee, K; Yang, W; Bofinger, ND. (2000). Impact of microenvironmental nitrogen dioxide concentrations on personal exposures in Australia. J. Air Waste Manage. Assoc. 50: 1739-1744.

[119] Son, B; Yang, W; Breysse, P; Chung, T; Lee, Y. (2004). Estimation of occupational and nonoccupational nitrogen dioxide exposure for Korean taxi drivers using a microenvironmental model. Environ. Res. 94: 291-296.

[120] Riediker, M; Williams, R: Devlin, R; Griggs, T; Bromberg, P. (2003). Exposure to Particulate Matter, Volatile Organic Compounds, and Other Air Pollutants Inside Patrol Cars. Environ. Sci. Technol., 37: 2084-2093.

The draft ISA does not cite any new on-roadway NO_2 data although several studies reporting on-road NO or NOx data are cited on page 2-40 of the ISA. Although the database is limited, there are no valid measurements in the literature cited by EPA indicating that on-road or in-vehicle exposures to NO_2 exceed the 1-hour NAAQS.

4. EPA Overstates the Magnitude of On-road or Near-Road Exposures in the ISA

There are a number of examples in the ISA where the stated increase in near-road NO_2 due to emissions from the roadway is misleading. The statement " ambient NO_2, NO, and NO_x concentrations have been shown to be 30% to 200% higher at locations within 15 m of a roadway (averaged over hours to weeks) compared with locations farther away from the road" appears in the Executive summary on pages lxix and lxxx, in Chapter 1 on page 1-54, and in Chapter 2 on page 2-41. The source of the 30 to 200% range is discussed on page 1-54. The 200% increase is seen in a number of cases for NO and NO_x but the increase in NO_2 is always much less. As shown in the previous section in Figure 2, the average roadway increase of NO_2 over background is about 1.6.

The statement, "emphasis is placed on studies with exposures that are relevant to human ambient exposures, defined as concentrations no greater than 5,000 ppb, which is about one to two orders of magnitude higher than peak concentrations of NO_2, NO, or NO_x that humans experience on roads," is repeated in the Executive Summary on page lxxi and on page 1-4. This implies that concentrations of 500 ppb of NO_2 are measured on the roads. While the ISA cites a maximum measured roadway concentration for NO_x of 850 ppb on page 2-40, the highest measured roadway NO_2 concentration in the ISA is about 60 ppb on page 2-42.

On pages lxxvii and lxxxi, EPA implies that a large percentage of the populations lives close to major roadways where the NO_2 is elevated but provides no quantitative information or references. Finally of page 1-50, they provide some information. They state:

> In Los Angeles, CA, 44% of the population was found to live within 100 meters of a major road (HEI, 2010). Such proximity to roadways can be characterized by higher concentrations of NO_2 than background. Thus, a large proportion of the U.S. population has the potential for elevated ambient NO_2 exposures and for increased risk of health effects that are related to higher NO_2 exposure.

It appears that EPA has misquoted HEI (2010).[121] On page 3-13 in HEI (2010), the caption for Figure 3.6 reads: "In 2000, 4,154,847 of 9,526,243 people (or 43.6%) of the

[121] HEI (Health Effects Institute). (2010). Traffic-related air pollution: A critical review of the literature on emissions, exposure, and health effects [HEI]. (Special Report 17). Boston, MA.

population of Los Angeles County live within **500 m of an expressway or** 100 m of a major road" [emphasis added].

This error underscores the loose usage of the term "near road" in the ISA. Almost everyone in the country lives in a "near road" environment if they have a street address. In many places the ISA fails to make a distinction between "near road" and next to a heavily traveled expressway. The rulemaking is concerned with exposures within 50 m of the heaviest traveled expressways while the ISA attempts to portray a more universal risk to roadways in general.

5. The Near-Road Monitoring Program in its Current Form Is Not Useful

As stated above, the draft ISA misstates the magnitude of the near-road exposures. Therefore, the potential health implications of the exposures are not properly characterized. In addition, the usefulness of the near-road monitoring program in aiding in the conduct of health effects studies and the resolution of existing uncertainties is limited. The errors in the 2008 ISA led the Agency to establish the near-road monitoring program in its current form, In order to review and modify the program in the current review so that the data are useful, the ISA needs to acknowledge the limitations of microscale monitoring at near-source sites that do not represent population exposure. The practical consequences of the siting mistakes in the near-road monitoring program are discussed in detail in the following.

EPA has not articulated the consequences of a near-road monitoring violation of the NAAQS. There are two main categories of concerns raised during the development of the near-roadway monitoring requirements. The first is in regards to what will be done with the data, especially as it pertains to nonattainment designations and the State Implementation Plan process. The second relates to the lack of a requirement that the monitoring site represent population exposure with the concern that any violations found will reflect the consequences of locating monitors where no-one lives or works.

a. Concerns Regarding Use of the Data in the Regulatory Process

With so many roadside monitoring sites coming on line now and in the immediate future, it is likely that some will show an exceedance of the 1-hour NAAQS. Besides industries' inquiries to EPA, states have also sought to know what EPA is going to do when an exceedance occurs, but to-date the agency has essentially been silent. During the development of the various final rules and the guidance on network design, industry, the Clean Air Scientific Advisory Committee (CASAC), various states and other interested parties raised concerns over how the data would be used in the attainment planning process.

CASAC in September 2009 was split with regard to the need for the monitoring program that was subsequently promulgated for NO_2.[122] A substantial number of CASAC panelists

[122] Dr. J. Samet letter to Administrator Jackson, September 09, 2009, EPA-CASAC-09-014.

supported the development of a special-purpose monitoring network oriented towards roadside monitoring that is not used for attainment purposes at this point but for research.

CASAC's Ambient Air Monitoring and Methods Subcommittee (AAMMS) was convened to provide consultation on the development of a Near-Road NO_2 Monitoring Technical Assistance Document (TAD).[123] A member of the CASAC Monitoring Panel asked "For example, how will nonattainment boundaries be established for these microscale environments?"[124]

In comments on the TAD, a CASAC panelist wrote:

> The end-point of near-road monitoring: Normally when an ambient monitor shows exceedance of NAAQS, state/local authorities are required to develop a State Implementation Plan (SIP) to bring the area into attainment with NAAQS. The State Implementation Plan will include some control measures to achieve attainment. If a near-road NO_2 monitor shows exceedance of NAAQS, how will a non-attainment area be delineated and what does EPA expect the state/local authority to do? Due to the nature of significant concentration gradient along the roadways, the area with high NO_2 concentrations could be extremely small. What will be the basis for designating an area as non-attainment area? The non-attainment is basically caused by mobile sources. In some areas, it is largely attributable to vehicles passing through the area on the interstate highways. What can the state/local authority do to achieve attainment? If the state/local authority cannot do anything, what is the point of requiring this type of near-road monitoring? EPA could conduct some studies and achieve attainment through regulations on vehicle emission standards.[125]

A number of the individual panelists provided other cogent recommendations for the Administrator. For example, a number of panelists were skeptical of the Agency's plan. One panelist indicated:

> I am not convinced that a substantial near-road monitoring program for NO_2 and other traffic-related species is a good use of Agency resources. I think it will be hard to implement in a meaningful way, and I don't see great potential value in the data it will produce.[126]

Another noted "It's not clear what EPA is trying to accomplish with its proposed near

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[123] U.S. Environmental Protection Agency (2012), supra note 106.
[124] Drs. Russell and Samet, letter to Administrator Jackson, November 24, 2010, EPA-CASAC-11-001 2010, at page 29.
[125] Ibid., at page 90
[126] Ibid., at page 89.

road monitoring program."[127]

The National Association of Clean Air Agencies noted a number of complicated implementation issues that are raised by the proposed near roadway network and nonattainment area designations. NAACA pointed out:

> There is a need to think creatively about challenging aspects of the network, including the general issue of how to address nonattainment based on a near roadway monitor reading. The Clean Air Act requires states to address and reduce emissions in order to achieve attainment, and the focus of the emission control effort is within a nonattainment area, typically a CBSA or county. In a near roadway, ultra-microscale environment, however, one issue that arises is what control measures – beyond federally required motor vehicle fleet standards that are beyond our control – are appropriate or effective for state and local agencies to take.[128]

Finally, individual state and local agencies also raised implementation issues during these rulemakings. For example, Illinois noted:

> By proposing to establish a micro-scale near-roadway monitoring network to quantify air quality impacts near congested urban highways, states may be required to seek reductions from on-road mobile sources that states don't have the authority to regulate.[129]

New Mexico strongly felt that it would be premature and resource intensive to require such a monitoring network at this time. The state indicated:

> Further research is needed regarding near-road monitoring and how this data would be used for nonattainment, attainment, and maintenance determinations. Without this research, it will be difficult or impossible for states to develop control strategies for a nonattainment or maintenance area if the area is designated based solely on near-road monitoring data.[130]

The Regional Air Pollution Control Agency for Dayton also had serious reservations, raising questions such as what will a nonattainment designation mean? Is the real solution to the problem proper implementation of the federal motor vehicle emissions control program? Is a nonattainment designation necessary? The agency urged EPA to seriously consider alternatives to the traditional nonattainment program to properly

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[127] Ibid., at page 29.
[128] National Association of Clean Air Agencies April 12, 2011comments to Docket No. EPA-HQ-OAR-2008-0015, at page 3.
[129] Illinois Environmental Protection Agency, September 14, 2009 comments to Docket ID Number EPA-HQ-OAR-2006-0922, at page 4.
[130] State of New Mexico Environment Department, April 15, 2011comments to Docket No. EPA-HQ-OAR-2008-0015

address this pollutant and its health effects.[131]

Other states such as Indiana, Virginia, North Carolina, Texas, Michigan, and South Dakota raised similar concerns.[132] Several groups raised concerns that any exceedances could be caused by exceptional events. Michigan indicated that use of near roadway measurements for attainment designations is problematic and that special consideration should be given as to what constitutes an exceptional event.[133]

Since near-road monitors will be monitoring hotspots, rather than background concentration levels, the American Association of State Highway and Transportation Officials (AASHTO) recommended that:

> EPA revise its Exceptional Events Rule (40 CFR 50.14) to specifically recognize unavoidable construction activities as a potential exceptional event. These activities are short term in duration, the areas affected are limited in size, and once completed they are unlikely to recur frequently at a particular location. We also recommend that the rule specifically recognize nonrecurring traffic congestion caused by accidents and/or natural events as exceptional events since they occur infrequently.[134]

b. EPA Response to these Concerns

In response to these various public inputs, the only indication EPA has given is that it has discretion to determine the extent of the nonattainment area based on relevant information and, if problems are found, guidance will be forthcoming.

For example, in the Federal Register (FR) notice evaluating nonattainment with the new 1-hour NO_2 standard, EPA indicated:

> Section 107(d)(1)(A)(i) of the CAA defines a nonattainment area as any area that does not meet an ambient air quality standard or that is contributing to ambient air quality in a nearby area that does not meet the standard. If an area meets either prong of this

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[131] Regional Air Pollution Control Agency of Dayton, Ohio September 14, 2009 comments to Docket ID Number EPA-HQ-OAR-2006-0922.

[132] State of Michigan Department of Environmental Quality, September 14, 2009 comment to Docket ID Number EPA-HQ-OAR-2006-0922; South Dakota Department of Environment and Natural Resources, September 11, 2009 comments to Docket ID Number EPA-HQ-OAR-2006-0922; Texas Commission on Environmental Quality, September 11, 2009 comments to Docket ID Number EPA-HQ-OAR-2006-0922; Virginia Department of Transportation September 14. 2009 comments to Docket ID Number EPA-HQ-OAR-2006-0922; Indiana Department of Environmental Management, March 24, 2011 comments to Docket No. EPA-HQ-OAR-2008-0015; North Carolina Department of Environment and Natural Resources, April 12, 2011 comments to Docket No. EPA-HQ-OAR-2008-0015.

[133] Michigan comments, supra note 132, at page 3.

[134] American Association of State Highway and Transportation Officials, March 30, 2011 comments to Docket No. EPA-HQ-OAR-2008-0015, at page 3.

> definition, then the EPA is obligated to designate the area as "nonattainment." Section 107(d)(1)(A)(iii) provides that any area that the EPA cannot designate on the basis of available information as meeting or not meeting the standards should be designated as "unclassifiable." The EPA believes that section 107(d) provides the agency with discretion to determine how best to interpret the terms in the definition of a nonattainment area (e.g., "contributes to" and "nearby") for a new or revised NAAQS, given considerations such as the nature of a specific pollutant, the types of sources that may contribute to violations, the form of the standards for the pollutant, and other relevant information.[135]

In the same FR notice, EPA designated the entire country as "unclassifiable/attainment" for the 1-hour NO_2 NAAQS to indicate that "the available information does not indicate that the air quality in these areas exceeds the 2010 NAAQS." The existing NO_2 air quality data meets both the 1-hour and annual standards, but with the advent of the near-roadway monitors, EPA has classified the entire country as also "unclassifiable" until the new data becomes available.

The NO_2 Final Rule indicates that if exceedances are measured in the new network:

> EPA will need to determine which sources and activities contribute to a NAAQS violation in each area. Depending on the circumstances in each area this may include sources and activities in areas beyond the area directly surrounding a major roadway. EPA intends to issue nonattainment area boundary guidance after additional information is gathered on the probable contributors to violating near-roadway NO_2 monitors.[136]

and

> The EPA intends to issue guidance on the factors that States should consider when determining nonattainment boundaries after additional information is gathered on the probable contributors to violating near-roadway NO_2 monitors.

In essence, EPA has "kicked the can down the road" and indicated that it will address the ramifications of any exceedances if and when they arise.

c. Relevance of the Data for Human Exposure

In comments on the proposed near-road monitoring rules and in comments on the draft NO_2 monitoring guidance, the Alliance stressed the need to measure near roadways at sites that represent population exposures. For example, the Alliance commented:

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[135] 77 Federal Register 9532, February 17, 2012, at page 9534.
[136] NO_2 Final Rule, supra note 2, at page 6521

> Any near-roadway monitoring should be carried out in locations where there is population exposure. Sites in the right-of-way of restricted access freeways should not be allowed since EPA regulations[137] define ambient air as "that portion of the atmosphere, external to buildings, to which the general public has access." Within that general definition, ambient air quality has become known to mean air quality as measured at a location that is representative of exposures to the general public. While the TAD refers to population exposure as a secondary consideration, it makes no sense to trigger non-attainment using measurements from a location where there is no exposure to the general public.[138]

The Alliance stressed that near-roadway monitors be sited in locations where there is actual human exposure to the ambient air for time periods that match the time period in the definition/form of the respective NAAQS, either 1-hour NO_2, 1-hour or 8-hour CO, 24-hour $PM_{2.5}$, or annual average NO_2 and $PM_{2.5}$. Several CASAC Panelists and State Agencies raise the same issue and concern. For example, comments by the New York Department of Health indicated that the focus of the monitoring network should not necessarily be to measure maximum ambient levels of NO_2, but to measure levels that are relevant to human exposure (i.e., in areas where people are likely to be exposed).[139] Texas indicated that the proposed monitoring "does not appear to account for the differences between maximum exposure and maximum ambient concentration" and that "Another serious concern is that the probe siting could be required to be placed in the highway right-of-way."[140] Illinois officials indicated:

> We are extremely troubled by the micro-scale of representativeness to be achieved by the 50 meters or less probe location from the roadway and how that data would relate or be extrapolated to represent population exposure in the adjacent neighborhoods.[141]

North Carolina officials indicated that the proposal would focus monitoring to sites along interstate highways with high speeds where there would be safety concerns but limited human exposure compared to other potential monitor locations.[142]

The CASAC Monitoring Panel, which was asked a series of questions concerning monitoring for NO_2, for CO, and for multiple pollutants near roadways, recognized the

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[137] 40 CFR 50.1.

[138] Alliance of Automobile Manufacturers *Comments on the U. S. EPA August 2011 Draft Near-Road NO_2 Technical Assistance Document (TAD)*, Prepared by J. M. Heuss and G. T. Wolff, January 18, 2012, at page 2.

[139] New York Department of Health September 11, 2009 comments to Docket No. EPA-HQ-OAR-2006-0922, at page 5.

[140] Texas Commission on Environmental Quality, April 12, 2011comments to Docket No. EPA-HQ-OAR-2008-0015, at page 1

[141] Illinois comments, supra note 129, at page 2.

[142] North Carolina comments, supra note 132, at pages 2-3.

importance of considering the exposure of human populations in the design of the network. In discussing the intended focus on NAAQS compliance, CASAC stressed the importance of exposure in the overall balance of siting considerations.[143]

A number of CASAC panelists stressed the importance of monitoring at locations that were relevant to people's exposures. One panelist indicated "Ambient monitoring is concerned with the current exposure to the population from sources of pollutants."[144] Another indicated "The purpose of near-road monitoring is to protect the health of residents living near roadways."[145] This panelist recommended that the monitoring take place in communities where there are residents living within the 50-m corridor and "In a particular CBSA, if there are no residents living within the 50-m corridor, near-road monitoring should be exempted." One panelist asked the question "Shouldn't proximity to where people live be a more important consideration" than the factors listed by the Agency.[146] Another indicated that high concentration locations may be the preferred locations for some CBSAs particularly if they are also significant for population exposure.[147] Referring to the plans for NO_2 and CO monitoring, a panelist indicated "For both pollutants, I think the objective should be to characterize near-road population exposures to mix of traffic-related emissions, and not just to witch-hunt for the worst-case locations of maximum single-pollutant concentrations."[148] Finally, a panelist pointed out "…that large fractions of the population spend time within a 5 or so meters of congested urban streets, but population proximity to the edges of high-speed interstates with maximum AADTs[149] is typically more distant.[150]

d. EPA Response to Comments Concerning Population Exposures

In the NO_2 Final Rule, EPA responded to comments that population exposure should be a primary factor in the near-roadway site selection noting:

> EPA notes that the intent of the revised primary NO_2 NAAQS is to protect against the maximum allowable NO_2 concentration anywhere in an area, which includes ambient air on and around roads. This would limit exposures to peak NO_2 concentrations, including those due to mobile source emissions, across locations (including those locations where population exposure near roads is greatest) in a given CBSA or area, with a relatively high degree of confidence. … If EPA were to allow population, population density, or another population weighted metric to be a primary factor in the decision on where required near-road NO_2 monitors are to be located, it is possible that the required near-road monitors

[143] Russell and Samet, supra note 124, at page xiv.
[144] Ibid., at page 54.
[145] Ibid., at page 90.
[146] Ibid., at page 31.
[147] Ibid., at page 55.
[148] Ibid., at page 76.
[149] AADT = annual average daily traffic.
[150] Ibid., at page 73.

> in a CBSA would not be located at a site of expected maximum hourly near-road NO_2 concentration.[151]

Further, EPA indicated:

> We are finalizing the near-road NO_2 monitor siting criteria, as proposed, where (1) required near-road NO_2 monitor probes shall be as near as practicable to the outside nearest edge of the traffic lanes of the target road segment; but shall not be located at a distance greater than 50 meters, in the horizontal, from the outside nearest edge of the traffic lanes of the target road segment,[152]

and,

> EPA strongly encourages States to place near-road sites, or at least monitor probes, as close as safely possible to target roads to increase the probability of measuring the peak NO_2 concentrations that occur in the near-road environment, again noting that Baldauf et al. (2009) indicate that monitor probes would ideally be situated between 10 and 20 meters from the nearest traffic lane for near-road pollutant monitoring.[153]

While the NO_2 Final Rule and the monitoring TAD refer to Baldauf et al. (2009)[154] to support its guidance to place monitor probes within 20 meters of the roadway, this is a misreading and misinterpretation of what Baldauf et al. recommend. The TAD indicates:

> Baldauf et al. (2009) note that a distance of 10 to 20 meters should be considered for near-roadway monitoring, and as such, the EPA strongly encourages state and local agencies to try to place near-road NO_2 monitor probes within 20 meters from target road segments when possible.[155]

In actuality, Baldauf et al. recommend multiple monitoring sites with the highest density within the first 100 meters. They then go on to indicate "If resource limitations prevent the establishment of multiple monitoring sites" which is the case under consideration for the new near-roadway network, "a distance most representative of population exposures may be more appropriate." Thus, Baldauf et al. actually recommend population exposure as the most appropriate factor in choosing the distance from the road.

Baldauf et al. go on to indicate:

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[151] NO_2 Final Rule, supra note 2, at page 6512.
[152] Ibid., at page 6515.
[153] Ibid., at page 6514.
[154] Baldauf, R; Watkins, N; Heist, D; Bailey, C; Rowley, P; Shores, R. (2009) Near-road air quality monitoring: Factors affecting network design and interpretation of data, Air Qual. Atmos. Health, 2, 1–9.
[155] EPA (2012), supra note 106, at page 45.

> A minimum distance of 10–20 m from the road should be considered in order to minimize the influence of vehicle-induced turbulence on the concentration variability of pollutant measurements.

EPA misinterprets the intent of this statement. Since vehicles produce mechanical turbulence that impacts dispersion, all Baldauf et al. are indicating is that if the goal is to minimize that influence, then the monitoring should be at least 10 to 20 meters away from the road. EPA turns that around to suggest that Baldauf et al. recommend that States monitor within 20 meters of the road. If anything, based on Baldauf et al., the EPA recommendation should be to measure at least 20 meters away from the road. In reality, there is no reason to minimize or even consider the influence of mechanical turbulence in choosing monitoring locations to protect public health. The human exposures are whatever they are and the appropriate distance should be chosen based on that most representative of population exposure in the given situation.

In the CO Final Rule, EPA reiterated that the intent is to measure peak ambient concentrations in the near-road environment.[156] With regard to the comments asserting that near-road monitoring would result in monitoring areas where there is little or no population exposure, EPA referred to the facts that on-road mobile sources are ubiquitous in urban areas and are a dominant component of the national CO emissions inventory, that a substantial portion of the population lives near major roads, and that the average citizen spends 70 minutes traveling per day.[157] While these facts are true, they do not address the fact that finding the peak concentration at a microscale site within the right-of-way next to the most heavily traveled expressway in an urban area is not indicative of the maximum CO or NO_2 exposure of either near-by residents or commuters.

In the $PM_{2.5}$ Final Rule, EPA was faced with an interesting challenge since the existing $PM_{2.5}$ monitoring regulations included a requirement that allowed for micro-scale $PM_{2.5}$ sites that are population-oriented when they represent many such locations throughout a metropolitan area.[158] The EPA definition was provided in 40 CFR 58.1:

> Population-oriented monitoring (or sites) means residential areas, commercial areas, recreational areas, industrial areas where workers from more than one company are located, and other areas where a substantial number of people may spend a significant fraction of their day.

In the Final Rule, EPA revoked the population-oriented requirement as a condition of comparability with the PM NAAQS, but included a requirement that micro-scale sites must be representative of area-wide air quality to be comparable with the annual standard. The decision as to the whether the data from a specific micro-scale site will be compared to both $PM_{2.5}$ standards or only the 24-hour standard will be made on a case-

[156] 76 Federal Register 54314, August 31, 2011.
[157] Ibid.
[158] Federal Register 3091, January 15, 2013.

by-case basis in the context of the review of the state agency's annual monitoring plan submission to EPA.[159]

Although the Final Rule states:

> Ideally, near-road sites would be located at the elevation and distance from the road where maximum $PM_{2.5}$ levels occur in this environment, representing locations where populations are exposed; for example, in apartments and other housing; schools located along major roadways; industrial parks where workers exposed; and in recreational areas such as greenways, bikeways, and other park facilities that are often developed along roads.[160]

Whether the final selected sites represent population exposures or not will depend on how the state and local agencies apply EPA's site selection guidance.

That guidance is provided in the final TAD. The TAD recommends that individual road segments be ranked by annual average daily traffic (AADT) corrected to weight heavy duty diesel traffic counts as a factor 10 higher in emissions compared to light duty vehicles. After candidate segments are evaluated for traffic counts, fleet mix and potential congestion, individual segments are evaluated for a range of other site conditions and factors. The TAD indicates "Controlled and limited access segments should not be avoided for monitoring site consideration; however, the evaluation of these segments should consider how potential monitoring sites will be accessed and maintained."[161] As noted above, EPA strongly encourages state and local agencies to place near-road NO_2 monitor probes within 20 meters from target road segments when possible. The TAD also indicates "If the prospective location is within the ROW of an existing road, state and local air agencies will need to engage their respective transportation agencies to gain access to the air rights of that property,"[162] and provides detailed guidance on how to arrange for sites within the ROW.

Once several candidate sites that are feasible have been identified, the TAD addresses the consideration of population exposure, noting:

> where a state or local air monitoring agency identifies multiple acceptable candidate sites where maximum hourly NO_{22} concentrations are expected to occur, the monitoring agency shall consider the potential for population exposure in the criteria utilized to select the final site location. Therefore, when considering all the available information (particularly AADT, fleet mix, congestion patterns, roadway design, terrain, meteorology, and siting criteria) to determine which candidate locations are

[159] Ibid., at pages 3240 and 3251.
[160] Ibid., at page 3239.
[161] TAD, supra note 106, at page 56
[162] Ibid., at page 62

> suitable for a required near-road NO_{22} station, population exposure should subsequently be considered. Specifically, among a pool of otherwise similar candidate near-road sites, the site that may represent a higher population exposure, or exposures to susceptible or vulnerable populations, should be given increased consideration.[163]

While this may seem like an adequate consideration of population exposure, the guidance refers to population in the vicinity of the site; it does not require or suggest that there be actual human exposure at the distance from the road chosen for the monitor probe. Thus, the locations of the near-road monitors sited according to EPA guidance will be very close to the edge of the most heavily travelled segments of the most heavily travelled expressways. As such, this approaches peak source monitoring rather than monitoring locations that represent population exposures. The distinction between monitoring as near as practicable to the nearest lane even if it is within the ROW rather than at an adjacent property where people are actually exposed is important since the roadway contribution of NO_2 is reduced by 50% within the first 50 meters of a highway due to mixing and dispersion and essentially reaches zero by 400 m in most cases.

[163] Ibid., at page 71.

D. Other Health Endpoints

In Sections A and B, we examined the data for the health endpoints that the ISA claims are the strongest and most consistent. In this Section, we provide additional input regarding the many other endpoints discussed in the ISA. Rather than critique each in detail, it is appropriate to note that the pattern in the data is mixed and inconsistent for each endpoint. In the following, we discuss the major reasons for the mixed pattern and provide additional perspective on the interpretation of the results for some of the endpoints.

1. Limitations of Observational Studies

The stochastic variability demonstrated in multi-city studies as well as in Figure 1 for an individual city is one of the major reasons for the inconsistent pattern. Model selection uncertainty, as discussed above, is a second major reason for the mixed and inconsistent results. There is an important example of model selection uncertainty discussed in the 2006 Ozone Criteria Document.[164] School absences were examined in a study of 1,933 fourth grade students from 12 southern California communities participating in the Children's Health Study. The association between school absences and air pollution from the Children's Health Study was first reported by Gilliland et al. (2001).[165] Subsequently, Berhane and Thomas (2002)[166] and Rondeau et al. (2005)[167] analyzed the same database using different statistical approaches and assumptions and came to very different conclusions concerning the presence and magnitude of an effect of ozone and other pollutants on school absences. This is an indication that the choice of the statistical approach used to analyze the data can change the findings dramatically.

Publication bias is another major issue in interpreting the epidemiology. The commentary by Goodman concerning meta-analyses is particularly insightful.[168] He notes a factor of at least three difference between the results of ozone meta-analyses and the NMMAPS data that is not affected by publication bias. Goodman concludes the implications of an EPA-sponsored exercise of funding three separate meta-analyses "go far beyond the question of the ozone mortality effect." He cautions "depending on published single-estimate, single-site analyses are an invitation to bias." He notes "the most plausible explanation is the one suggested by the authors, that investigators tend to

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[164] U. S. EPA. (2006) Air Quality Criteria for Ozone and Related Photochemical Oxidants Volume I. EPA 600/R-05/004aF, at page 7-58 to 7-60.

[165] Gilliland, FD; Berhane, K; Rappaport, EB; Thomas, DC; Avol, E; Gauderman, WJ; London, SJ; Margolis, HG; McConnell, R; Islam, KT; Peters, JM. (2001). The effects of ambient air pollution on school absenteeism due to respiratory illnesses. Epidemiology 12: 43-54.

[166] Berhane, K; Thomas, DC. (2002) A two-stage model for multiple time series data of counts. Biostatistics 3: 21-32.

[167] Rondeau, V; Berhane, K; Thomas, DC. (2005) A three-level model for binary time-series data: the effects of air pollution on school absences in the southern California Children's Health Study. Stat. Med. 24: 1103-1115.

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

report, if not believe, the analysis that produces the strongest signal; and in each single-site analysis, there are innumerable model choices that affect the estimated strength of that signal." A separate review by a panel of ten knowledgeable scientists[169] concluded "Taken together, the meta-analyses provide evidence of a disturbingly large publication bias and model selection bias."

There are important implications from the findings concerning stochastic variability, model selection uncertainty, and publication bias with regard to the EPA causality framework. The framework recommends a suggestive relationship if "at least one high-quality epidemiologic study shows an association with a given health outcome although inconsistencies remain across other studies that are or are not of comparable quality."[170] Thus, it only takes one observational study that EPA considers of high-quality to implicate a pollutant in causing health effects. However, the true uncertainty around any given observational association is much larger than the statistical uncertainty reported in the study and plotted in the various Figures in the ISA. This results in a false appearance of consistency in the ISA figures and leads the Agency to characterize the data as suggestive of causality for every health endpoint evaluated.

2. Factors to Consider in the Integrative Synthesis

The current integrative synthesis in the ISA is less than rigorous. It marshals the evidence for NO_2 health effects, but it does not present or discuss the substantial evidence against NO_2 causing the associations highlighted in the ISA. The following factors should be discussed in the ISA and weighed in the integrative synthesis.

The cardiovascular observational studies, as with the respiratory observational studies, evaluated many pollutants and do not implicate NO_2 over other pollutants. Both the cardiovascular and the respiratory studies implicate many pollutants but also demonstrate an inconsistent pattern of results, making attribution of effects to NO_2 or any other pollutant problematic.

Although NO_2, like ozone, is an oxidizing and irritant gas, the controlled human studies continue to show that it is distinctly less toxic than ozone. Although both gases demonstrate similar types of responses in controlled tests, the doses required to cause those effects are much higher for NO_2. Since the mean and peak ambient concentrations of NO_2 in urban areas are significantly below the mean and peak ambient ozone concentrations in urban, suburban, and rural areas, it is highly unlikely that NO_2 is a causal factor for associations reported in observational studies.

Both NO and NO_2 are present endogenously in human cells. There are two aspects of this that should be considered in the integrative synthesis. The first relates to the beneficial effects of NO, nitrate, and nitrite. The ISA acknowledges that NO is used in

[169] Report of a Working Conference. (2007) Critical Considerations in Evaluating Scientific Evidence of Health Effects of Ambient Ozone. Held in Rochester, New York.
[170] ISA, supra note 1, at page l.

therapeutic applications typically with concentrations of 10,000 to 80,000 ppb,[171] where NO acts as a pulmonary vasodilator. Although every effort is made to remove NO_2 from the source of NO and to limit the exposure to oxygen as NO is administered, it is impossible to keep NO_2 from forming in the respiratory system as NO is administered due to the thermal oxidation of NO with O_2 which is a well-established third order reaction. Thus, there is an unknown dosage of NO_2 that is always accompanying the therapeutic doses of NO.

There is also evidence that nitrate and nitrite which are major products from the absorption of NO_2 are beneficial. Lundberg et al. (2011) point out "A theory is now emerging suggesting nitrate as an active component in vegetables contributing to the beneficial health effects of this food group, including protection against cardiovascular disease and type-2 diabetes."[172]

The second aspect of endogenous NO is that exhaled NO, eNO, is now measured as a biomarker, with the thought that it may be a sensitive biomarker of inflammation. Anderson et al. (2011)[173] point out that NO is an important endogenous regulating molecule with dual roles of enhancing and suppressing inflammation. They also point out that it is currently unclear whether NO is primarily a positive effector of inflammation, whether it is primarily generated to attenuate the inflammatory response in asthma, or whether its actions are determined by the balance of its pro- and anti-inflammatory effects. Thus, it is not clear what a measure of eNO means with regard to health effects. While it may be a sensitive marker of inflammation or represent the early activation of the body's defense mechanisms, it may also just be a signaling molecule involved in cellular homeostasis. Thus, it is not clear what the percent changes in eNO displayed in Figure 4-2 mean for human health.

While there are large differences between the distributions of eNO in asthmatics compared to non-asthmatics, interpreting the small differences shown in Figure 4-2 is problematic. Taylor et al. (2006)[174] discuss the difference between a statistically significant change in eNO and a clinically significant change in eNO. They recommend that an increase of 60 % or an eNO measurement of 45 ppb or higher should be used to diagnose significant eosinophilic airway inflammation. In addition, Berlyne et al. (2000)[175] investigated the relationships among eNO and eosinophilic airway inflammation as measured by induced sputum and physiologic parameters of disease severity. They found weak correlations and concluded that eNO in many cases is likely to have limited utility as a surrogate clinical measurement for either the presence or

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[171] Ibid., at page 3-21.
[172] Lundberg, JO; Carlstro, M; Larsen, FJ; Weitzberg, E. (2011) Roles of dietary inorganic nitrate in cardiovascular health and disease. Cardiovascular Research 89: 525–532.
[173] Anderson, JT; Zeng, M; Deshane, JS. (2011) Elevated levels of NO are localized to distal airways in asthma. Free Radic Biol Med 50: 1679-1688.
[174] Taylor, DR; Pijnenburg, WM; Smith, AD; De Jongste, JC.(2006) Exhaled nitric oxide measurements: clinical application and Interpretation. Thorax 61: 817–827.
[175] Berlyne, GS; Parameswaran, K; Kamada, D; Efthimiadis, A; Hargreave, FE. (2000) A comparison of exhaled nitric oxide and induced sputum as markers of airway inflammation J Allergy Clin Immunol 106: 638-44.

severity of eosinophilic airway inflammation. Ferrante et al. (2013)[176] also evaluated the utility of eNO as a marker of inflammation and point out several limitations, particularly the large variation in eNO levels between individuals, which may reflect the natural heterogeneity in baseline epithelial nitric oxide synthase activity.

Importantly, in addition to the question of what level of eNO or change in eNO is clinically important, the various studies of eNO potentially implicate many different pollutants. For example, in the Berhane et al. (2011)[177] study, eNO was significantly associated with three other pollutants but not with NO_2. The fact that the distributions of changes in eNO for asthmatics and non-asthmatics are similar in Figure 4-2 argues against using these data as evidence of air pollution-related adverse health effects, much less NO_2 health effects.

[176] Ferrante, G; Malizia, V; Antona, R; Corsello, G; La Grutta, S. (2013) The value of FeNO measurement in childhood asthma: uncertainties and perspectives. Multidisciplinary Respiratory Medicine 8: 50-57.
[177] Berhane, K; Zhang, Y; Linn, WS; Rappaport, EB; Bastain, TM; Salam, MT; Islam, T; Lurmann, F; Gilliland, FD. (2011). The effect of ambient air pollution on exhaled nitric oxide in the Children's Health Study. Eur Respir J 37: 1029-1036.