

# **Comments on March 2008 Second External Review Draft of “Integrated Science Assessment of Oxides of Nitrogen –Health Criteria”**

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## **Executive Summary**

The draft Integrated Science Assessment (ISA) and its technical annexes review the state of science concerning ambient oxides of nitrogen and their health effects and provide the data that will inform the ultimate choices for the indicator, form, and level of the air quality standard to protect the public health. Although all the oxides of nitrogen and their gaseous reaction products are considered in the ISA, nitrogen dioxide (NO<sub>2</sub>) is properly acknowledged as the most toxic and the only compound for which there is an extensive data base on health effects.

We appreciate the agency’s efforts to continually enhance the review process and note the introduction of the Integrated Science Assessment as a replacement for the Criteria Document. We note a number of changes and improvements in the second draft ISA, particularly the introduction and application of a framework for making causal determinations. However, we believe the following areas can be improved through the continued attention of staff and CASAC:

- First, the ISA still focuses on epidemiological studies and needs to give more attention to controlled studies that can establish cause and effect. Since NO<sub>2</sub> occurs in conjunction with other common air pollutants, issues of confounding and surrogacy plague the interpretation of the epidemiological literature. Even in the case of indoor NO<sub>2</sub> sources, such as gas stoves or unvented appliances, it is now known that other gases and particles that are potential confounders are also emitted by these sources. Furthermore, a recent detailed study of asthmatics in Fresno, California found that both central monitoring site NO<sub>2</sub> and personal exposures to NO<sub>2</sub> were associated with concentrations of several bioaerosols - endotoxin, *Cladosporium* mold, and agricultural fungi. Thus, NO<sub>2</sub> is not only a marker for combustion, but also for bioaerosol components.
- Second, the ISA must consider dose plausibility when integrating the results of controlled studies with the results of observational studies. Biological plausibility involves considerations of both the kinds of effects a pollutant can cause as well as the dose that is required to cause the effects. All the effects considered are non-

specific, and questions of NO<sub>2</sub> acting as a surrogate are prevalent throughout the literature. Therefore, the ISA must address the plausibility for NO<sub>2</sub> along with the plausibility for other anthropogenic and natural materials causing various potential health effects. For example, the ISA acknowledges that while NO<sub>2</sub> and several other pollutants are correlated with reduced lung function growth in children in the Children's Health Study in Los Angeles, ozone is not. Since ozone and NO<sub>2</sub> have similar mechanisms of action but ozone is a much stronger oxidant and shows toxicity at lower levels than NO<sub>2</sub>, it is extremely unlikely that NO<sub>2</sub> is causing the observed lung function growth associations.

- Third, the ISA still focuses on single pollutant model results rather than evaluating the results in the context of the full suite of air pollutants. This can lead to double-counting or triple-counting of health effects as different pollutants are reviewed. By including only NO<sub>2</sub> associations from selected literature and not putting them into context with the full range of results in the individual studies or the literature in general, the ISA gives a false impression of consistency for this data. Many of the studies cited evaluated a suite of pollutants and report results for many more outcomes. In most cases, the authors implicate air pollution in general rather than NO<sub>2</sub> in particular as being associated with a given health endpoint.
- Fourth, to ensure scientific credibility the ISA must further address the issues of publication bias, model selection uncertainty, and confounding that hinder the interpretation of air pollution epidemiological studies. CASAC has pointed out, where systematic analyses have been carried out, as in NMMMAPS, Stieb et al. 2002, 2003 and Ito 2003, similar patterns of associations are reported for many pollutants. While there are many more observational studies than available in the prior review, there is an implausibly wide range of results from positive to negative in systematic analyses. The ISA needs to acknowledge and consider the wide range of associations with regard to both biological plausibility and the limitations on the use of time series studies to set ambient standards. One implication of the variability documented in the body of these comments is that it is not surprising to find some positive NO<sub>2</sub> associations in the literature for any health endpoint that is evaluated, even for endpoints where there is no underlying effect. This raises a serious question about the approach taken in the ISA of documenting any and all NO<sub>2</sub> associations in the observational literature. Such an approach is insufficient to establish consistency or coherence. A more holistic and rigorous evaluation of the observational literature is needed if double- and triple-counting of health effects is to be avoided.

As a result of these limitations, the draft ISA conclusions overstate the evidence for NO<sub>2</sub> respiratory health effects and the certainty of these effects. Human clinical studies, when reproducible, represent the best source of information on NO<sub>2</sub> effects. The interpretation of the clinical studies has not changed significantly since the previous review. The only substantive new data is the addition of several studies reporting increased airways responsiveness to allergen-induced inflammation and allergen-induced bronchoconstriction at 0.26 ppm. These data, however, do not materially change the understanding of risk assumed in the previous review.

Finally, in order to aid the reader in judging the adequacy of the current standard, the ISA should clarify the extent of new information since the previous review and provide additional information on the levels and trends of ambient NO<sub>2</sub> concentrations.

## **Introduction**

The March 2008 second external review draft of “Integrated Science Assessment of Oxides of Nitrogen –Health Criteria” (ISA)<sup>1</sup> and its draft Technical Annexes<sup>2</sup> are the replacement for the traditional Criteria Document. The ISA does not include the Agency staff’s recommendations and conclusions concerning the standards, but it provides the data and scientific rationale that will inform those recommendations. The ISA and its technical annexes give the staff’s evaluation of the relevant data related to health effects and the ultimate choices for the indicator, form, and level of the air quality standard to protect the public health from exposure to ambient oxides of nitrogen. Although all the oxides of nitrogen and their gaseous reaction products are considered in the ISA, nitrogen dioxide (NO<sub>2</sub>) is acknowledged as the most toxic and the only compound for which there is an extensive data base on health effects. AIR, Inc. provided comments<sup>3</sup> on the first external review draft of the oxides of nitrogen ISA.

In the following, we provide both general and specific comments on the second draft ISA, noting areas of improvement from the first draft and areas that need additional work. These comments are offered so that the final ISA accurately reflects the latest scientific knowledge useful in indicating the kind and extent of effects on public health from ambient concentrations of oxides of nitrogen, as required by the Clean Air Act.

## **General Comments**

We support the agency’s efforts to continuously improve the review process and note the introduction of a new process which begins with the Integrated Science Assessment. We share the agency’s view that this assessment will provide the foundation for regulation development and ultimately the final rule. With that mutual goal in mind, our comments focus on several critical areas requiring improvement in the second draft ISA. These improvements are outlined generally below and in greater detail in the “Specific Comments” section. First, we commend the Agency for introducing and applying a rigorous framework for making causal determinations. The framework is introduced and discussed in Section 1.6.

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<sup>1</sup> U. S. Environmental Protection Agency, Integrated Science Assessment for Oxides of Nitrogen –Health Criteria, Second External Review Draft, EPA/600/R-07/093, March 2008.

<sup>2</sup> U. S. Environmental Protection Agency, Annexes for the Integrated Science Assessment for Oxides of Nitrogen –Health Criteria, Second External Review Draft, EPA/600/R-07/093, March 2008

<sup>3</sup> J. M. Heuss, Air Improvement Resource, Inc. Report, Comments on August 2007 First External Review Draft of “Integrated Science Assessment of Oxides of Nitrogen –Health Criteria.” Prepared for the Alliance of Automobile Manufacturers, October 31, 2007.

Section 1.6 clearly indicates the most compelling evidence of a causal relationship comes from controlled human exposure studies.<sup>4</sup> The section also notes that epidemiology studies do not establish cause and effect. Chapter 3 of the draft ISA, where the bulk of the discussion of NO<sub>2</sub> health effects occurs, focuses primarily on epidemiology since most of the new information since the last review comes from epidemiology.<sup>5</sup> Section 1.6 notes that association and causation are not the same. The section goes on to indicate that inferring causation from observational (epidemiologic) associations involves consideration of a range of factors, including the Hill criteria. The framework used in the ISA of judging the overall weight of evidence and putting various categories 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 sound.

However, even though the framework is generally applied throughout the second draft, its application is not as rigorous or complete as it should be. In particular, the way consistency is evaluated in the epidemiology is less than scientifically rigorous or sound. Since NO<sub>2</sub> occurs in conjunction with other common air pollutants, issues of confounding and surrogacy plague the interpretation of the epidemiological literature. Even in the case of studies of indoor NO<sub>2</sub> sources, such as gas stoves or unvented appliances, it is now known that other gases and particles that are potential confounders are also emitted by these sources.<sup>6</sup> Therefore, it is particularly important to fully and carefully consider the results of controlled studies in the ISA.

**The draft ISA sometimes fails to consider dose plausibility when integrating the results of controlled studies with the results of observational studies.**

Biological plausibility involves two considerations - the effects that a pollutant can cause and the pollutant concentrations that can cause the effects. The ISA sometimes ignores dose plausibility in the integration sections. This leaves a misleading impression regarding the plausibility of certain outcomes. All the effects are non-specific, and questions of NO<sub>2</sub> acting as a surrogate are prevalent throughout the literature. Therefore, the ISA must address the plausibility for NO<sub>2</sub> along with plausibility for other anthropogenic and natural materials causing various potential health effects.

**The draft ISA still focuses on single pollutant model results rather than evaluating the epidemiological results in the context of the full suite of air pollutants. This can lead to double-counting or triple-counting of health effects as different pollutants are reviewed.**

Both Chapter AX6 and Chapter 3 include a focus on the single-pollutant NO<sub>2</sub> results and on multi-pollutant analyses that include NO<sub>2</sub>. However, many of the studies evaluated a suite of pollutants and report results for many more outcomes. In most cases, the authors implicate air pollution in general, not specifically NO<sub>2</sub>, as being associated with a given health endpoint.

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<sup>4</sup> ISA at page 1-7.

<sup>5</sup> ISA at page 1-8.

<sup>6</sup> A. Seaton and M. Dennekamp, Thorax, 58, 1012-1015 (2003).

The results for multi-pollutant models are very difficult to evaluate because the results are often mixed or inconsistent and the co-pollutants vary from study to study. There are also methodological issues raised with multi-pollutant models that can lead to misleading results. However, single-pollutant models are known to be biased high.

In the recent PM and ozone reviews, single-pollutant model results were used to estimate the strength and consistency of association. Selected single-pollutant model results were utilized as the baseline for the risk assessments. If selected single-pollutant model results are also used to claim health effects are caused by NO<sub>2</sub>, it will be a clear case of double- or triple-counting. For example, single-pollutant ozone associations were used in the recent ozone review as evidence of a causal relation between ozone and respiratory morbidity<sup>7</sup> and now single-pollutant NO<sub>2</sub> associations are used in a similar manner to implicate a causal relation between NO<sub>2</sub> and the same health endpoints in the ISA.<sup>8</sup> Single-pollutant PM associations were used in the recent PM review as evidence of a causal relation between PM and the same respiratory endpoints.<sup>9</sup>

In another example, the Mortimer et al. 2002<sup>10</sup> study was used in the ozone review as evidence of respiratory effects in asthmatic children and now, in the ISA, is used as evidence of NO<sub>2</sub> effects.<sup>11</sup> The authors of the study implicate summertime air pollution, not NO<sub>2</sub> itself. The ISA also refers to the Schildcrout et al. 2006 study as evidence of respiratory effects of NO<sub>2</sub>. However, the Schildcrout study reported no effect of ozone and that finding was not considered by the Agency in its recent proposed ozone rule. In addition, Schildcrout et al. believe that their findings may represent fine particulate matter effects.

The current practice of selecting specific studies and selecting specific results from those studies results in a false appearance of consistency. If the ISA is to be a scientifically sound basis for policy, a more thorough analysis considering the full suite of pollutants is mandatory.

**The draft ISA still downplays the issues of model selection uncertainty, confounding, and publication bias that hinder the interpretation of air pollution epidemiological studies**

Although the draft acknowledges<sup>12</sup> that the summary of health effects evidence in chapter 3 is vulnerable to the errors of publication bias and multiple testing, and indicates that efforts have been made to reduce the impact of multiple testing errors on the conclusions by giving priority to effects observed at 0- or 1-day lags rather than at longer lags, the balance of Chapter 3 and Chapter 5 do not adequately reflect these concerns. For

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<sup>7</sup> See Figure 1 in proposed ozone rule, 72 Federal Register 37818, July 11, 2007.

<sup>8</sup> ISA at page 5-9, Figure 5.3-1.

<sup>9</sup> See Figure 1 in proposed PM rule, 71 Federal Register 2620, January 17, 2006.

<sup>10</sup> References included in the ISA are referred to by author and date in these comments.

<sup>11</sup> ISA at 3-23.

<sup>12</sup> ISA at page 5-2.

example, Figure 5.3-1 utilizes data from single-pollutant models from a wide range of different lags.

In interpreting the epidemiological evidence, EPA downplays major new findings concerning uncertainty due to model selection issues. Model selection uncertainty relates to confounding of air pollutant associations by temporal trends, weather and co-pollutants. In the ozone review, EPA acknowledged that the uncertainties in the estimates of pollutant effects are understated by consideration of the statistical uncertainty of the fitted model alone. Much more uncertainty arises from the lack of information regarding the choice of appropriate models for adjusting confounding by other covariates, and the choice of appropriate lag structures. As 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 can dominate their results. Because the possible mechanisms of action and their latencies are uncertain, the biologically correct models are unknown. This model selection problem is exacerbated by the common practice of screening multiple analyses and then selectively reporting only a few important results.<sup>13</sup>

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

From a statistical point of view, the common epidemiological practice of choosing variables (including lagged variables, co-pollutants, etc.) that maximize the resulting effect estimates is a dangerous approach to model selection, particularly when the effect estimates are close to 0 (i.e., RR close to 1).<sup>14</sup>

Smith et al. note that Lumley and Sheppard (2000)<sup>15</sup> showed that the effect of choosing lags in this fashion has a bias which is of the same order of magnitude as the relative risk being estimated.

The revised analyses necessitated by the problems with the commonly used software for time-series analyses clearly show that methods used for controlling temporal trends and weather can profoundly affect the results. To make matters worse, there appears to be no objective statistical test to determine whether these factors have been adequately

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<sup>13</sup> T. Lumley and L. Sheppard, "Time series analyses of air pollution and health: straining at gnats and swallowing camels?" *Epidemiology*, 14, 13-14, 2003.

<sup>14</sup> R. Smith, P. Guttorp, L. Sheppard, T. Lumley, and N. Ishikawa, "Comments on the Criteria Document for Particulate Matter Air Pollution," Northwest Research Center for Statistics and the Environment Technical Report Series No. 66, July 2001.

<sup>15</sup> T. Lumley and L. Sheppard, "Assessing seasonal confounding and model selection bias in air pollution epidemiology using positive and negative control analyses," *Environmetrics*, 11, 705-717 (2000).

controlled. The HEI Expert Panel<sup>16</sup> for the re-analysis states, “Ritov and Bickel (1990)<sup>17</sup> 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.” The expert panel concluded 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”. In other words, it is impossible to adjust temporal trends without accurate information from external sources regarding the appropriate degrees of freedom to use. Such information simply does not exist.

With regard to uncertainty due to model selection, the Koop and Tole 2004<sup>18</sup> conclude:

Point estimates of the effect of numerous air pollutants all tend to be positive, albeit small. However, when model uncertainty is accounted for in the analysis, measures of uncertainty associated with these point estimates became very large. Indeed they became so large that the hypothesis that air pollution has no effect on mortality is not implausible. On the basis of these results, we recommend against the use of point estimates from time-series data to set regulatory standards for air pollution exposure.

Publication bias is another major issue in interpreting the epidemiology. The commentary by Goodman concerning meta-analyses is particularly insightful.<sup>19</sup> He notes a factor of at least three differences 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 that “depending on published single-estimate, single-site analyses are an invitation to bias.” He notes that “the most plausible explanation is the one suggested by the authors, that investigators tend to 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<sup>20</sup> concluded that “Taken together, the meta-analyses provide evidence of a disturbingly large publication bias and model selection bias.”

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<sup>16</sup> Health Effects Institute, Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health, Health Effects Institute, Cambridge, Massachusetts, at 267, 269 (2003).

<sup>17</sup> Y. Ritov and P. Bickel, “Achieving information bounds in non- and semi-parametric models,” *Ann. Stat.*, 18, 925-938 (1990).

<sup>18</sup> G. Koop and L. Tole, Measuring the Health Effects of Air Pollution: to What Extent Can We Really Say that People are Dying from Bad Air, *J. of Environmental Economics and Management*, 47, 30-54. (2004).

<sup>19</sup> S. Goodman, “The Methodologic Ozone Effect,” *Epidemiology*, 16, 430-435 (2005).

<sup>20</sup> Report of a Working Conference, Critical Considerations in Evaluating Scientific Evidence of Health Effects of Ambient Ozone, held in Rochester, New York, June 2007.

**The draft ISA omits key information and/or key caveats when summarizing and drawing conclusions.**

The extensive use of tables and short paragraphs summarizing studies is a way to summarize a great deal of information, but key information concerning the interpretation of a single study or a group of studies is often missed. The way the scientific evidence is summarized and reported leaves much to be desired. The Mortimer et al. and Schildcrout et al. example above shows that the ISA ignores issues, interpretations, and caveats that the studies' authors thought were important regarding NO<sub>2</sub> causality. The ISA includes the NO<sub>2</sub> associations in Erba et al. 2005 without mentioning the cautions in Erba and Hyndman 2005 that real time series data have greater complexity than any of the commonly-used existing models allow and that results from single-city studies should be interpreted with caution. This caution is particularly critical if only one method of analysis has been used to demonstrate these associations. Our specific comments include additional examples of cases where the original authors' conclusions with respect to pollutants implicated and/or causality are omitted. These omissions result in an overestimate of the consistency and coherence of the epidemiologic evidence for NO<sub>2</sub> health effects.

**The first draft ISA failed to adequately distinguish the extent of new information since the previous review to aid the reader in judging the adequacy of the current standard. The second draft is improved in this area but still needs additional discussion and clarification.**

A key issue in the review of the nitrogen oxides standard is the extent to which new information materially changes our understanding of the health effects of NO<sub>2</sub>. The ISA should be very specific in this regard. Table 5.3-1 is a good start at the comparison but needs additional discussion and interpretation as noted below in the specific comments.

In addition, the ISA needs to be specific regarding the evidence concerning the impact of long-term average exposures versus acute peaks and/or repeated peaks. In the previous review, the annual average standard was chosen to avoid peak 1-hr ambient concentrations of 0.20 ppm and above.<sup>21</sup> In the current review, a separate short-term standard may be considered. The ISA should be specific on data that will be useful for this analysis.

### **Summary of General Comments**

The major new studies published since the previous review focus on epidemiology using ambient monitoring data. While this is an extensive literature, the pattern of results is often similar for all pollutants and does not implicate NO<sub>2</sub> over any of the common air pollutants. Several reviews of this literature conclude that there is a lack of consistency and/or that single-pollutant model results should not be used to set ambient standards.

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<sup>21</sup> U. S. Environmental Protection Agency, 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.

As a result of the reliance on single-pollutant results and the lack of a holistic analysis of the epidemiology, the conclusions drawn in Chapter 5 overstate the evidence for NO<sub>2</sub> acute respiratory health effects and the certainty with which those effects have been established. In the following sections, the evidence for various categories of potential effects is discussed and specific examples of overstatement are documented.

## Specific Comments

### Acute Respiratory Morbidity

The ISA notes that a large body of epidemiologic studies has been published since the previous Criteria Document relating to respiratory morbidity but that relatively few new clinical and animal toxicologic studies have been published since 1993. Although the discussion of controlled studies is more extensive in the second draft ISA than in the first draft, the second draft ISA still focuses on the epidemiological studies and still gives insufficient attention to controlled studies that can establish cause and effect.

### **The interpretation of the controlled studies of NO<sub>2</sub> exposure is very similar to that in the previous review**

The human and animal evidence for NO<sub>2</sub> health effects was summarized in the 1995 Staff Paper (SP). The evidence regarding susceptibility to respiratory illness, pulmonary function decrements, respiratory symptoms, and increased airway resistance and increased airway responsiveness in asthmatics was discussed in detail in the 1995 Staff Paper.<sup>22</sup> The conclusions regarding impaired host-defense systems and increased risk of susceptibility to infections are similar in the 1995 Staff Paper and current draft ISA. For example, the 1995 SP concluded that the weight of evidence provided by animal toxicology and human clinical studies supports the contention that NO<sub>2</sub> impairs the ability of host defense mechanisms to protect against respiratory infection.<sup>23</sup>

While there is new information on airways inflammation, the effects are found at higher than ambient levels.<sup>24</sup> While the ISA concludes that exposure to NO<sub>2</sub> has been found to enhance the inherent responsiveness of the airways to subsequent nonspecific challenges in human clinical studies, there are inconsistencies in the results and the lowest effect levels are similar to those found in the previous review. The ISA notes that there is now suggestive evidence for increased airways responsiveness to specific allergen challenges following NO<sub>2</sub> exposure. However, the small inflammatory responses to the allergen challenge were not accompanied by any changes in pulmonary function or subjective symptoms and the lowest effect levels are not substantially different from the nonspecific challenge levels.

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<sup>22</sup> See 1995 Staff Paper at pages 15 to 46.

<sup>23</sup> 1995 Staff Paper at page 31.

<sup>24</sup> ISA at page 3-15.

Similar to the previous review, the ISA notes that clinical studies have not provided compelling evidence of NO<sub>2</sub> effects on pulmonary function. The ISA notes that for asthmatics, the effects of NO<sub>2</sub> on pulmonary function have also been inconsistent at exposure concentrations of less than 1-ppm NO<sub>2</sub>. Overall, the ISA concludes, clinical studies have failed to show effects of NO<sub>2</sub> on pulmonary function at exposure concentrations relevant to ambient exposures.<sup>25</sup>

Another line of evidence that argues against substantive human effects from low level NO<sub>2</sub> exposure comes from the therapeutic use of nitric oxide. The ISA notes that nitric oxide, NO, is used in humans therapeutically as a pulmonary vasodilator, and has shown little evidence for adverse respiratory effects.<sup>26</sup> The ISA indicates that nitric oxide is used clinically at concentrations ranging from five ppm to as high as 80 ppm. Although the ISA notes<sup>27</sup> “one of the concerns about NO therapy is the potential for NO to be oxidized to NO<sub>2</sub>, so administration systems are designed to avoid this,” the presence of NO<sub>2</sub> cannot be avoided. It can only be minimized. The thermal oxidation of nitric oxide is a well-known reaction that will form some NO<sub>2</sub> whenever NO is in the presence of oxygen or air.<sup>28</sup> The thermal oxidation is second order in NO so the amount of NO<sub>2</sub> formed at atmospheric levels of NO is small, but during administration of NO in the 5 to 80 ppm range, there will be some NO<sub>2</sub> formed. Tsukahara et al.<sup>29</sup> note that any system for the delivery of inhaled NO must aim at predictable and reproducible levels of NO and as low concentrations of NO<sub>2</sub> as possible. Tsukahara et al. also provide mechanistic information so that one can make reliable predictions about NO<sub>2</sub> formation for any set of NO inhalation therapy conditions.

### **The ISA miss-characterizes the findings in the prior review relative to evidence from epidemiology**

The ISA notes that many of the available epidemiologic studies in the previous review were gas stove exposure studies and concludes “Although there was some evidence suggesting that increased NO<sub>2</sub> exposure was associated with increased respiratory symptoms in children aged 5 to 12 years, the main conclusion was that there was insufficient epidemiologic evidence for an association between short-term exposure and health effects.”<sup>30</sup> This statement is a miss-characterization of the findings from the previous review. The 1995 Staff Paper did not indicate that there was insufficient evidence for an association, rather it notes issues that limit the use of the reported associations in developing a basis for the NAAQS.

With regard to indoor gas stove exposure studies, the 1995 Staff Paper concluded that there was an increased risk of developing respiratory symptoms and disease for children

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<sup>25</sup> ISA at page 3-45.

<sup>26</sup> ISA at page 3-65.

<sup>27</sup> ISA at page 3-66.

<sup>28</sup> W. Glasson and C. Tuesday, “The atmospheric thermal oxidation of nitric oxide, *J. Am. Chem. Soc.*, **85**, page 2901 (1963).

<sup>29</sup> H. Tsukahara, T. Ishada, and M. Mayumi, “Gas-Phase Oxidation of Nitric Oxide: Chemical Kinetics and Rate Constant,” *Nitric Oxide*, **3**, pages 191-198 (1999).

<sup>30</sup> ISA at page 3-4.

5 to 12 years of age based on a meta-analysis.<sup>31</sup> The most significant factor limiting the use of this data in standard-setting was that the indoor exposure patterns are quite different from outdoor exposure patterns so the results could not be extrapolated to ambient exposure conditions.

With regard to outdoor epidemiological studies, the 1995 Staff Paper concluded that outdoor studies do appear to provide limited evidence of an association between ambient exposures to NO<sub>2</sub> and increases in respiratory symptoms and illness.<sup>32</sup> The Staff Paper went on to indicate that the extent to which other factors may have contributed (noting other pollutants, allergens, and weather) tend to limit development of a quantitative relationship. Thus staff concluded that this information should be factored into developing an adequate margin of safety.

By miss-characterizing the extent and interpretation of epidemiologic results in the previous review, the draft ISA sets up a false comparison between the state of knowledge in the previous review and that in the current review.

### **The ISA still overstates the consistency of results for increased Emergency Department (ED) visits and respiratory hospital admissions associated with NO<sub>2</sub>.**

In Chapter 3, the first draft ISA concluded that “overall, there is strong evidence that increased ED visits and hospital admissions for respiratory causes, including asthma and COPD, are associated with ambient concentrations of NO<sub>2</sub>”<sup>33</sup> but also noted that uncertainty remains regarding the role of NO<sub>2</sub> as a surrogate. Chapter 5 of the first draft concluded “the strongest new epidemiological evidence exists for associations with increased ED visits and hospital admissions for respiratory causes, especially asthma and COPD, with ambient concentrations of NO<sub>2</sub>”<sup>34</sup> and described the recent studies on respiratory health effects as strong scientific evidence of “a likely causal relationship.”

The second draft qualifies these conclusions somewhat. In particular, the ISA now restricts the main conclusion to positive associations between ambient NO<sub>2</sub> concentrations and ED visits and hospitalizations for all respiratory diseases and asthma.<sup>35</sup> The ISA notes, however, that the limited evidence does not support a relationship between ED visits and hospitalizations for COPD and ambient NO<sub>2</sub> levels. Further the ISA also acknowledges that there were limited studies providing inconsistent results for many of the respiratory health outcomes other than asthma, making it difficult to draw conclusions about the effects of NO<sub>2</sub> on these diseases.<sup>36</sup> Despite these changes and qualifications, the ISA still overstates the consistency for ED visits and hospital admissions.

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<sup>31</sup> 1995 Staff Paper at pages 26-27.

<sup>32</sup> 1995 Staff Paper at pages 23-24.

<sup>33</sup> First draft ISA at page 3-57.

<sup>34</sup> First draft ISA at page 5-8.

<sup>35</sup> ISA at page 3-58.

<sup>36</sup> ISA at page 3-59.

- **The ED studies EPA relies on implicate air pollution, in general, not NO<sub>2</sub> in particular.**

A careful reading of the studies of ED visits and hospital admissions for respiratory causes demonstrates that the NO<sub>2</sub> associations with asthma and other respiratory endpoints are not as consistent or robust as suggested by the ISA. In fact, none of the studies conclude that NO<sub>2</sub>, per se, is the prime causal factor in exacerbation of asthma as it relates to air pollution. Most implicate a number of air pollutants, but not necessarily the same pollutants. In some cases, NO<sub>2</sub> is robust to consideration of other pollutants in multi-pollutant models but, in others, the NO<sub>2</sub> association is reduced and non-significant. There is much less consistency than the ISA indicates.

While the ISA indicates that there are now more than 50 well-conducted research publications in this area, only selected single-pollutant results are included in the main data presentations in the ISA. However, the ISA also notes that there are additional studies that show negative or null results and still others that are characterized as studies that “could not inform” the associations with NO<sub>2</sub>. The rationale for why some studies are highlighted in the text and included in Figure 5.3-1 and others are relegated to tables in the Annex is not clear.

There are numerous examples of studies that implicate pollutants other than or in addition to NO<sub>2</sub> but this fact is not discussed in the ISA. For example, the NO<sub>2</sub> association from the Tolbert et al. 2000 study listed in Table 5.3-4 is actually an association with 1-hour NO<sub>x</sub>, not NO<sub>2</sub>. More importantly, Tolbert et al. conclude that ozone and PM<sub>10</sub> had positive associations but describe the NO<sub>x</sub> association as near unity and not statistically significant. In the Stieb et al. 1996 study that was listed in the first draft ISA but is now relegated to a study that does not inform, the authors conclude that of all the pollutants considered, only ozone exhibited consistent positive associations. The only reported association that included NO<sub>2</sub> in that study was from a two-pollutant model that included ozone. The Stieb et al. 2000 study and the Peel et al. 2005 study that are listed in Table 5-B reported positive associations with several correlated gaseous and particulate pollutants. The Andersen et al. 2007a and 2007b studies that are included in Table 5.3-4 and Figure 5.3-1 implicate PM and only discuss NO<sub>2</sub> as a proxy for traffic. There are a number of single-pollutant associations from the Atkinson et al. 1999b study that are included in Figure 5.3-1, but the authors evaluated six pollutants and reported that increases in the ambient levels of each of the pollutants studied were associated with short-term increases in hospital admissions for one or more disease groups. The authors concluded that PM<sub>10</sub> and SO<sub>2</sub> were most evidently associated with respiratory disease admissions in children although they noted there were weaker associations with the other pollutants.

By including only NO<sub>2</sub> associations from selected literature and not putting them into context with the full range of results in the individual studies or the literature in general, the ISA gives a false impression of consistency for this data. Although the text of the ISA indicates that the focus should be on lags that make biologic sense, the data used in Chapter 5 to give the impression of consistency reports best lags that vary from day 0 to

day 5, without any discussion of the issue of best lag bias. Similarly, the issues of multiple hypothesis testing and publication bias need to be considered more carefully in the integration sections.

- **Several reviews of this ED literature acknowledge the inconsistencies of the implicated pollutant and health endpoints.**

The Anderson, et al. 1998 study of asthma admissions in London from 1987-1992 concludes that ozone, SO<sub>2</sub>, NO<sub>2</sub>, and particles all had positive associations with asthma admissions in the dataset, but that there was a lack of consistency across age groups and seasons. Anderson et al. also identified 15 other studies of air pollution and daily asthma admissions in the literature with satisfactory methodology. They evaluated the consistency of these studies and report that, in the all-age group, 3 studies did not find significant associations with any of the pollutants assessed and the proportions with significant findings for ozone, SO<sub>2</sub>, NO<sub>2</sub>, and particles were 7/14, 6/12, 2/9, and 7/15, respectively. Similar results were found for adults and children considered separately.

Anderson et al. conclude “Taken overall, it is apparent that the evidence is not coherent as to whether there is an effect of pollution or the responsible pollutant.” They go on to indicate that ozone, SO<sub>2</sub>, and particles were significant in no more than half the studies and that only about a quarter of the studies found significant effects for NO<sub>2</sub>. They list a number of possible reasons for the lack of consistency, including false negatives due to lack of statistical power and false positives due to chance, multiple significance testing, post hoc hypothesis testing, or publication bias. They also note differences in pollution level and mix between cities, the presence of highly correlated pollutants, and that pollutants acting as surrogates for unmeasured pollutants or ambient aeroallergens may be involved. They conclude that, while there is evidence that all of the pollutants may have an effect on asthma, there is a lack of consistency in the specific pollutant responsible.

Atkinson et al. 1999a, also note that a number of studies have examined emergency room admissions, predominantly for asthma, with no consistent results emerging. In their London study, Atkinson et al. reported significant positive associations of asthma emergency room visits with five different pollutants including NO<sub>2</sub>. Atkinson et al. focus on the associations of respiratory complaints with SO<sub>2</sub> and PM10 and acknowledge that it was difficult to identify a single pollutant that might be responsible for the associations they report because of high correlation among the pollutants. They further indicate:

“In evaluating the results of this study, a greater emphasis has been placed on results which are highly significant,  $p < 0.01$ , and consistent in terms of direction, magnitude and statistical significance across the various lags of each pollutant tested. In this way, we have attempted to avoid placing too much importance on isolated significant associations amongst a large number of statistical tests.”

The Yang et al. 2007 study notes that numerous studies investigated the relationship with air pollution and asthma hospital admissions in the past decade but the results are not entirely consistent. Although Yang et al. report an association with NO<sub>2</sub> and other pollutants with admissions, they also note that the ecological design precludes the inference of cause and effect. The Galen et al. 2003 study also notes that studies of the acute effects of air pollutants on asthma morbidity with time-series methods have proved somewhat inconsistent as to the pollutants implicated. Specifically for NO<sub>2</sub>, Galen et al. note studies with positive associations and others with no association.

A major reason for the inconsistent results is demonstrated by the extremely wide variability in individual city associations for hospital admissions and other health endpoints reported in multi-city studies. For example, the Medina-Ramon, et al. 2006<sup>37</sup> study of respiratory hospital admissions in 36 U. S. cities shows that the a 0.010 ppm increase in ozone is associated with anywhere from a 10 % increase to a 10 % decrease in COPD admissions in individual cities in a single-pollutant model. Similarly a 10 µg/m<sup>3</sup> increase in PM10 is also associated with anywhere from a 10 % increase to a 10 % decrease in COPD admissions. For pneumonia admissions, the ranges were almost as wide. While Medina-Ramon et al. did not consider NO<sub>2</sub> in their analyses, there are a number of other multi-city or systematic analyses that show a biologically implausible wide range of positive and negative associations with air pollutants including NO<sub>2</sub> in epidemiological analyses of mortality and morbidity.

One multi-city study that includes NO<sub>2</sub> is the Barnett et al. 2005 study of 7 cities in Australia and New Zealand. Barnett et al. report positive associations of respiratory admissions in children for three measures of PM and two gases (NO<sub>2</sub> and SO<sub>2</sub>) but not with two other gases (ozone and CO). Importantly, Barnett et al report significant heterogeneity between cities in the NO<sub>2</sub> associations. As shown in their Figure 1, associations for the 1-4 age group in four of the seven cities are not statistically significant and the range in individual city associations is – 3 to + 6 % for an interquartile increase in NO<sub>2</sub>. For the 5-14 age group, again four cities are not significant and the range of associations is from about –1 to + 12 %. Also importantly, in only one of the cities is there a positive association for both age groups. In the two other cities with positive associations in the 5-14 age group, the association in the 1-4 age group is actually negative. This pattern is not consistent with a causal relation yet the ISA relies on the combined associations without showing the range of individual city associations or the lack of consistency and coherence between the two age groups.

Although the wide range (both positive and negative) is clearly evident in systematic studies, the authors of the studies either do not mention the range or mention it only in regard to there being heterogeneity in the results. The ISA needs to acknowledge and consider the wide range of associations with regard to both biological plausibility and the

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<sup>37</sup> M. Medina-Ramon, A. Zanobetti, and J. Schwartz, “The effect of ozone and PM-10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: A national multi-city study,” *Am. J. Epidemiol.*, 163, 579-588 (2006).

limitations on the use of time series and other epidemiological studies to set ambient standards.

- **The discussion of respiratory symptoms also overstates the role of NO<sub>2</sub>.**

The ISA uses the results of respiratory symptom studies to claim coherence with the hospital admissions and ED admissions results.<sup>38</sup> However, as noted above, the authors of the Mortimer and Schildcrout multi-city studies do not implicate NO<sub>2</sub>, per se, but summer time air pollution and fine PM, respectively. In addition, the Schwartz et al. 1994 six-city study highly discounts the NO<sub>2</sub> cough association highlighted in the ISA because of the significant non-linearity in the dose-response. In fact, Schwartz et al. note that at the relatively low NO<sub>2</sub> ambient concentrations observed in this study, no clear associations with cough incidence could be observed. In contrast, Schwartz et al. concluded that particulate matter was associated with the incidence of all the respiratory symptoms they evaluated and that ozone was the other pollutant most likely associated with cough incidence.

Several of the single city studies of respiratory symptoms also implicate other pollutants or air pollution generally. For example, von klot et al. 2002 conclude that ultrafine and fine particles are associated with asthma medication use and symptom increases. They also implicate NO<sub>2</sub>, but specifically note that the gases NO<sub>2</sub> and CO were highly correlated with ultrafine particles, and showed similar results as the ultrafine particles in the majority of the analyses. Another study used in Figure 5.3-1 - Ostro et al. 2001 – focuses on effects of PM and bioaerosols and concludes that several pollutants and bioaerosols are associated with respiratory symptoms.

By focusing on and plotting only NO<sub>2</sub> results and not putting the full results of the studies in context with the author's interpretation of the data, the ISA overstates the evidence for respiratory symptoms that might be caused by NO<sub>2</sub>.

- **The ISA focuses on the Pilotto et al. 2004 intervention study as evidence of the detrimental effects from exposure to NO<sub>2</sub> but the study must be considered in the context of the prior NO<sub>2</sub> review.**

The Pilotto et al. 2004 intervention study is noted as particularly important.<sup>39</sup> However, that study must be put into context with the understanding of NO<sub>2</sub> effects found in the prior review. In the prior review, studies of health effects in homes with and without gas stoves, a major indoor source of NO<sub>2</sub>, were a prominent consideration. In particular, based on a meta-analysis of nine epidemiological studies of children (5 – 12 years old), the EPA concluded that children living in homes with gas stoves were at increased risk for developing respiratory diseases and illnesses.<sup>40</sup> A similar meta-analysis for infants

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<sup>38</sup> ISA at page 3-61.

<sup>39</sup> ISA at 3-60 and 5-13.

<sup>40</sup> U. S. Environmental Protection Agency, 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 viii.

had conflicting results and EPA concluded there was no evidence of increased risk. Given the fact that exposure data showed high peak concentrations in the gas stove homes and the difficulties in extrapolating the data to ambient exposures, the meta-analysis was not useful in providing data to support specific limits for either short-term or long term ambient standards. Nevertheless, the data was considered by EPA and CASAC during the previous review and was important in choosing a standard that would provide a reasonable measure of protection against repeated 1-hour peaks of potential health concern.

In the current review, the important question is whether the Pilotto et al. study or other new studies of indoor NO<sub>2</sub> combustion sources materially change the understanding of NO<sub>2</sub> health effects. The NO<sub>2</sub> exposures from school-building unvented heaters in the Pilotto study were substantial compared to the indoor levels expected from attainment of the current NO<sub>2</sub> standard and the children were exposed to repeated peaks. Therefore, the study is not particularly useful in choosing an appropriate ambient standard. In addition, the question of whether other emissions from the heaters such as ultrafine PM contributed to the effect is now a greater concern than realized in the prior review.

The Chauhan et al. 2003 study is also identified by the ISA as important. This new study reports an association of personal NO<sub>2</sub> exposures with virus-associated symptoms in asthmatic children. However, ascribing this finding to ambient NO<sub>2</sub> is difficult since the authors specifically note great variation from week to week in personal NO<sub>2</sub> exposure with little if any of this variation the result of fluctuations in the concentrations of NO<sub>2</sub> in outside air. They also note the possibility that NO<sub>2</sub> was not the causative agent but a marker of other unmeasured gas-related indoor pollutants such as particulate matter. Furthermore, a recent detailed study in Fresno, California found that both central monitoring site NO<sub>2</sub> and personal exposures to NO<sub>2</sub> were associated with concentrations of several bioaerosols - endotoxin, *Cladosporium* mold, and agricultural fungi.<sup>41</sup> Tager et al. report that it appears that NO<sub>2</sub> not only is a marker for mobile sources, but also for bioaerosol components. Tager et al. indicate that their analyses highlight the importance of the consideration of effects of bioaerosols in the assessment of health effects related to anthropogenic pollutants.

### **Acute Mortality**

The first draft ISA concluded that epidemiological evidence is suggestive of associations between NO<sub>2</sub> and nonaccidental and cardiopulmonary-related mortality but that the underlying mechanism has not been established.<sup>42</sup> The second draft characterizes the epidemiologic evidence on the effect of short-term exposure to NO<sub>2</sub> on total nonaccidental and cardiopulmonary mortality as suggestive but not sufficient to infer a causal relationship.<sup>43</sup> It further notes that the epidemiologic studies are generally consistent in reporting positive associations but that there is little evidence available to

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<sup>41</sup> I. Tager, et al., Fresno Asthmatic Children's Environment Study, Final Report, ARB Contract No. 99-322, April 25, 2006, prepared for the Research Division, California Air Resources Board at page 5-6.

<sup>42</sup> First draft ISA at page 5-10.

<sup>43</sup> ISA at page 3-77.

evaluate coherence and plausibility for the observed associations, particularly for cardiovascular and total mortality. Effect estimates are said to range 0.5 to 3.6 % excess risk, and to be robust to adjustment for co-pollutants. It is acknowledged that NO<sub>2</sub> may be acting as a marker for other pollutants or traffic-related mixtures.

**The ISA is properly cautious about the interpretation of studies of NO<sub>2</sub> and short-term mortality as a causal association.**

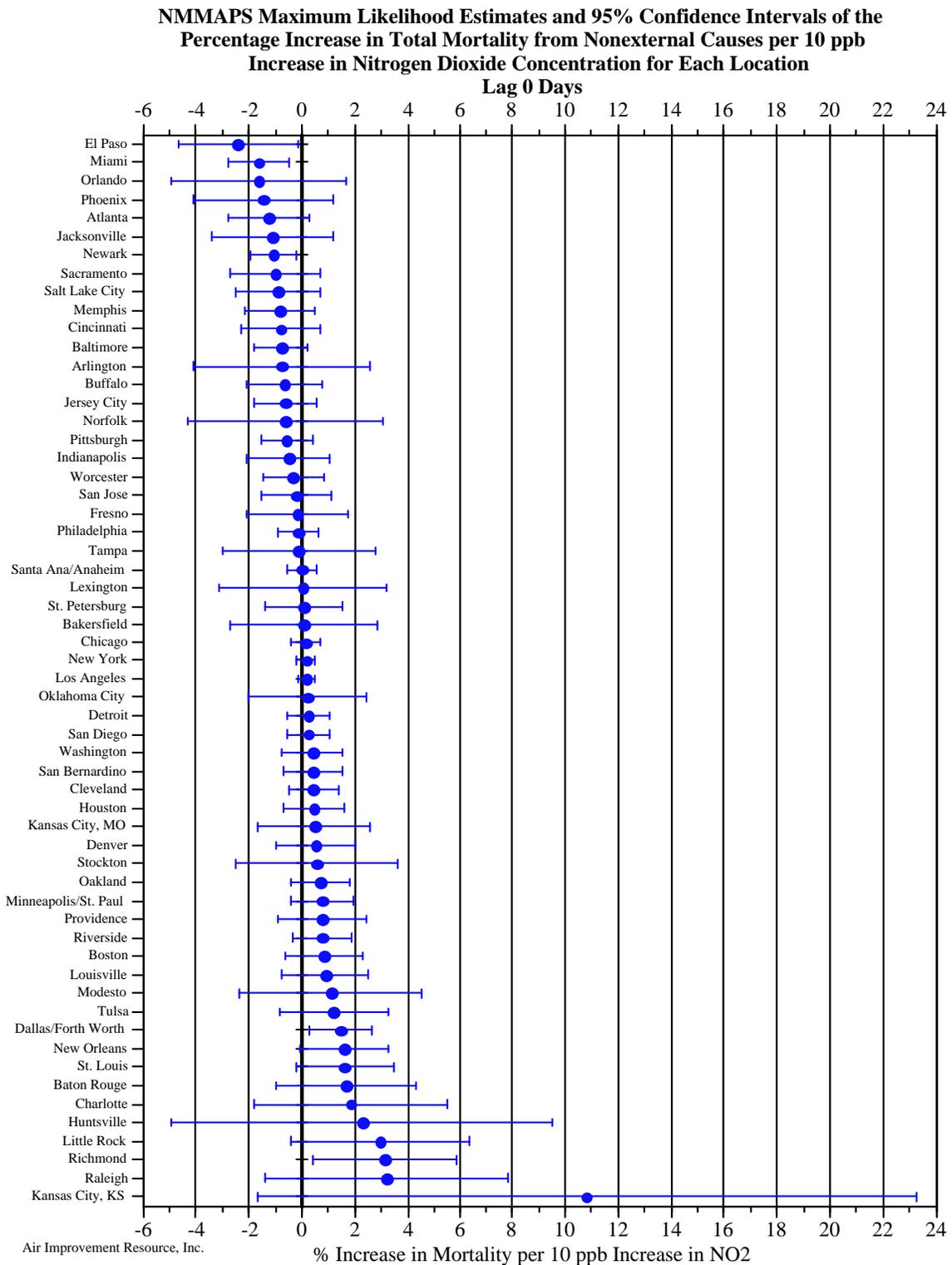
In addition to the points questioning causality in the draft ISA, the ISA should acknowledge the much wider range of associations of NO<sub>2</sub> with mortality in the literature. The ISA notes that NMMAPS (The National Morbidity and Mortality Air Pollution Study) is by far the largest multi-city study and that the study's authors concluded that the results did not indicate an association of NO<sub>2</sub> with mortality.<sup>44</sup> Nevertheless, the ISA uses the combined association in single-pollutant models at lag 1 of 0.5 % as the low end of the range noted above. In reality, there is a wide range of individual city associations ranging from positive to negative at all three lags evaluated in NMMAPS. The individual city single-pollutant NO<sub>2</sub> results are shown below in Figures 1 to 3. At each lag, even the lags for which there was no combined association (as shown in Figure 3.3-1 of the ISA), the individual city results range from minus 2 or 3 percent to plus 3 or more percent per 10 ppb (0.010 ppm) increase in ambient NO<sub>2</sub>. As also shown in Figure 3.3-1, the combined association was not statistically significant in any multi-pollutant model.

Where other multi-city studies report individual city results, a wide range from positive to negative is also shown, for example from - 3 % to + 5 % in 12 Canadian cities evaluated in Burnett et al. 2004. Samoli et al. 2005 also shows a wide range from positive to negative for total nonaccidental mortality, respiratory mortality, and cardiovascular mortality in 29 European cities.

Such a wide range from strongly positive to strongly negative is not biologically plausible. Since people spend between 80 and 90 % of their time indoors where the exposure to ambient NO<sub>2</sub> is roughly half of the ambient concentration, a  $\pm 3$  % change in mortality per 10 ppb (0.010 ppm) increase in ambient NO<sub>2</sub> is equivalent to a  $\pm 6$  % change in mortality per 10 ppb increase in personal exposure to NO<sub>2</sub> of ambient origin. This is even less biologically plausible. The wide range includes a substantial portion of negative associations and there is a lack of evidence of significant respiratory or cardiovascular effects in controlled studies at the concentrations implicated by the epidemiology. This indicates that the likelihood of NO<sub>2</sub> causing premature mortality is nil.

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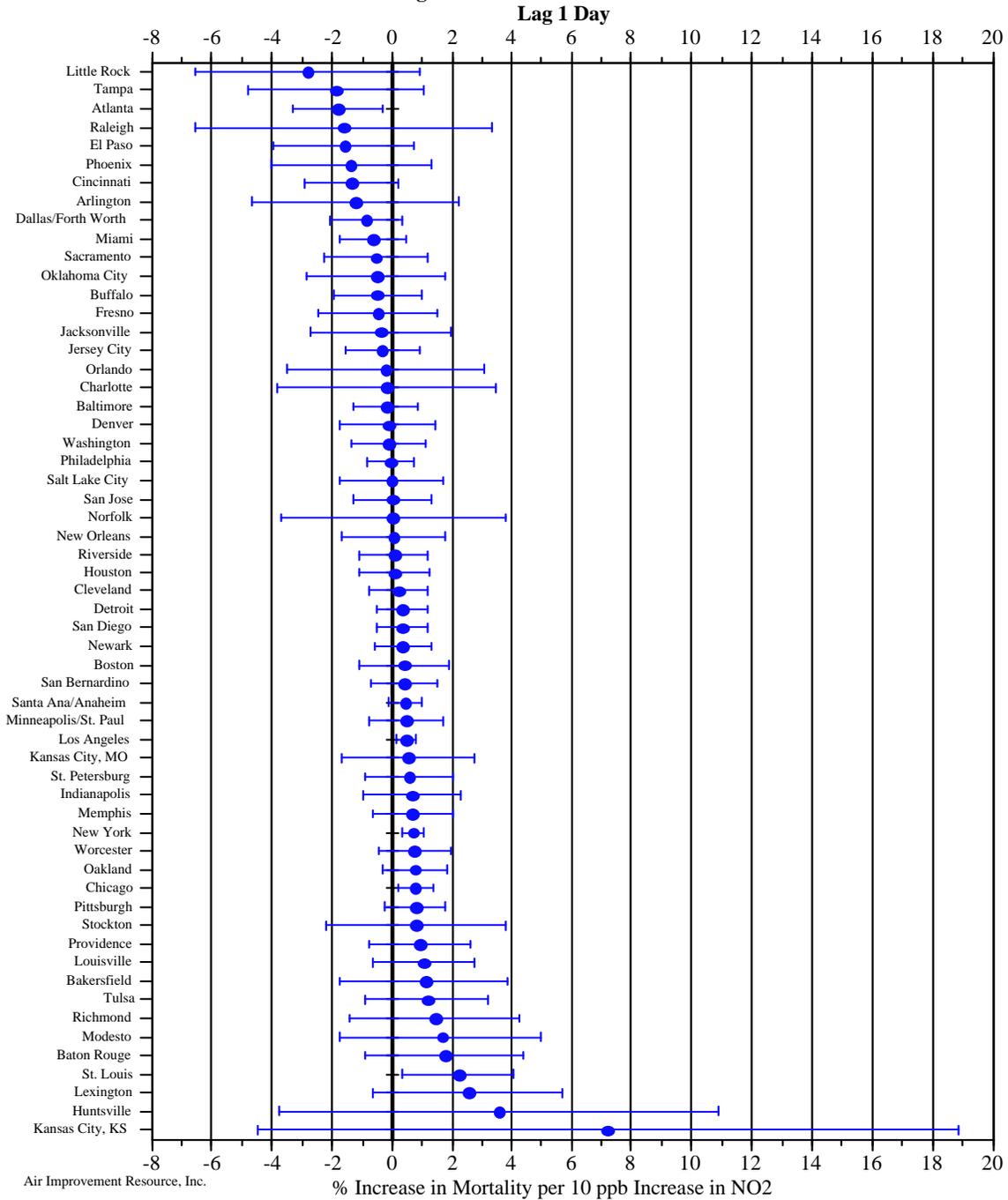
<sup>44</sup> ISA at 3-81.

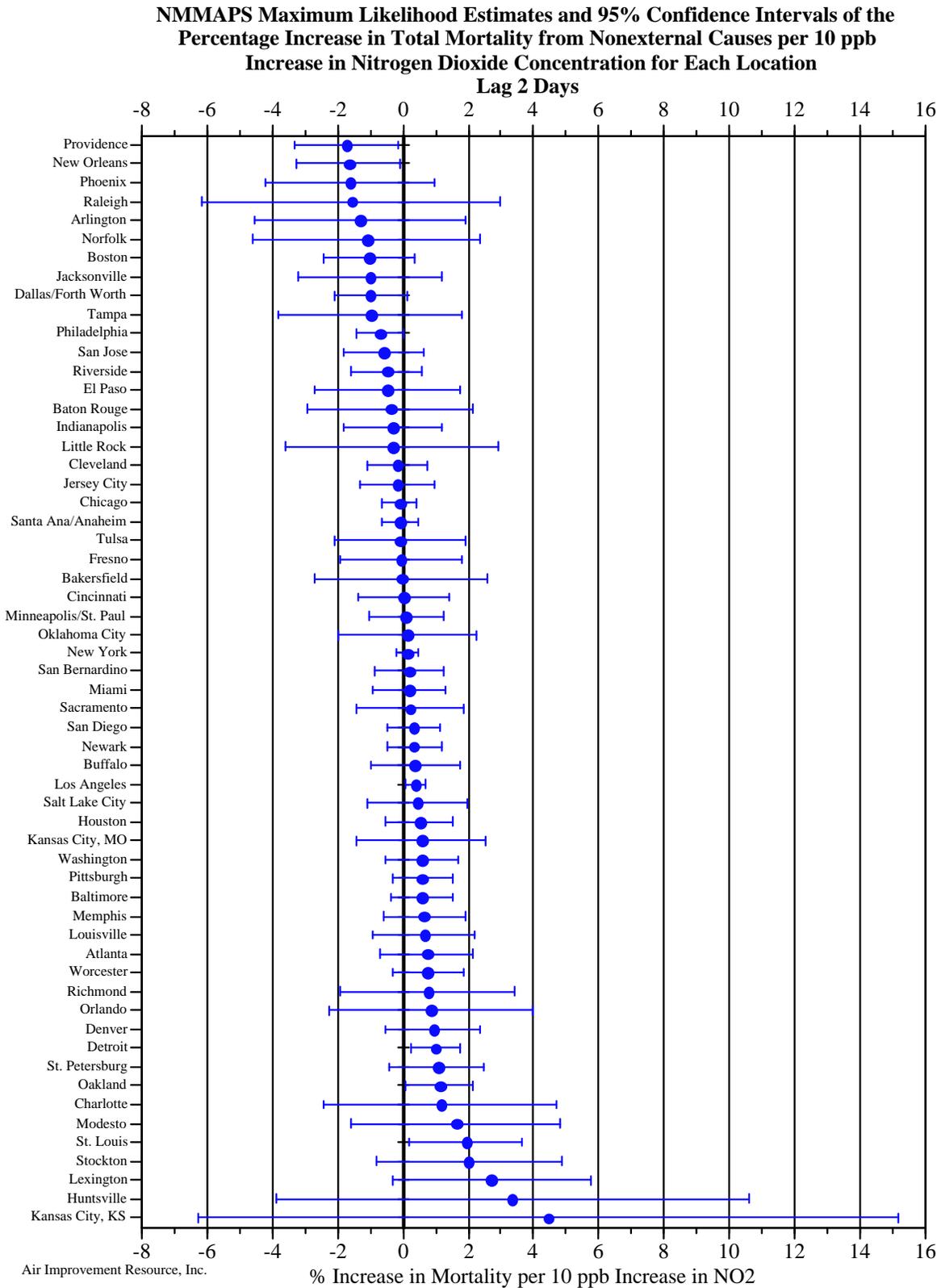


**Figure 1**

**Figure 2**

**NMMAPS Maximum Likelihood Estimates and 95% Confidence Intervals of the Percentage Increase in Total Mortality from Nonexternal Causes per 10 ppb Increase in Nitrogen Dioxide Concentration for Each Location**

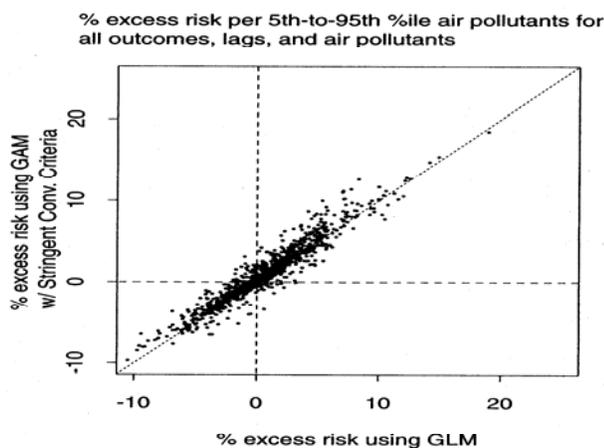




**Figure 3**

While there are some inverse or negative air pollution associations reported in the literature (implying an unlikely protective effect from exposure to the pollutant), the NMMAPS study shows that there are actually many more “negative” associations in the data than reported in the literature. When the statistical issues with the General Additive Model (GAM) were raised, Ito<sup>45</sup> systematically re-analyzed the 1220 separate air pollution mortality and morbidity associations that were included in the original Lippmann et al. 2000 study of Detroit. Comparing the results using the General Linear Model (GLM) to those with the suspect GAM (Figure 4) shows a wide range of negative and positive excess risks (associations) in Detroit when a large number of pollutants, lags and morbidity and mortality endpoints were considered. All the combinations of pollutant, lag and health outcome evaluated in the original Lippmann study were considered plausible candidates for air pollution health effects. Ito showed in separate figures that the wide range of associations occurred for each pollutant. Although the focus in the original Lippmann study, like most published literature, was on the positive associations, Ito’s plot shows that there are many negative associations in the data.

**Figure 4 Comparison of results using the General Additive Model with the General Linear Model, Figure 2 From Ito 2003**



Although there may be somewhat more positive associations than negative associations, there is significant noise or variability in the data. It is beyond the capability of current methods to identify which positive associations may be real health effects and which are not. Time-series epidemiology of air pollution associations is only capable of very blunt analysis. CASAC raised this issue in a June 2006 letter to the Administrator, noting that “because results of time-series studies implicate all of the criteria pollutants, findings of

<sup>45</sup> K. Ito, “Associations of Particulate Matter Components with Daily Mortality and Morbidity in Detroit, Michigan,” in Health Effects Institute, Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health, May 5, 2003, at 143-156.

mortality time-series studies do not seem to allow us to confidently attribute observed effects specifically to individual pollutants.”<sup>46</sup> Further, due mainly to exposure misclassification concerns, they questioned the utility of the time-series mortality estimates. The ISA needs to acknowledge the stochastic variability in time series associations (both positive and negative) and consider the implications of that variability in both the interpretation of the epidemiology and its integration with results from controlled studies.

One implication of the variability documented in Figures 1 to 4 and in other systematic analyses is that it is not surprising to find some positive NO<sub>2</sub> associations in the literature for any health endpoint that is evaluated, even for endpoints where there is no underlying effect. This raises a serious question about the approach taken in the ISA of documenting any and all NO<sub>2</sub> associations in the observational literature. Such an approach is insufficient to establish consistency or coherence. A more holistic and rigorous evaluation of the observational literature is needed if double- and triple-counting of health effects is to be avoided.

The lack of a consistent acute cardiovascular morbidity signal in the data also argues against the presence of an acute causal mortality effect of NO<sub>2</sub>. The ISA concludes that the available evidence on the effect of short-term exposure to NO<sub>2</sub> on cardiovascular health effects is inadequate to infer the presence or absence of a causal relationship at this time.<sup>47</sup> Evidence from epidemiologic studies of HRV, repolarization changes, and cardiac rhythm disorders among heart patients is described as inconsistent. In most studies, the ISA indicates that observed associations with PM were similar or stronger than associations with NO<sub>2</sub>. The ISA also indicates that generally positive associations between ambient NO<sub>2</sub> concentrations and hospital admissions or ED visits for cardiovascular disease have been reported in single-pollutant models but that most of the effect estimates were diminished in multipollutant models also containing CO and PM indices. Mechanistic evidence of a role for NO<sub>2</sub> in the development of cardiovascular disease from studies of biomarkers of inflammation, cell adhesion, coagulation, and thrombosis is described as lacking. Furthermore, the ISA indicates that effects of NO<sub>2</sub> on various hematological parameters in animals are inconsistent and, thus, provide little biological plausibility for effects of NO<sub>2</sub> on the cardiovascular system.

### **Chronic Morbidity**

The ISA describes the overall evidence examining the effect of long-term exposure to NO<sub>2</sub> on respiratory morbidity as suggestive but not sufficient to infer a casual relationship at this time. The first draft ISA focused on lung function growth decrements in children from the Southern California Children’s Health Study (CHS) as especially important.<sup>48</sup> The second draft includes discussion of the Rojas-Martinez et al. 2007 and Oftedal et al. 2008 studies as well noting that studies of lung function demonstrate some of the strongest effects of long-term exposure to NO<sub>2</sub>.<sup>49</sup>

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<sup>46</sup> R. Henderson, CASAC letter, EPA-CASAC-06-07, June 5, 2006 at page 3.

<sup>47</sup> ISA at page 3-70.

<sup>48</sup> First draft ISA at page 5-11 and page 5-15.

<sup>49</sup> ISA at page 3-81.

**The ISA overstates the case for NO<sub>2</sub> causing the decrements in lung function growth in children observed in cohort studies.**

The ISA shows in Figure 3-4.3 that while NO<sub>2</sub> and several other pollutants are correlated with reduced lung function growth in children in the CHS, ozone is not. Similarly, Figure 3-4.2 in the first draft ISA showed a correlation of asthma with a number of pollutants including NO<sub>2</sub> but not with ozone in the CHS. The Rojas-Martinez study of lung function growth in Mexico City reported positive associations with a number of pollutants including NO<sub>2</sub>, PM<sub>10</sub>, and ozone. However, the ozone association in multi-pollutant models was smaller and non-significant in boys, the group that would be expected to have the greatest exposure to ambient ozone. Oftedal et al. reported associations of NO<sub>2</sub> and PM with reduced expiratory flow variables, especially in girls, but not with forced volumes, FVC and FEV<sub>1</sub>. In all three studies, independent effects of correlated pollutants could not be determined. Therefore, the ISA properly concludes that the high correlation among related pollutants made it difficult to accurately estimate the independent effects in these long-term exposure studies.<sup>50</sup>

- **Since ozone and NO<sub>2</sub> have similar mechanisms of action but ozone is a much stronger oxidant and shows toxicity at lower levels than NO<sub>2</sub>, it is extremely unlikely that NO<sub>2</sub> is causing the observed lung function growth effects.**

Both ozone and NO<sub>2</sub> are irritating and oxidizing gases. However, the chemical oxidizing power (as measured in the neutral KI method) of NO<sub>2</sub> is only one-fifth that of ozone. In addition, although both gases demonstrate similar types of responses in controlled tests, the doses required to cause those effects are much higher for NO<sub>2</sub>. Since the mean ambient concentration of NO<sub>2</sub> in urban areas is somewhat below the mean ambient ozone concentration in urban, suburban, and rural areas, it is highly unlikely that NO<sub>2</sub> is the causal factor for lung function growth effects. Thus, the lung growth studies do not provide a basis for an annual standard.

Section 3.4.5 is a summary and integration of the evidence for long-term effects on respiratory illness and lung function. It considers the issue of biological plausibility by discussing the results of various types of NO<sub>2</sub> exposure experiments. It should be broadened to discuss the relative toxicity of NO<sub>2</sub> and ozone, as noted above. It should also be broadened to include PM since PM is also implicated in lung function growth effects.

- **The ISA properly acknowledges that the many studies evaluating the effect of chronic ambient exposure on respiratory symptoms and asthma prevalence are highly inconsistent and of limited value.**

The ISA concludes that epidemiologic studies conducted in both the United States and Europe have produced inconsistent results regarding an association between long-term exposure to NO<sub>2</sub> and respiratory symptoms.<sup>51</sup> It goes on to note that while some positive

<sup>50</sup> ISA at page 5-17.

<sup>51</sup> See ISA at section 3.4.3 and page 5-17.

associations were noted, a large number of symptom outcomes were examined and the results across specific outcomes were inconsistent. In relation to asthma, the ISA concludes that overall, results from the available epidemiologic evidence investigating the association between long-term exposure to NO<sub>2</sub> and increases in asthma prevalence and incidence are inconsistent.<sup>52</sup>

### **Chronic Mortality**

The ISA concludes that the data is “inadequate to infer the presence or absence of a causal relationship” noting that the studies were generally inconsistent and that, when associations were suggested, they were not specific to NO<sub>2</sub>.<sup>53</sup>

### **The U. S. studies that the Agency relies on to implicate PM in chronic mortality demonstrate no association of NO<sub>2</sub> with chronic mortality.**

Chapter 3 of the ISA discusses three major U. S. studies that report no association of NO<sub>2</sub> with long-term mortality. The large American Cancer Society study, the AHSMOG study which includes the high NO<sub>2</sub> areas of California, and the new Women’s Health Initiative Study each show no association of NO<sub>2</sub> with chronic mortality. The lack of a chronic mortality signal raises additional questions as to how there could be an acute mortality effect of NO<sub>2</sub>.

### **Causality or Surrogacy?**

**The ISA properly concludes that it is difficult to determine when there are positive NO<sub>2</sub> associations in the epidemiological literature whether NO<sub>2</sub> is the causal agent or a surrogate or marker for the effects of another traffic-related pollutant or mix of pollutants.**

This caution also makes any conclusions regarding causality problematic and limits the usefulness of the epidemiological data in setting the ambient air quality standard. Throughout the literature reviewed in the ISA, when NO<sub>2</sub> seems to have a consistent association, the authors caution that it may be acting as a surrogate for something else, with traffic often being mentioned.

However, as noted above, the Fresno study demonstrates that NO<sub>2</sub> might be a surrogate for non-anthropogenic as well as anthropogenic substances. In addition, the assumption that NO<sub>2</sub> is a good surrogate for traffic emissions is questionable since NO<sub>2</sub> formation occurs displaced in time and space from the point of NO<sub>x</sub> emission. The factors that determine the day-to-day differences in NO<sub>2</sub> levels include not only the factors that influence day-to-day differences in emission rates and the day-to-day differences in the meteorological factors that influence dispersion and transport, but also the day-to-day and seasonal factors that influence the rate of conversion of NO to NO<sub>2</sub>.

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<sup>52</sup> ISA at page 3-92.

<sup>53</sup> ISA at 5-18.

There are inconsistencies in the traffic studies also. For example, the Gauderman et al. 2005 study reported associations of asthma with some traffic measures but not others. In particular, residential proximity to freeways had a positive association with asthma. Yet, traffic counts in close proximity to the home did not. This suggests that something other than NO<sub>2</sub> is the causal factor.

One candidate that has not received sufficient attention is allergic materials re-suspended by traffic. Miguel et al.<sup>54</sup> in a study prepared for the Air Resources Board indicates that when road dust is re-suspended into the atmosphere by passing vehicles the allergen concentrations in the air are increased above levels that would prevail without the vehicles. Miguel et al. identified 20 different allergens, including molds, tree pollens, grass pollens, and animal dander in road dust and airborne samples. Therefore, re-suspended dust from high-speed high-traffic freeways is another candidate for explaining the respiratory symptom associations reported in the traffic proximity studies.

The ISA acknowledges that it is difficult to distinguish the effects of NO<sub>2</sub> from other traffic-related pollutants due to high correlation with other measured or unmeasured pollutants. While it might appear prudent to regulate NO<sub>2</sub> as a surrogate, it is not logical. Regulating NO<sub>2</sub> will result in reductions in NO<sub>x</sub> emissions which may or may not reduce other pollutants, depending on the technology chosen. However, NO<sub>x</sub> is already being reduced through major national control programs as well as programs to attain the federal PM and ozone standards. In addition, to the extent other factors such as bioaerosols are involved in explaining the epidemiological associations, reducing NO<sub>2</sub> further will have no effect on public health. Therefore, the prudent course of action is to unravel the causal factors through controlled studies before regulating any pollutant based on the fact that it may be a surrogate for something else.

### **Controlled Human Exposure Studies**

#### **The clinical studies, when reproducible, represent the best source of information on NO<sub>2</sub> effects.**

The interpretation of the clinical studies has not changed significantly since the previous review. The only substantive new data is the addition of several studies reporting increased airways responsiveness to allergen-induced inflammation and allergen-induced bronchoconstriction at 0.26 ppm. The data, however, do not materially change the understanding of risk assumed in the previous review. Although NO<sub>2</sub>, like ozone, is an oxidizing and irritant gas, the controlled human studies continue to show that it is distinctly less toxic than ozone.

The summary in the ISA indicates that, for normal subjects, the controlled human studies show no consistent effects on lung function, airway responsiveness, or airway inflammation below 1 ppm. The recent California review that evaluated controlled human exposure in greater detail than the ISA concluded that NO<sub>2</sub> concentrations below

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<sup>54</sup> A. Miguel, G. Cass, M. Glovsky, and J. Weiss, Allergens in Paved Road Dust and Airborne Particles, Final Report Contract No. 95-312, prepared for California Air Resources Board, August 1998.

4 ppm do not cause symptoms or alter pulmonary function in healthy individuals.<sup>55</sup> That review also noted that there is evidence of mild inflammation in healthy subjects exposed to 1.5 to 2.0 ppm for several hours. Given the low exposures to ambient NO<sub>2</sub> noted in the ISA, with few 1-hour NO<sub>2</sub> concentrations above 0.10 ppm in recent years, it is clear that there is a large margin of safety between current ambient exposures and the exposures that cause even the first mild effects in normal individuals.

However, new clinical studies also suggest that NO<sub>2</sub> exposures near 0.25 ppm may enhance the response to inhaled allergen in people with allergic asthma. 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, 2005a). The California review 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. It is further acknowledged that the NO<sub>2</sub> exposures did not lead to clinical asthma exacerbation in these studies.

During the previous review, EPA staff concluded that for a subset of asthmatics, exposures in the range of 0.10 to 0.30 ppm may cause increased airway reactivity. As in the previous review, the ISA relies on the Follinsbee 1992 analysis of 25 studies of NO<sub>2</sub> and airway responsiveness conducted between 1976 and 1991. Follinsbee reported that, on balance, there were more asthmatic subjects that had increased airway reactivity than had decreased airway reactivity when exposed to NO<sub>2</sub> (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 also puzzling since the “at rest” studies, where the effect was seen, were of shorter duration than the “with exercise” studies. Follinsbee posits several possible explanations, but to date none have been identified as the cause of this counterintuitive finding. Follinsbee notes that the health implications of an acute increase in nonspecific airway responsiveness are unclear. He further notes that it could potentially lead to a temporary exacerbation of asthma symptoms and possibly increased medication use but he also notes that in the 25 studies he evaluated, there was no reported incidence of increased medication usage following NO<sub>2</sub> exposure.

Regarding other endpoints in clinical studies, the ISA indicates that evidence for other effects is either inconclusive or inconsistent. Based on the clinical studies then, the only effects that may be expected due to current ambient NO<sub>2</sub> would involve possible enhancement in asthma in some asthmatics. The clinical significance of the mild first effects on asthmatics is unknown, and the authors acknowledge that the NO<sub>2</sub> exposures in these laboratory studies did not lead to clinical asthma exacerbation. Even these subclinical effects would only be expected to occur rarely from exposure to NO<sub>2</sub> of ambient origin.

## **Methodological and Other Issues**

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<sup>55</sup> CalEPA, TSD, Chapter 6.

**The discussion of exposure and measurement error for observational studies is incomplete.**

The wide range of associations, positive and negative, in multi-city studies and other systematic analyses needs to be acknowledged in the ISA; it contradicts the assumption, based on theoretical considerations, that most measurement error issues bias towards the null. In addition, the common assumption that NO<sub>2</sub> of ambient origin is independent of NO<sub>2</sub> from indoor sources<sup>56</sup> is not true for naturally ventilated spaces, complicating the interpretation of acute epidemiology studies.

Wind speed is both a determinant of the degree of dilution of outdoor pollutant sources as well as one of the major factors that determines air exchange in naturally-ventilated buildings, where people spend the bulk of their time. The rate of air exchange, in turn, determines the build-up or dilution of indoor sources. Thus, there is a physical basis for expecting some degree of correlation of indoor pollution with ambient pollution. The basic physics driving air exchange is well established. Wind-driven and temperature-driven pressure differences operate on cracks, crevices and other openings to determine the flow through the openings in naturally-ventilated buildings. When wind-driven pressure differences dominate, wind speed affects the concentrations of both primary outdoor pollutants and the concentrations of indoor sources in the same way. Thus, a portion of the time, exposure to nonambient NO<sub>2</sub> will not be independent of exposure to ambient NO<sub>2</sub>. This is important because thereby nonambient pollution sources can be a confounder of ambient air pollutant/health associations. It also influences the issue of measurement error since most of the existing evaluations of measurement error assume independence to simplify the analysis.

**The acknowledged interferences in the Federal Reference Method for NO<sub>2</sub> make it incumbent on the Agency to develop more specific NO<sub>2</sub> measurement techniques.**

The ISA acknowledges that ambient NO<sub>2</sub> measurements include unknown contributions from other oxidized nitrogen products. This positive bias should be considered in the evaluation of the adequacy of the current standard.

Concerns over the sensitivity and specificity of the routine monitoring instrumentation for both NO and NO<sub>2</sub> have been raised in the technical community. The NARSTO (North American Research Strategy for Tropospheric Ozone) Ozone Assessment, in discussing the inability to measure critical species needed to understand ozone-precursor relationships with regular monitoring, noted that the chemiluminescence instrumentation used routinely in North America often lacks a sensitivity for NO and specificity for NO<sub>2</sub>.<sup>57</sup> The chemiluminescence method directly measures the concentrations of NO and NO<sub>x</sub> and determines the concentration of NO<sub>2</sub> by difference. The NO<sub>x</sub> measurement is made by passing the sample through what is described as a thermal converter in which

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<sup>56</sup> See ISA discussion at page AX6-3.

<sup>57</sup> An Assessment of Tropospheric Ozone Pollution: A North American Perspective, authored by the Synthesis Team for the North American Research Strategy for Tropospheric Ozone (NARSTO), June 2000 at page 3-41.

NO<sub>2</sub> is reduced to NO. However, Parrish and Fehsenfeld,<sup>58</sup> in their critical review of air pollution instrumentation, note that a variety of materials have been used to convert NO<sub>2</sub> to NO and that these surface conversion techniques have proven to be relatively nonspecific for NO<sub>2</sub> also converting other nitrate compounds to NO thus tending to overestimate NO<sub>2</sub>.

Because of these concerns, there is a variable degree of positive bias in the data. The ISA notes that this bias may be as high as 25 % during the summer.<sup>59</sup> Such a large positive bias is not acceptable. First, the specific techniques used to convert NO<sub>2</sub> to NO currently in use throughout the country should be documented by EPA and the States and the biases and interferences in those techniques should be carefully evaluated. Second, it is incumbent on the Agency to develop more specific NO<sub>2</sub> measurement techniques.

**A careful consideration of trends in and current exposure levels to ambient NO<sub>2</sub> are needed to aid in the interpretation of health effect studies and consideration of the adequacy of the current standard.**

To rigorously compare and interpret the various NO<sub>2</sub> health studies, a number of findings illustrated in the ISA need to be considered. The ISA summarizes the current ambient NO<sub>2</sub> concentrations in Figure 2.4-2, noting that mean ambient levels are about 0.015 ppm and that peak daily 1-hour levels are typically about 0.030 ppm. The trend in mean U. S. ambient NO<sub>2</sub>, for a set of 87 monitors from 1980 to 2006, is shown in Figure 2.4-2. Additional data on the distribution of historic ambient levels, both mean and peak, should be added to aid in the interpretation of the relevant epidemiology from the U. S. and other countries.

For example, Figure 5 below shows the distribution of annual average concentrations at all U. S. monitoring locations from 1970 through 2007. While the number of monitoring sites differs somewhat from year to year, a downward trend that has reduced ambient NO<sub>2</sub> concentrations by a factor of about three over the past 30-some years is evident.

Since most of the NO<sub>2</sub> monitoring is conducted in urban or suburban locations, the ambient trend is primarily indicative of emission reductions in and around urban areas. Since highway vehicle emissions are a major source of NO<sub>x</sub> in urban areas, a comparison of the ambient trend with the trend in highway vehicle emissions is illustrative. Figure 6 shows the trend in highway vehicle emissions on a gram per mile basis from 1970 through 2020 calculated with the U. S. EPA's MOBILE6 emission model, using the model's default inputs. The trend in NO<sub>x</sub> emissions from highway vehicles from 1970 to 2007 is very similar to the trend in ambient NO<sub>2</sub>. Moreover, the downward trend in highway vehicle NO<sub>x</sub> emissions will continue well into the 2020s.

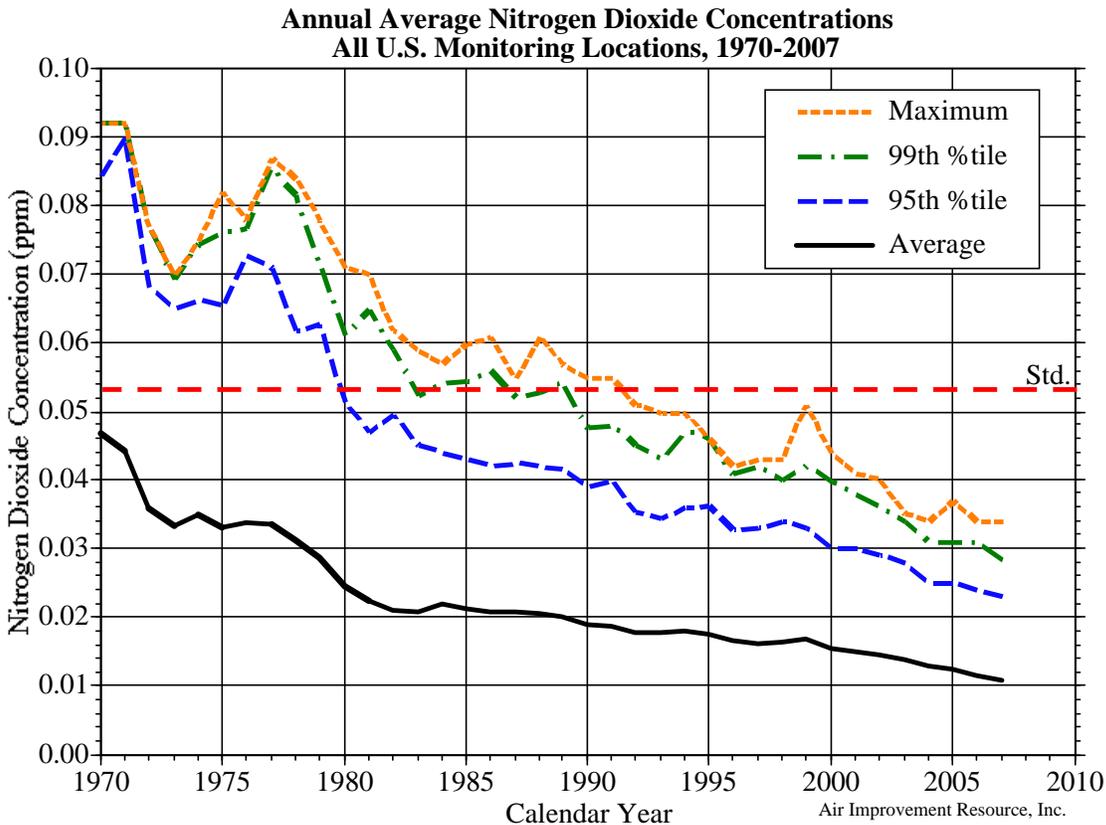
The data in Figures 5 and 6 provide strong evidence that (1) NO<sub>2</sub> exposures in and around urban areas have been reduced substantially since 1970, and (2) that it will continue to

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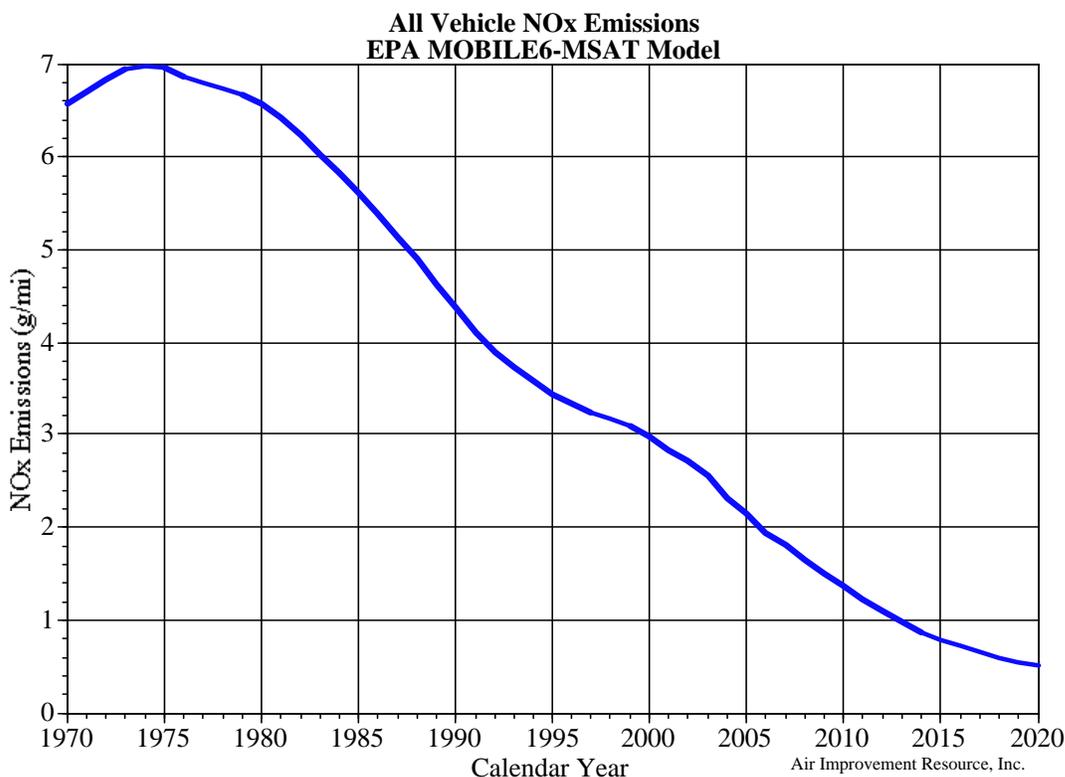
<sup>58</sup> D. Parrish and F. Fehsenfeld, "Methods for gas-phase measurements of ozone, ozone precursors, and aerosol precursors," *Atmospheric Environment*, 34, 1921-1957.(2000).

<sup>59</sup> ISA at 5-3.

fall for the next several decades as the current fleet of highway cars and trucks is replaced with new, low-emitting vehicles under the current Federal motor vehicle control program.



**Figure 5**



**Figure 6**

Since there is concern for peaks and repeated peaks of NO<sub>2</sub>, additional data on the distribution of peak 1-hour levels should be added. California has had a state 1-hour standard for NO<sub>2</sub> for many years so the state has focused its monitoring on both mean and peak levels. For example, during the recent review of the California air quality standard, CalEPA documented the data from over 100 monitoring sites in California. They reported that 99.9 percent of peak daily 1-hour NO<sub>2</sub> concentrations statewide were below 0.12 ppm in 2002, below 0.13 ppm in 2003 and below 0.10 ppm in 2004.<sup>60</sup> Since Southern California has historically had the highest NO<sub>2</sub> levels in the country, such statistics establish that exposures of 0.10 ppm for 1-hour occur only rarely.

As noted above, to aid in the interpretation of historic observational studies, additional detail on the trend of peak 1-hour levels should also be added to the ISA. In the recent California review, CalEPA documented<sup>61</sup> that the maximum 1-hour concentration declined by 70 % between 1980 and 2004 in the South Coast Air Basin, which has historically had the highest NO<sub>2</sub> levels in the nation and was the last area designated as attainment of the federal standard. Since yearly maximum concentrations are extreme values with significant stochastic variability, CalEPA also calculates a peak 1-hour

<sup>60</sup> CalEPA, Review of the California Ambient Air Quality Standard for Nitrogen Dioxide, Technical Support Document (TSD), January 5, 2007, at pages 5-17 to 5-28.

<sup>61</sup> CalEPA, TSD, at page 5-40.

indicator that is more robust. That indicator for the South Coast Air Basin declined 63 % from 1980 to 2004, a period during which the population and vehicle miles traveled in the Basin increased dramatically. With the regulations already in place, the fleet-wide emissions of NO<sub>x</sub> from highway vehicles will continue to decline due to fleet turnover replacing older higher-emitting vehicles with new low-emitting vehicles. To provide perspective on past, current, and future NO<sub>x</sub> and NO<sub>2</sub> exposures from highway vehicles, the trend in highway vehicle emissions, as shown above in Figure 6, should be documented in the ISA.

Figure 2.5-1 documents that adults and children spend much more time indoors than outdoors or inside a vehicle. For example, children spend an average of 4 % of their time in vehicles compared to 86 % of their time indoors while adults spend 7 % of their time in vehicles compared to 87 % indoors. In each case the balance of the time is spent outdoors, 10 % for children and 6 % for adults. One major implication of the various indoor/outdoor studies is that the mean personal exposures to NO<sub>2</sub> from ambient sources are substantially below (about half) the levels measured by ambient monitors, since people spend the bulk of their time indoors.

Indoor sources of NO<sub>2</sub>, gas stoves and other unvented combustion sources, are responsible for higher mean and peak NO<sub>2</sub> exposures than ambient NO<sub>2</sub>. Although there is a review of relevant data in Chapter AX3 and in Chapter 2, there is little use of this information in the integration discussion in Chapter 3. In addition, the Fortman et al. 2001 study that is highlighted in Table AX3.4-3 as reporting short term NO<sub>2</sub> concentrations from cooking also reported PM<sub>2.5</sub> concentrations that were often 1 mg/m<sup>3</sup> or higher from the same common cooking activities with gas stoves. There were elevated PM<sub>2.5</sub> exposures from cooking with both electric and gas stoves, but the median levels in the kitchen were higher in the gas stove tests at 524 µg/m<sup>3</sup> versus 294 µg/m<sup>3</sup> in the comparable electric stove tests. These important findings need to be included in the ISA.

The exposures to NO<sub>2</sub> and other combustion products from unvented gas and kerosene heaters are also important because of the Australian intervention study, Pilotto et al. 2004. Table AX3.4-3 indicates that peak NO<sub>2</sub> levels (averaging time unspecified) are 1 ppm and higher for such exposures. Any data that is available on the mass and/or size distribution of PM exposures from such sources should be included in the ISA. If insufficient data are available, the emission rates reported by manufacturers or by Rogge et al. 1993 for a gas fired residential space heater can be used together with an indoor pollution model to calculate exposures for typical home sizes and air exchange rates. Rogge et al characterized the PM emission rates as low, but that was in the context of all outdoor PM emissions. Sources with low emission rates in that context can still provide significant exposures when operated unvented in indoor spaces.

The discussion of studies of the effect of these indoor sources in relation to the distribution of exposures can be helpful in bounding the discussion of the health effects of ambient NO<sub>2</sub>. The evaluation of the relevance of the indoor studies requires a knowledge of the distribution of exposures and the presence or absence of potential confounders. Since many of these studies were conducted in the past in several different

countries, with different appliances (for example, with pilot lights), homes of different sizes, different cultural practices, and different ambient concentrations, estimates of the exposures at the time of the study will be particularly important.

## Chapter 5 Integrated Summary and Conclusions

The second draft ISA, using the framework regarding causality noted above, draws separate conclusions regarding the overall weight of evidence for various potential health effects. For short-term exposures to NO<sub>2</sub> and cardiovascular morbidity, the chapter concludes that the available evidence is inadequate to infer the presence or absence of a causal relationship at this time. For short-term exposure and mortality, the data is described as suggestive but not sufficient to infer a causal relationship. For long-term exposure and respiratory morbidity, the evidence is also described as suggestive but not sufficient to infer a causal relationship. For long-term exposure and other morbidity effects, the evidence is described as inadequate to infer the presence or absence of a causal relationship. For long-term exposure and mortality, the evidence is described as inadequate to infer the presence or absence of a causal relationship. As described elsewhere in these comments, the evidence for those categories of effect noted as suggestive is actually weaker than described in the draft.

Only in the case of short-term exposure and respiratory effects does the second draft conclude that the data is sufficient to infer a likely causal relationship. Likely, in this case, is defined as more likely than not.<sup>62</sup> With respect to the conclusion regarding short-term respiratory effects, we note four concerns or caveats that should be considered,

First, the conclusion is drawn with regard to the general category of acute respiratory effects, with the ISA referring to a range of respiratory effects. When the evidence for each category of respiratory effect is examined, the results are mixed and inconsistent. The types of evidence as well as the consistency and coherence vary substantially with the type of respiratory effect. Each is discussed in turn below.

Second, for integrating and interpreting the epidemiological results, the reliance on single pollutant model results weakens the case for causality.

Third, with regard to the epidemiology, the strong possibility that NO<sub>2</sub> is acting as a surrogate for another pollutant(s) or the mix of pollutants generally also weakens the case for causality.

Fourth, the ISA itself highly qualifies the argument for consistency and coherence. For example, the ISA notes that:<sup>63</sup>

“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. Considering this large

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<sup>62</sup> ISA at 5-2.

<sup>63</sup> ISA at 5-8.

body of epidemiologic studies alone, the findings are coherent in the sense that the studies report associations with respiratory health outcomes that are logically linked together. The consistency and coherence of findings for respiratory effects is illustrated in Figure 5.3-1; this figure combines effect estimates for respiratory symptoms, hospitalizations or ED visits, and respiratory mortality, drawn from figures presented in Chapter 3.”

This weak definition of consistency and coherence is akin to the counting of studies that the ISA argues in Chapter 1 is not credible:

“For example, one cannot simply count the number of studies reporting statistically significant results or statistically nonsignificant results for health effects and reach credible conclusions about the relative weight of the evidence and the likelihood of causality.”<sup>64</sup>

In the Conclusions (Section 5.4), the new body of epidemiological studies is said to provide an abundance of evidence of associations with ED and hospital admissions for respiratory causes, that when supported with evidence from toxicological and human clinical studies, justifies the conclusion that:

“These data sets form a plausible, consistent, and coherent description of a relationship between NO<sub>2</sub> exposures and an array of adverse health effects that range from the onset of respiratory symptoms to hospital admission.”<sup>65</sup>

Based on the comments and analysis in these AIR comments, this broad a statement is unwarranted. While there is evidence for respiratory effects from NO<sub>2</sub>, the evidence for which there is strong causal support is similar to that in the last review.

The findings underlying the draft causal statement regarding acute respiratory effects are discussed at pages 5-12 to 5-15 of the ISA and a comparison of the conclusions from the previous review with the draft conclusions in the current review is given in Table 5.3-1. An examination of these sections reveals that the evidence, while more extensive, does not materially change the understanding of NO<sub>2</sub> health effects from the previous review. For impairment of lung host defenses, there was ample evidence in the previous review from animal studies and no major change in understanding in the current review. For airways inflammation, there were no studies in the previous review, but there are no effects in controlled studies below 1 ppm for 2 to 3 hours in the current review. For airways responsiveness, which was noted as the most sensitive indicator in the previous review, the level of concern in the current review, 0.2 to 0.3 ppm, is the same as that in the previous review. In addition, the effects are small, subtle changes and there is still no clear dose-response.

For respiratory symptoms, there was a meta-analysis of 9 gas stove studies in the previous review that was assumed to represent a causal relation. It was difficult,

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<sup>64</sup> ISA at 1-15.

<sup>65</sup> ISA at 5-21.

however, to translate the results from indoor gas stove exposures to an equivalent ambient exposure in order to use the results directly to set the ambient standard. In the current review there are a number of additional epidemiological studies, but, as noted above, these studies implicate many pollutants and are also difficult to interpret as effects of NO<sub>2</sub>, per se. For lung function changes, the current review concludes that epidemiologic studies are generally inconsistent and the recent clinical evidence generally confirms prior findings.

The only potential respiratory health effect for which the evidence is markedly different in the current review is ED visits and hospital admissions for respiratory causes. However, as detailed above, the pattern of results is implausibly wide and similar to that for other pollutants, making the assumption of likely NO<sub>2</sub> causality highly suspect. The current annual standard was set to control both peak and mean NO<sub>2</sub> with few if any exceedances of 1-hr peaks of 0.20 ppm. There is nothing in the clinical data showing substantive effects on public health for healthy or compromised individuals below short-term exposures of 0.20 ppm. The only data suggesting effects below the current standard comes from epidemiology. However, as documented throughout these comments, these studies do not directly implicate NO<sub>2</sub>, per se, and do not provide a scientifically sound basis for choosing the air quality standard.

There is a major disconnect between the results of controlled human or animal studies and the current interpretation of the epidemiological results in the ISA. The first draft ISA, in discussing the strengths and limitations of controlled human studies, indicates that they are limited, for ethical and practical reasons, to concentrations expected to produce only mild and transient responses.<sup>66</sup> Since concentrations as high as 4 ppm have been used in human clinical studies, it is clear that the authors did not think that acute exposures in the ppm range would cause 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. Since there is a biologically implausible wide range of associations from positive to negative in systematic analyses of observational data, the epidemiological studies should be severely discounted in the ISA and in the current NO<sub>2</sub> review.

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<sup>66</sup> First draft ISA at AX5-3.