January 31, 2007

By electronic mail: nkado@arb.ca.gov

Dr. Norman Kado, Ph.D
California Air Resources Board
Research Division
P.O. Box 2815
Sacramento, CA 95812

Reference: Comments on the NO_2 Staff Report

The Alliance of Automobile Manufacturers (Alliance) are providing as attachment 1 comments regarding the January 5, 2007, Staff Report "Review of the California Ambient Air Quality Standard for Nitrogen Dioxide."

If you have any questions concerning these comments, please contact Giedrius Ambrozaitis at (248) 357-4717.

Sincerely,

Casimer J. Andary

Casimer Andary
Director, Regulatory Programs
Alliance of Automobile Manufacturers

Attachment

Comments on January 5, 2007 Staff Report and Technical Support Document "Review of the California Ambient Air Quality Standard for Nitrogen Dioxide"

By
Jon M. Heuss
Air Improvement Resource, Inc.

Prepared for the
Alliance of Automobile Manufacturers
January 29, 2007

Introduction

On January 5, 2007 the Air Resources Board (ARB) of the California Environmental Protection Agency (CalEPA) issued a Staff Report (SR) entitled "Review of the California Ambient Air Quality Standard for Nitrogen Dioxide."[1] The Staff Report and an accompanying Technical Support Document (TSD)[2] Report co-authored by the ARB Staff and the Office of Environmental Health Hazard Assessment (OEHHA) review the science of nitrogen dioxide formation, exposure patterns, and health effects and provide staff's recommendations for revisions to the California nitrogen dioxide (NO_2) air quality standard. In particular, the staff recommends lowering the current 1-hour average standard of 0.25 ppm to 0.18 ppm. The staff also recommends establishing a new annual average standard for nitrogen dioxide at 0.030 ppm. Both standards would be defined as concentrations "not to be exceeded." In addition the staff recommends retaining the current chemiluminescence method for measuring NO_2, and re-evaluating the spatial distribution of air monitoring sites to determine if they adequately characterize exposures for individuals living near high volume roadways. The staff recommendations will be considered by the Air Resources Board at its February 27, 2007 meeting.

This document presents comments on several portions of the Staff Report and TSD. In particular, it identifies factors that were not adequately considered during the development of the OEHHA and ARB recommendations. AIR provided comments[3] on the draft Staff Report[4] and draft Technical Support Document[5] that were issued on April

[1] California Environmental Protection Agency, Staff Report, Review of the California Ambient Air Quality Standard for Nitrogen Dioxide, January 5, 2007.
[2] California Environmental Protection Agency, Technical Support Document, Review of the California Ambient Air Quality Standard for Nitrogen Dioxide, January 5, 2007.
[3] Air Improvement Resource, Inc. report "Comments on April 14, 2006 Draft Staff Report 'Review of the California Ambient Air Quality Standard for Nitrogen Dioxide,'" Prepared for the Alliance of Automobile Manufacturers and the Engine Manufacturers Association, May 31, 2006.
[4] California Environmental Protection Agency, Draft Staff Report, Review of the California Ambient Air Quality Standard for Nitrogen Dioxide, April 14, 2006.
[5] California Environmental Protection Agency, Draft Technical Support Document, Review of the California Ambient Air Quality Standard for Nitrogen Dioxide, April 14, 2006.

14, 2006. Although the TSD includes Appendix D that summarizes public comments and staff responses, we are concerned that staff only responded to a portion of the comments we provided.

The Staff Report includes discussion of both health and non-health issues. As noted in Section 1.1.1 of the Executive Summary, information and discussion of non-health issues is included in the Staff Report to provide a context for the health review and staff recommendations. We begin with comments on the staff and OEHHA recommendations. In the subsequent sections, we first provide comments on non-health issues, focusing on material that is important for interpreting the health effects literature. We then discuss the SR and TSD's summary of the literature on controlled human exposures, epidemiological studies, and laboratory toxicological studies.

Comments on Staff and OEHHA Recommendations

The staff findings for short-term effects in Section 2.7 of the SR re-states the effects reported in asthmatics in controlled studies. Based on these findings, OEHHA and the ARB staff recommend lowering the current 0.25 ppm 1-hour standard to 0.18 ppm. The basis for this recommendation includes factoring in the epidemiological results although staff and OEHHA indicate that these results should be viewed with caution. When the additional issues noted below of publication bias and model selection uncertainty are taken into account, along with the inconsistencies identified in the asthma hospital admission and emergency room visits studies, there is ample reason to re-consider the need for as large a margin of safety as staff has proposed. The OEHHA report indicates that the level of 0.18 ppm was chosen because it is half-way between 0.26 ppm where effects have been consistently demonstrated and 0.1 ppm which is the lowest level studied that appears to have no effect. Thus, the margin of safety appears to be rather arbitrary and been chosen entirely based on the concentration where effects may be observed, not considering the frequency of occurrence of those concentrations. Specifying a "not to be exceeded form" for the 1-hour standard thus adds a large margin of safety that is not acknowledged or discussed in the report.

Based on these considerations, ARB should reconsider the need to reduce the 1-hour standard to 0.18 ppm. In the alternative, since the report notes the difficulties in using the yearly maximum to determine trends or exposures, staff should consider an 0.18 ppm standard with a more robust statistic, such as the 95^{th} or 98^{th} percentile, that would aid in implementation planning yet still protect against repeated exposures in the vicinity of 0.25 ppm. At a minimum, staff should consider replacing the "not to be exceeded" language with the peak indicator value that is actually used in determining and designating attainment.

The staff findings and OEHHA recommendations for long-term exposure effects focus on time-series studies reporting associations with asthma symptoms and medication use as well as asthma hospital admissions and emergency department visits. Evidence for premature mortality and cardiovascular admissions is noted as being less robust. In

addition, evidence from long-term studies of reduced lung growth and asthmatic symptoms in children is noted.

Given the many qualifications in the CalEPA documents concerning the interpretation of the time-series studies and the additional issues raised below in these comments, this is an overstatement of the confidence that the reported associations are health effects caused by NO_2. The April 2006 draft OEHHA report specifically noted the contradictory and inconsistent results in the literature for hospital admissions and emergency room visits noting that in many studies, with control for other pollutants, the single pollutant NO_2 association is reduced and becomes statistically insignificant.[6] The draft OEHHA recommendation described the data for respiratory and cardiovascular hospital admissions as "at least suggestive" of an effect, but noted that "the problem of co-pollutants prevents a more definitive conclusion" on adult morbidity and mortality.[7] For cardiac arrhythmias, inconsistent results were also noted.[8] When the factors and issues documented below are considered, there is even more uncertainty and less consistency in the epidemiology than assumed by staff. While there are some positive NO_2 associations in the ambient air pollution/health effects literature, systematic analyses such as NMMAPS show that it is possible to find both significant positive and significant negative associations in the data for a pollutant for which combined analyses utilizing both single- and multi-pollutant models demonstrates that there is no overall association. Due to publication bias, the positive associations tend to appear in the literature. Because of the many weaknesses in the interpretation of premature mortality as being caused by ambient NO_2, the reference to premature mortality and cardiovascular disease should be removed from the proposed amendments to Section 70200 (Table of Standards) of title 17 of the California Code of Regulations.

As noted below, the staff findings on long-term exposures also indicate that epidemiological studies show that NO_2 may lead to changes in lung function growth in children. The results of the Children's Health Study are noted in the OEHHA recommendation as being particularly important. However, it is also acknowledged that the finding relates to NO_2 and other co-varying pollutants. Among the reasons given to ascribe the lung growth effects to NO_2 is that it causes airway inflammation. However, the human exposure studies clearly show that there is a threshold for inflammatory effects in the normal population that is substantially above any of the ambient exposures reported recently in California. In addition, since ozone, a stronger irritating and oxidant gas than NO_2, has been shown in the same studies not to be associated with changes in lung function growth, it is unlikely that NO_2 is the causal factor. Therefore, the lung growth studies do not provide a basis for an annual standard

OEHHA recommends a 0.030 ppm annual standard based on the seriousness of the potential effects identified by epidemiology.[9] However, as is demonstrated below, there is more uncertainty and less consistency in the epidemiology than assumed by staff.

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[6] CalEPA, Draft Staff Report, *supra* note 4, at page A-23.
[7] CalEPA, Draft Staff Report, *supra* note 4, at page A-23.
[8] CalEPA, Draft Staff Report, *supra* note 4, at page A-24.
[9] CalEPA, Technical Support Document, *supra* note 2, at page A-36.

Given the lack of effects in normal subjects from current California ambient NO_2 exposures in controlled human studies, it is extremely unlikely that NO_2 is causing premature mortality. Because of the issue of publication bias noted by Goodman and the issue of model uncertainty identified by HEI and Koop and Tole, it would be inappropriate for ARB to rely on the use of point estimates from time series data to set regulatory standards for air pollution exposure. Therefore, ARB does not have a basis upon which to establish an annual standard.

Comments on Non-health Issues – Section 1.1.1 and Sections 2.2 to 2.4 of the SR and Chapters 2 through 5 of the TSD

Physics and chemistry of nitrogen dioxide

The physics and chemistry affecting the dispersion and reactions of nitrogen oxides and their atmospheric products are well described in Chapter 2 of the TSD. For example, Chapter 2 correctly notes that usually less than 10 percent of the total NOx emissions from combustion sources is NO_2 and that the major source of atmospheric NO_2 is atmospheric oxidation of NO from combustion sources. The chemical reactions involved in the oxidation are also appropriately described in Chapter 2.

However, there is a misleading section in Chapter 5 of the TSD (Section 5.4.6) that indicates that NO_2 forms from nitrogen oxide in the presence of sunlight on a scale of minutes and that the highest NO_2 levels thus occur during the morning and afternoon rush hours. These statements are misleading because they imply that the conversion of NO to NO_2 usually takes only a few minutes whereas it is well established - based on the known chemistry and ambient measurements - that the conversion of NO to NO_2 in the presence of sunlight occurs more on the scale of hours than minutes. For example, the morning peak NO_2 concentrations occur in the South Coast Air Basin from 1 to 3 hours after the morning peak NOx concentrations. This delay is apparent in every season of the year.

Since the extent of NO_2 exposures on and near roadways is an issue that is relevant to the setting of an appropriate NO_2 air quality standard and the siting of monitors at appropriate locations, this is an important distinction. Although peak NOx levels occur near sources, peak NO_2 levels will occur substantially downwind of sources.

Measurement of nitrogen dioxide

The SR and TSD recommend that the current chemiluminescence method be continued to be designated as the approved method and further that all federally approved chemiluminescence methods be designated as California approved samplers. The SR and TSD include a long list of federally approved analyzers and provide information of the precision and accuracy of the current California monitors based on state audits. This recommendation implies that use of any of the federally approved monitors would be fine. However, concerns over the sensitivity and specificity of the routine monitoring instrumentation for NO and NO_2 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_2.[10]

The TSD notes that the chemiluminescsence method in use in California directly measures the concentrations of NO and NOx and determines the concentration of NO_2 by difference. The NOx measurement is made by passing the sample through what is described as a thermal converter in which NO_2 is reduced to NO. However, Parrish and Fehsenfeld,[11] in their critical review of air pollution instrumentation, note that a variety of materials have been used to convert NO_2 to NO and that these surface conversion techniques have proven to be relatively nonspecific for NO_2 also converting other nitrate compounds to NO thus tending to overestimate NO_2.

Because of these concerns, staff should report the sensitivity and specificity of the monitors currently in use in California at the Board hearing. In addition, the specific techniques used to convert NO_2 to NO currently in use in California should be reported along with the conversion techniques used in all the monitors staff is proposing to qualify as California approved monitors. If measurements of the conversion of other NOx products in the current California monitors have not been made, they should be made and reported to the Board along with any recommendations for changes in the measurement technique.

Sources and emissions

Since NOx emissions and NO_2 concentrations have been decreasing in California and elsewhere, any discussion of the relevance and interpretation of exposure measurements needs to include consideration of the emissions occurring at the time of the study. For example, the emission inventory included in Chapter 2 of the SR and Chapter 4 of the TSD indicates that NOx emissions from on-road vehicles were reduced by over 25 % between 1990 and 2000 and are forecast to be reduced by another 72 % between 2000 to 2020. The reduction in NOx from gasoline on-road vehicles is forecast at 75 % between 2000 and 2020 while the reduction from diesel vehicles is forecast at 67 %. [12] Since these reductions include estimated increases in vehicle miles traveled across the state, the reductions in emissions on many specific road segments in populated urban areas will be even greater.

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[10] 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.

[11] D. Parrish and F. Fehsenfeld, "Methods for gas-phase measurements of ozone, ozone precursors, and aerosol precursors," Atmospheric Environment, **34**, 2000, pages 1921-1957.

[12] These NOx reductions from diesel vehicles are based on EMFAC2007, and the Engine Manufacturers Association (EMA) has submitted comments to the effect that NOx deterioration from diesel vehicles in EMFAC2007 is significantly overestimated. Therefore, the diesel NOx reductions are probably much greater than 67% (See EMA report, Comments on ARB's Tampering, Malfunction, and Malmaintenance Assumptions for EMFAC2007, submitted in December, 2006 meeting with ARB Staff)

Exposures to nitrogen dioxide

In the May 31, 2006 AIR comments, we asked that additional data on the distribution of ambient levels be added to the draft SR to aid the reader in evaluating the biologic plausibility of the health effects implied by the statistical associations reported in the epidemiological section. The staff response to comments noted that such distributions were included in the draft TSD, implying that such detail was not needed in the SR. However, most readers will only read the SR. Therefore, it is important that key data be added to the SR to help the reader evaluate the overall risk of NO_2 health effects and the margin of safety associated with establishing an extreme value statistical form for the short-term standard.

For example, the SR and TSD indicate that human clinical studies suggest that NO_2 exposures near the level of the current 1-hour standard of 0.25 ppm may enhance the response to inhaled allergen in people with allergic asthma. Staff also concludes that for a subset of asthmatics, exposures near the current standard may cause increased airway reactivity. However, the risk of these effects occurring in the California population depends on the overall distribution of exposures associated with a given peak level. Indeed, the SR notes that the maximum concentrations are not the best measure for evaluating population exposures and long-term trends because of year-to-year meteorological variability. Despite this caution, the peak 1-hour NO_2 concentrations measured in various air basins in recent years are prominently included in the SR and the full distributions are relegated to the TSD.

To aid the many readers that will not take the time to search out the distributions in the TSD, a very short summary of relevant information should be included in the SR. Based on Tables 5.4 to 5.6 in the TSD, 99.9 percent of peak daily 1-hour NO_2 concentrations statewide were below 0.12 ppm in 2002, below 0.13 ppm in 2003 and below 0.10 ppm in 2004 at the over 100 monitoring sites in California.[13] Such statistics establish that exposures of 0.25 ppm for 1-hour (the level of concern identified by OEHHA for asthmatics) only occur very rarely.

When the Air Quality Advisory Committee reviewed the draft SR and draft TSD, the committee suggested that the NO_2 monitoring network be realigned to provide better spatial distribution and include monitoring of "hot spots." In response, staff added a section on the spatial variability issue and added a recommendation to re-evaluate the spatial distribution of air monitoring sites to determine if they adequately characterize exposures for individuals living near high volume roadways.

In order to evaluate the potential for 'hot spots" or the exposures of individuals living near roadways or elsewhere in California, one needs to have information on activity and the exposures in various microenvironments. The SR and TSD include information concerning both indoor and outdoor NO_2 levels. Table 5.10 of the TSD includes information on the percent of time Californians spend in major locations by age. In

[13] CalEPA, Technical Support Document, *supra* note 2, at pages 5-17 to 5-28.

addition, the issue of 'hot spots' particularly around roadways has already been the subject of a number of studies that are referenced in the SR and TSD. An examination of this material provides several important insights that are not presently highlighted in the SR.

The SR and TSD indicate that indoor/outdoor ratios are less than one when there are no indoor sources of NO_2 but that the indoor/outdoor ratio can exceed three when there are unvented combustion sources indoors such as gas stoves or unvented space heaters. The presence of elevated exposures due to indoor sources and reduced NO_2 exposures indoors when indoor sources are absent has implications for the evaluation of the overall distribution of NO_2 exposures as well as for the evaluation of epidemiological studies.

One major implication is that the mean personal exposures to NO_2 from ambient sources are substantially below the levels measured by ambient monitors, since people spend the bulk of their time indoors. Table 5.10 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.

The TSD includes an 11-page section, 5.5 which estimates the range of peak outdoor 1-hour concentrations to which people in different parts of California are potentially exposed. The text specifically uses the term 'potentially' because the TSD acknowledges that daily activity patterns influence a person's exposure and that being inside will decrease a person's exposure to outdoor NO_2. This section, therefore, is not particularly useful and can be omitted.

It would be better to give the reader a more accurate picture of the indoor/outdoor NO_2 ratios in spaces without NO_2 sources. The TSD already includes a discussion of the Linn et al., 1996 study that reported a mean indoor/outdoor ratio of 0.5 at three Southern California schools. The results of the NO_2 measurements in the recently completed Fresno Asthmatic Children's Environment Study (FACES)[14] are also relevant. While the mean concentration at the Fresno central site was 0.020 ppm, the mean of 332 2-week passive sampler measurements in homes of asthmatic children was 0.013 ppm and the mean in the homes without gas stoves was 0.009 ppm. The Roorda-Knape et al. 1998 study of NO_2 as a function of distance from a roadway in the Netherlands includes data on the mean NO_2 concentrations in classrooms in schools located near motorways. A comparison of the classroom data with the ambient data also suggests a factor of two reduction in NO_2 indoors. In the Kramer et al. 2000 study of 317 children living near major roads in Germany, mean values of personal NO_2 were below 50 % of outdoor NO_2 and the indoor/outdoor ratio was below 0.5. Thus, there are several data sets that indicate a major reduction in NO_2 indoors in spaces that do not have indoor sources of NO_2.

[14] 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.

The Singer et al., 2004 study that is discussed in the SR and TSD is similar to the Roorda-Knape et al, study in that measurements were made at various distances from roadways. However, the monitoring at schools and residences was outside. The authors recognized that the actual exposures while the children attended school would be different and noted that this important issue was not addressed in the study. Therefore, the finding that ambient NO_2 exposures were moderately elevated above regionally monitored levels at schools immediately adjacent to heavily traveled roadways does not establish that the personal exposures to ambient NO_2 in these locations would be substantially different from those estimated from the ambient monitoring network. In addition, the mean NO_2 concentrations measured over 19 or 20 weeks at ten schools ranged from 0.019 to 0.030 ppm. The highest mean concentration was 0.030 ppm, at a school located 60 meters from I-880 which has average daily traffic of 190,000 vehicles. The school is also located adjacent to a shopping center parking lot and a freeway off-ramp. Even at this site, which would be anticipated to be a "hot spot" for NO_2, the mean outdoor concentration was at the proposed annual standard of 0.030 ppm. Since these measurements were made in 2001 and early 2002, the continuing reduction in NOx emissions from on-road vehicles that is occurring due to the motor vehicle control program has been and will continue to reduce NO_2 concentrations and exposures at this site through 2020 and beyond.

The SR and TSD also discuss the Wu et al. 2005 exposure modeling analysis that was developed for the Southern California Children's Health Study. However, the only finding from the Wu et al. paper that is discussed is that the overall within-community variability was highest for NO_2. The Wu et al. analysis accounted for decreased NO_2 exposures indoors and increased exposures in traffic. The assumption they used that in-vehicle exposures would be three times the ambient monitor concentrations is inconsistent with the Westerdahl et al. 2005 measurements of NO_2 exposures in heavy traffic. Westerdahl et al. note that on-roadway NO_2 concentrations were usually no more than twice the measurements at the nearest ambient monitors. For this reason, the Wu et al. analysis would be expected to overestimate personal exposures, particularly peak short-term exposures. Nevertheless, a comparison of the mean personal exposures estimated by Wu et al. to the monitoring data should be included to the SR and TSD.

The data from roadway studies can be used to determine the relation between in-vehicle exposures and ambient concentrations measured by the monitoring network and the current and proposed 1-hour standard. The Westerdahl et al. study reported a peak NO_2 concentration (measured with 20 second time resolution) of 0.200 ppm which is similar to the proposed 1-hour standard. The mean roadway concentrations during the 2 hour experiments were between 0.031 and 0.055 ppm which is well below the proposed 1-hour standard. Westerdahl et al. also compared their results to other roadway studies that reported lower concentrations for all pollutants. Westerdahl et al. indicate that their measurements were substantially higher because they monitored roadway exposures on routes that were dominated by very high traffic density Los Angeles freeways.

Given the steady reduction in on-highway NOx emissions that is continuing in California, future roadway exposures should be substantially below those reported by Westerdahl.

Because of the turbulence generated by traffic, even unfavorable meteorological conditions which limit dispersion and lead to higher NO_2 concentrations at monitoring sites will not materially increase on-road exposures.

Comments on Relevant Health Effects – Sections 1.1.2 and 2.5 of the SR and Appendix A and Chapters 6, 7, and 8 of the TSD

Controlled Human Exposure Studies

The summary in the SR indicates that, for normal subjects, the controlled human studies show no effects on lung function, airway responsiveness, or airway inflammation below 1 ppm. Chapter 6 of the TSD that evaluates controlled human exposure in greater detail concludes that NO_2 concentrations below 4 ppm do not cause symptoms or alter pulmonary function in healthy individuals. Chapter 6 also notes 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_2 noted in the TSD, 99.9 % of all 1-hour NO_2 concentrations at over 100 monitoring sites below 0.10 to 0.13 ppm in recent years, it is clear that there is a large margin of safety between current exposures in California and the exposures that cause even the first mild effects in normal individuals.

However, the clinical studies reviewed by OEHHA and the ARB staff also suggest that NO_2 exposures near the level of the current 1-hour standard may enhance the response to inhaled allergen in people with allergic asthma. The TSD notes 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_2 exposures did not lead to clinical asthma exacerbation in these studies.

The staff also concludes that for a subset of asthmatics, exposures near the current standard may cause increased airway reactivity. Chapter 6 of the TSD summarizes the situation somewhat differently, concluding that some, but not all, clinical studies of asthmatics have found that subjects with asthma appear to be more sensitive to effects of NO_2 on airway responsiveness compared to healthy subjects, noting that the findings have not been consistent across studies with similar protocols. The TSD discussion also relies on the Follinsbee 1992 analysis of 25 studies of NO_2 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_2 (in the range of 0.1 to 0.3 ppm) as compared to clean air. (For healthy subjects, an increase in airway responsiveness was seen only at concentrations above 1.0 ppm.) The effect in asthmatics was evident only in exposures conducted at rest, which he described as puzzling, since the subjects received higher doses when exercising. It is 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_2 exposure.

Regarding other endpoints in clinical studies, the TSD 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_2 in California would involve possible enhancement in asthma in some asthmatics. The clinical significance of the mild first effects on asthmatics is unknown, and OEHHA and the ARB staff acknowledge that the NO_2 exposures in these laboratory studies did not lead to clinical asthma exacerbation. However, OEHHA is concerned over the potential for a flare up or exacerbation of the asthmatics underlying respiratory disease. Since as noted above, 99.9 percent of peak daily 1-hour NO_2 concentrations are below 0.10 to 0.13 ppm at the over 100 monitoring sites in California, exposures that have the potential to exacerbate asthma occur very rarely in California. Whether such exposures actually exacerbate asthma to a clinically significant degree is unknown, so the overall public health significance of the effects that are being used to support a lowering of the 1-hour standard is not clear.

Epidemiological Studies

The staff recommendation for an annual average standard of 0.030 ppm is based on epidemiological studies. During the state review, OEHHA provides detailed analyses of the available health information and its recommendations for the state standard. The OEHHA report is included as Appendix A of the TSD. In the May 2006 AIR comments, we focused on the inconsistencies and limitations of the epidemiologic database for NO_2, focusing on premature mortality. In staff's response to our comments on epidemiology, they indicated that the most robust epidemiological findings related to respiratory effects and that these respiratory studies form the basis for the recommendations for the annual standard.[15] In particular, staff notes that the effects on asthmatics appear particularly plausible.

Indeed, the December 8, 2006 OEHHA report and recommendation (Appendix A of the TSD), while not changing the recommendations from the April 7, 2006 draft, did change the rationale for the choice of the level for the annual standard. The final OEHHA recommendation is based primarily on 11 studies of the respiratory effects of NO_2 that are listed in Figure 1 of the OEHHA report.[16] The April 2006 draft OEHHA report had drawn upon a range of epidemiological findings including mortality, hospital admissions, and potential cardiac effects.[17]

The Staff Findings concerning epidemiology also changed somewhat from the April 2006 draft SR to the December 2006 SR. The April 2006 draft had lumped the effects implied by positive associations of NO_2 with premature mortality, emergency room visits for asthma in children, and hospital admissions for respiratory and cardiovascular disease

[15] CalEPA, Technical Support Document, *supra* note 2, at page D-6.
[16] CalEPA, Technical Support Document, *supra* note 2, at pages A-36 and A-54.
[17] CalEPA, draft Staff Report, *supra* note 4, at pages A-34 and A-49.

together.[18] The December 2006 SR, in contrast, first notes the associations of NO_2 with asthma symptoms and medication use as well as hospitalization and emergency rooms visits for asthma, especially in children. The text goes on to indicate that there is also evidence, though not as robust, for premature mortality and hospitalization for cardiovascular disease.[19]

Since staff did not fully respond to our earlier general comments on the limitations of time series epidemiological studies, we repeat many of those comments. In addition, we include a section specifically commenting on the 11 studies listed by OEHHA in their Figure 1.

General comments In contrast to the limited evidence implicating current ambient NO_2 in health effects from controlled human exposure studies, there are many epidemiological associations in the literature potentially implicating ambient NO_2 in a wide range of effects including premature mortality, hospital admissions, and cardiovascular effects. The SR raises a number of issues regarding the interpretation of the epidemiological data. For example, the SR notes the difficulty of separating NO_2 effects from all other air pollutant effects. It notes that, in many studies, the NO_2 risk estimates were greatly reduced and often became non-significant when an adjustment for particles was made. It raises concerns regarding the actual exposure conditions including indoor sources. It notes the issue of separating out confounding variables such as co-pollutants, seasonality, and weather.

Nevertheless, the staff concludes that a number of studies provide data supporting the need for a long-term standard. In fact, the staff notes that support for the long-term standard is derived primarily from epidemiological studies. The staff also states that the results of the epidemiological studies are consistent with the health effects when only NO_2 alone is tested in the controlled chamber studies, and in the toxicological studies. This last statement is overly broad and not defensible in relation to the detailed material presented and discussed elsewhere in the documents made available for review.

The OEHHA recommendations note the same issues with interpretation of the epidemiological data and raise several more. OEHHA characterizes the epidemiological studies as indicating the potential for severe adverse health outcomes. While OEHHA indicates that there is a real possibility that the NO_2 associations are due to other factors, given the seriousness of the potential effects, OEHHA recommends that an annual average standard of 0.03 ppm for NO_2 be adopted.

While ARB and OEHHA staff recognize a number of factors that argue against interpreting the NO_2 associations as causal, they conclude that prudent public health policy warrants some level of protection from annual exposure to NO_2 be specified. However, either the current 1-hour standard or the proposed 1-hour standard will provide protection since OEHHA recognizes that attaining a 1-hour standard will lower the entire

[18] CalEPA, draft Staff Report, *supra* note 4, at page 15.
[19] CalEPA, Staff Report, *supra* note 1, at page 27.

distribution of daily exposures[20] and attaining an annual standard will reduce peak exposures as well. In fact, the reductions in annual average concentrations (below the federal annual average standard) that have occurred in California over the past decades have occurred during a period in which the state did not have an annual average standard.

In addition to the reservations concerning the NO_2 epidemiology that are already discussed in the staff report, the OEHHA recommendation, and the TSD, there are a number of other issues and factors that argue against interpreting the epidemiological associations as health effects due to NO_2. These include issues related to publication bias, model selection uncertainty, and the biologically impossible wide range of associations – from positive to negative - found in systematic studies.

Publication bias As numerous weak but positive associations of various air pollutants with serious health outcomes have appeared in the literature, there is increasing concern over the issue of publication bias. In California, such associations have been prominent factors in the recent state review of PM and ozone standards, and they are now an issue with the NO_2 review. For the recent federal ozone review, the U. S. EPA commissioned three new meta-analyses of ozone/mortality associations. When these studies were published they were accompanied by two commentaries. The commentary by Goodman is particularly insightful. It notes that the implications of the EPA-sponsored exercise of funding three separate meta-analyses "go far beyond the question of the ozone mortality effect."[21] He notes a major discrepancy between the estimated associations from the comprehensive National Mortality and Morbidity Air Pollution Study (NMMAPS) that evaluated the 90 largest U. S. cities and the meta-analyses. The discrepancy raises the issue of publication bias. Goodman cautions that "depending on published single-estimate, single-site analyses is an invitation to bias."[22] 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."[23]

Model selection uncertainty An important systematic analysis was carried out by Koop and Tole[24] who used Bayesian model averaging to evaluate model uncertainty in time series analyses using an extensive set of pollutants and meteorological variables from Toronto, Canada. They summarize their results as follows:

> 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

[20] CalEPA, Technical Support Document, *supra* note 2, at page A-34.
[21] S. Goodman, Epidemiology , **16**, pages 430-435 (2005) at page 430.
[22] Id. at page 430.
[23] Id. at page 431.
[24] G. Koop and L. Tole, J. of Environmental Economics and Management, **47**, pages 30-54, 2004.

> the use of point estimates from time series data to set regulatory standards for air pollution exposure.[25]

Importantly, the authors demonstrate that the results of a single model based on a sequence of hypothesis tests will overestimate the certainty of the results. This is not a new finding in the statistical literature but it has not been carefully considered in the air pollution literature. They use an example to show how the results of a single regression "…may lead researchers to make misleading inferences about pollution-mortality effects, thereby seriously underestimating the true uncertainty in the statistical evidence."[26]

In 2003, when issues were raised with the statistical model used to analyze many time series data sets during the review of the particulate matter standards, many time series studies were re-analyzed. The Health Effects Institute Special Panel that reviewed the re-analyses concluded "…neither the appropriate degree of control for time in these time-series analyses, nor the appropriate specification of the effects of weather, has been determined." [27] They went on to indicate that "this awareness introduces an element of uncertainty into the time-series studies that has not been widely appreciated previously." In fact, the Koop and Tole analysis is the kind of analysis the HEI Panel recommended to investigate the sensitivity of results to model selection issues. By rigorously evaluating the uncertainty with Bayesian model averaging, they show that there is much greater uncertainty in the time series studies than commonly reported.

Koop and Tole, as noted above, show that individual model results are unreliable. During the federal particulate matter review, AIR presented evidence that led us to the same conclusion. [28] By empirically comparing the results of different time series studies of the same city by different investigators, AIR showed that the results change, often substantively. Subtle differences in model selection can shift the strength of association with a given pollutant, can change the pollutant or pollutants implicated by a given study, and can change the health endpoints that are supposedly affected by the pollutant or pollutants. During the California review of the state ozone standard, the staff made the same point noting that "alternative analyses of data from the same city sometimes resulted in differing results".[29] There are, in fact, many examples in the literature of this phenomenon. It is a practical example of the model selection issue that has been raised in the HEI Special Report on re-analysis of time-series studies.

Given the many issues raised by ARB and OEHHA staff concerning the NO_2 epidemiology, as well as the additional issues raised in these comments, the only conclusion that can be drawn is that while there are many positive epidemiological associations in the literature, individual city studies are not reliable due to model selection issues. This conclusion may be considered controversial. It contrasts with the

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[25] Id. at pages 46 and 47.
[26] Id. at page 40.
[27] Health Effects Institute, Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health, May 5, 2003, at page 269.
[28] See AIR, Inc. comments on 2nd, 3rd, and 4th drafts of USEPA PM Criteria Document.
[29] California Environmental Protection Agency, June 21, 2004 Public Review Draft for Ozone Standard at page 12-76.

view that any statistically significant positive association is likely real and causal. However, many competent investigators are becoming more skeptical about the interpretation of weak air pollution associations.

For example, Moolgavkar has expressed severe reservations. He published several studies of mortality and hospital admissions in Los Angeles. In one of his studies, Moolgavkar noted discrepancies between his findings and that of other studies in Los Angeles. Moolgavkar acknowledged that he did not know how to explain the discrepancies. Although there were differences in the methods of analysis, Moolgavkar at the time did not think the differing statistical analyses could explain the discrepancies. However, he went on to indicate that "If indeed they do, then one must conclude that results of time series analyses can be quite sensitive to statistical approaches."[30]

In the re-analysis of his results in 2003, Moolgavkar reported that some results changed and some did not. Based on his results and those of other investigators, he concluded, "given that different analytical strategies can substantially affect the estimates of effects of individual pollutants, I believe that no numerical estimates are very meaningful."[31]

Vedal and co-workers[32] have also expressed the concern that pollutant/health associations may not be effects of the pollutants themselves, but rather of some other factors present in the air pollution-meteorology mix.

In addition, Lumley and Sheppard point out that "estimation of very weak associations in the presence of measurement error and strong confounding is inherently challenging. Prudent epidemiologists should recognize that residual bias can dominate their results." [33]

The current practice of using central station monitoring data, central station weather data, and available health statistics yields many weak positive associations for various pollutants. However, it is known that the methodology is subject to problems of measurement error and exposure miss-classification as well as severe collinearity between weather and pollution variables. When the uncertainty due to model selection issues is added, and the potential for publication bias is considered, the interpretation of a subset of positive findings as causal becomes problematic.

Results of systematic studies There are now a number of systematic studies of air pollution associations that demonstrate a biologically impossible wide range of associations - from positive to negative - in individual-city results. The Health Effects Institute NMMAPS work is the most robust data base on mortality associations. When single-pollutant and multi-pollutant models for several pollutants were evaluated in the HEI re-analysis, Dominici et al. concluded that the results did not indicate associations of

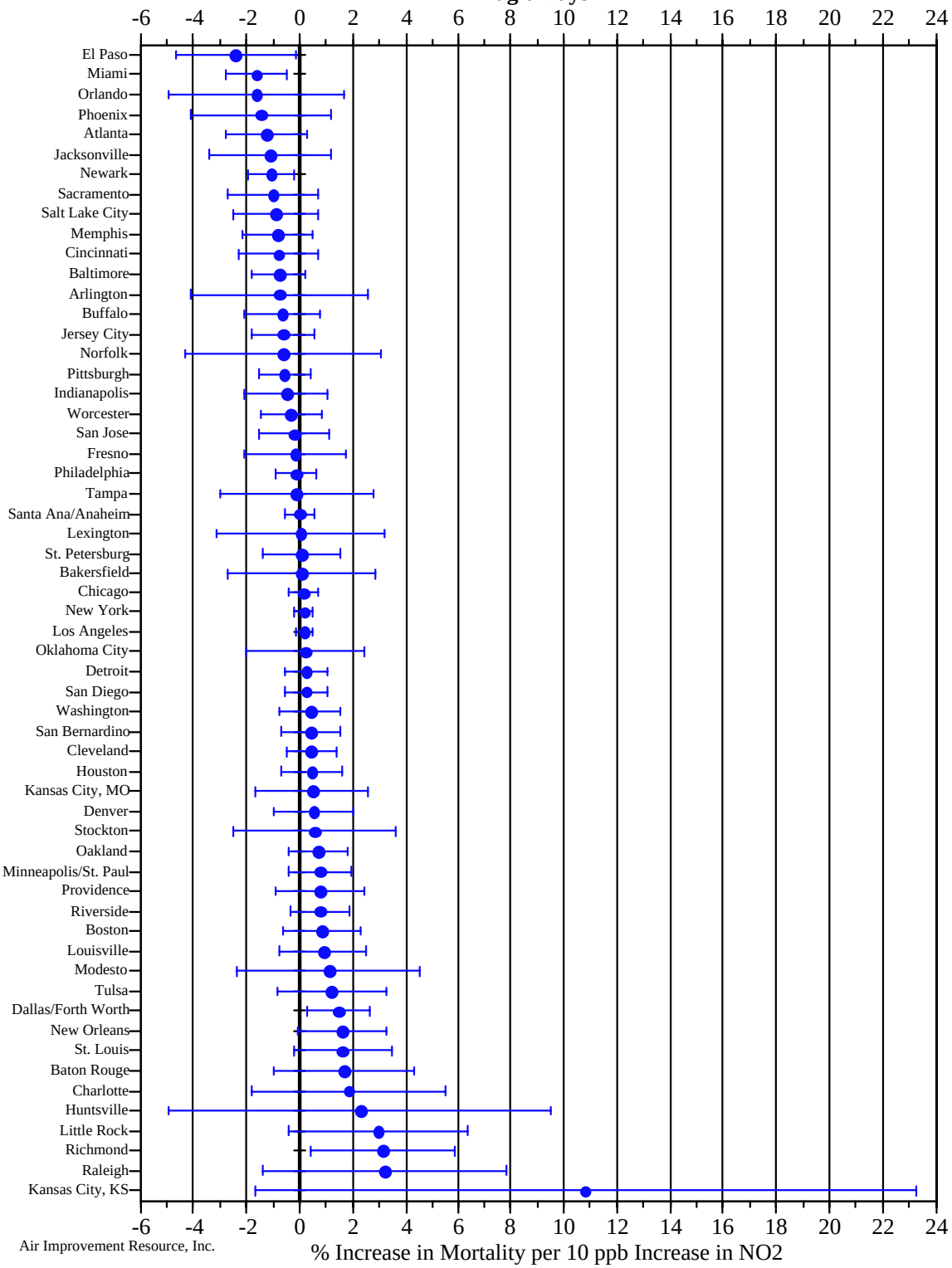
[30] S. Moolgavkar, Environmental Health Perspectives, **108**, pages 777-784 (2000) at page 781.
[31] S. Moolgavkar, in Health Effects Institute, Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health, May 5, 2003, at page 198.
[32] S. Vedal et al., Environmental Health Perspectives, **111**, 45-51, 2003.
[33] T. Lumley and L. Sheppard, Epidemiology, **14**, 13-14, 2003.

NO_2 with total mortality.[34] The re-analyzed city-by-city single-pollutant NMMAPS results for nitrogen dioxide are available on the author's website. They are plotted below for the association of daily mortality with same day nitrogen dioxide and nitrogen dioxide lagged 1 day and 2 days in single pollutant models, arranged in order of increasing association.

The pattern of results for all three lags is similar, with a range of associations from about 2 or 3 % negative per 0.010 ppm (10 ppb) increase in daily nitrogen dioxide to about 4 % positive association with a 0.010 ppm increase in daily nitrogen dioxide. This wide a range in individual-city associations is not only biologically implausible, it is biologically impossible. For each lag, there are only three statistically significant positive associations. However, there are also a small number of statistically significant negative associations at each lag. The OEHHA recommendation notes that the combined NO_2 association in this data was positive (although for only one of the three lags) but became statistically insignificant in multi-pollutant models.

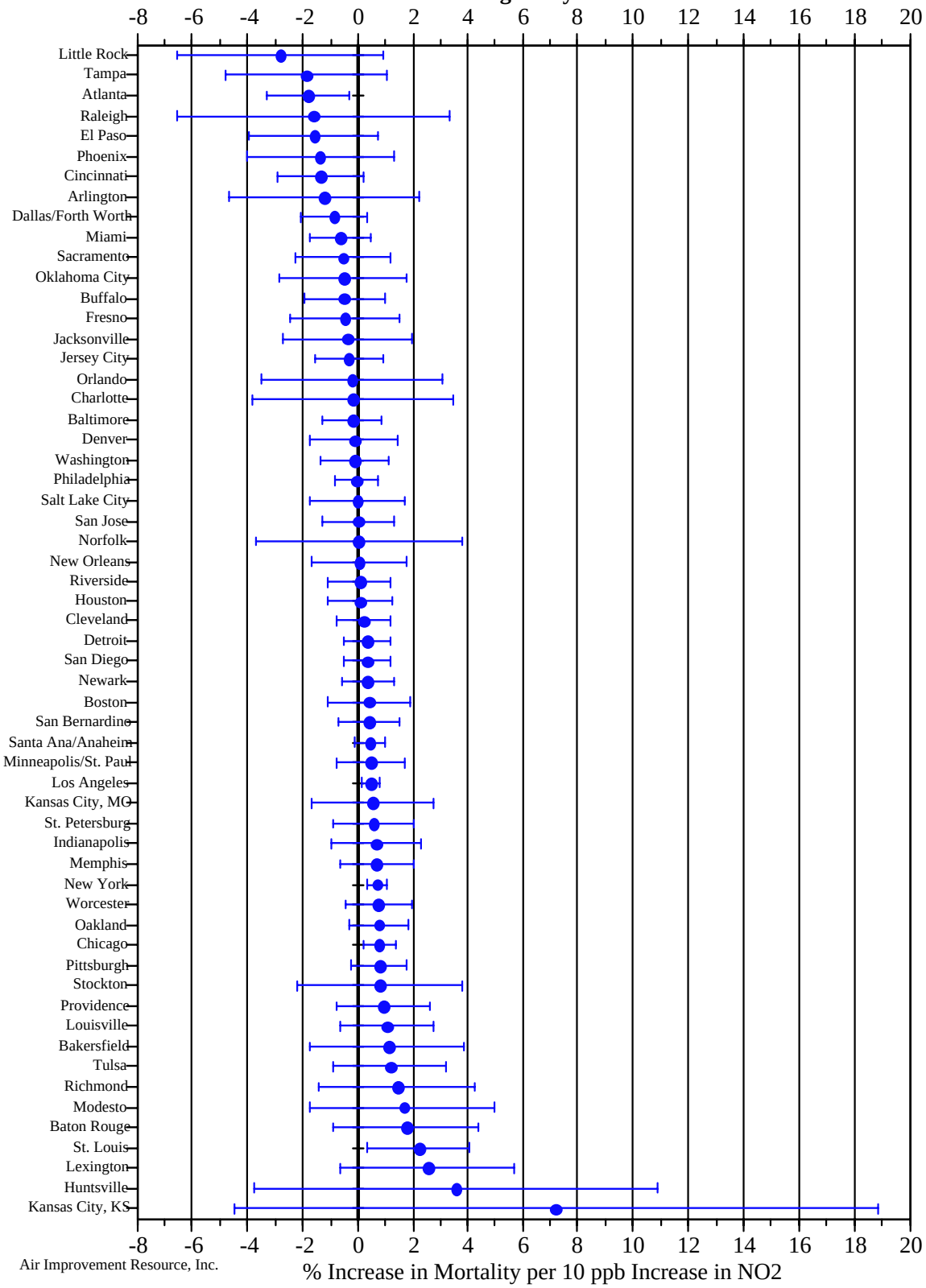
[34] F. Dominici et al. in Health Effects Institute, Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health, May 5, 2003, at page 18.

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
Lag 0 Days



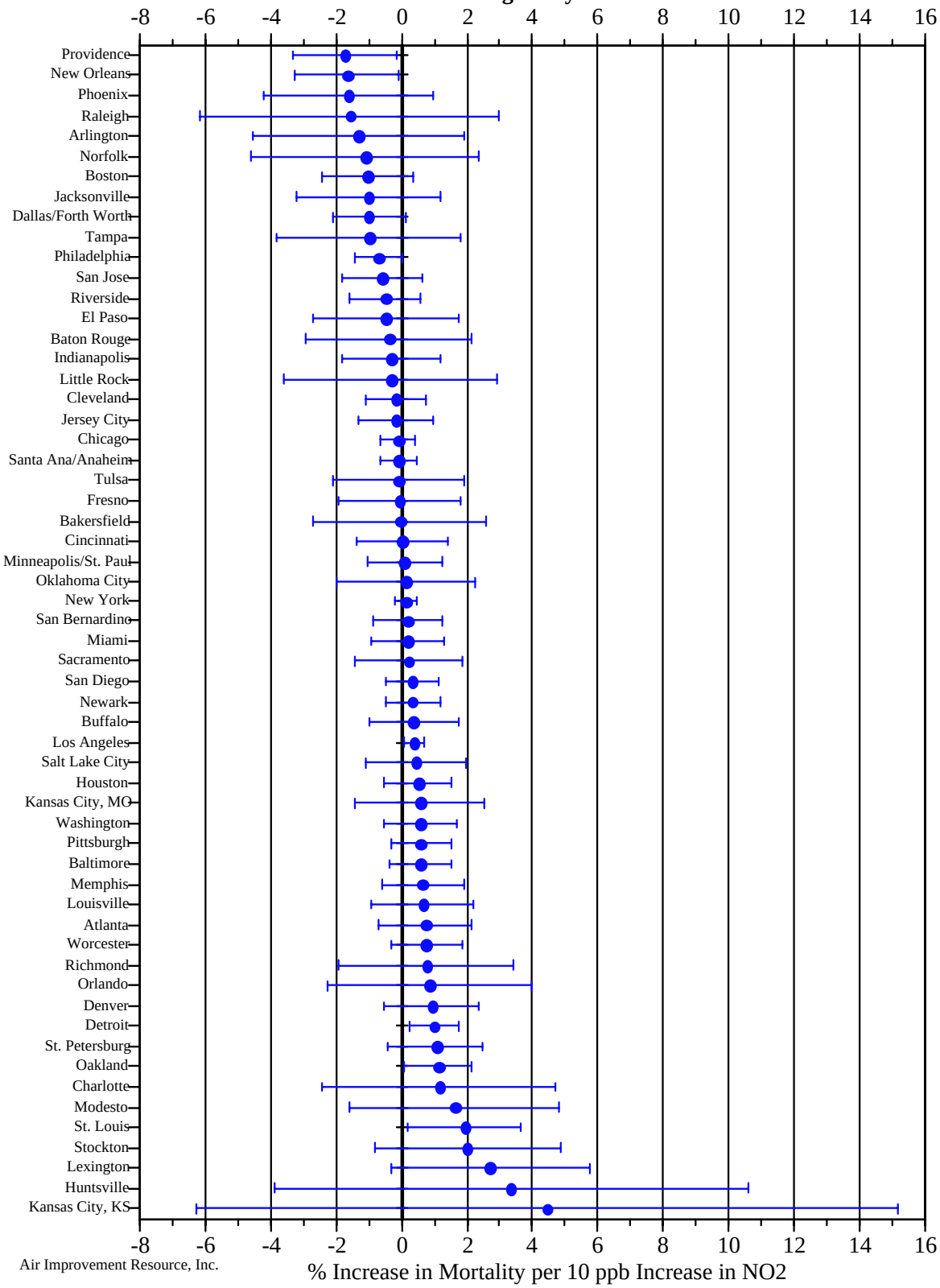
Air Improvement Resource, Inc.

NMMAPS Maximum Likelihood Estimates and 95% Confidence Intervals of t
Percentage Increase in Total Mortality from Nonexternal Causes per 10 ppb
Increase in Nitrogen Dioxide Concentration for Each Location
Lag 1 Day



Air Improvement Resource, Inc.

NMMAPS Maximum Likelihood Estimates and 95% Confidence Intervals of th Percentage Increase in Total Mortality from Nonexternal Causes per 10 ppb Increase in Nitrogen Dioxide Concentration for Each Location
Lag 2 Days



Air Improvement Resource, Inc.

The NMMAPS database is particularly important because, by including all the 90 largest U. S. cities with data, it avoids the issue of publication bias. The wide range of pollutant associations in the data, using the same methodology, demonstrates the inherent noise or variability in the data. The same wide pattern of associations ranging from strongly positive to strongly negative is observed in the individual NMMAPS data for all the pollutants studied at all the lags studied.[35] A comparison of the wide range of positive and negative associations in the robust NMMAPS data set compared to a truncated range of associations in the published literature as summarized by Stieb et al.[36] indicates that publication bias is a major issue in the air pollution epidemiology literature. Since the TSD and OEHHA recommendation notes several forms of bias in the data, the issue of publication bias needs to be added to the list. The Stieb et al. meta-analysis also demonstrates a puzzling and remarkably similar pattern of associations for each pollutant in single-pollutant models that makes it difficult to implicate one pollutant over any other.

While there are some inverse or negative air pollution associations reported in the literature, the NMMAPS study shows that there are many more negative associations in the data than in the literature. When the statistical issues with the General Additive Model were raised and many time series studies were re-analyzed, Ito[37] systematically re-analyzed the 1220 separate air pollution mortality and morbidity associations that were included in the original Lippmann et al. 2000 HEI study of Detroit. As shown below, there was a wide range of negative and positive risks in Detroit when all pollutants, lags, and endpoints were considered. Ito showed in separate figures that the wide range of associations occurred for each pollutant, including NO_2. Although the focus in the original Lippmann study, as it is in almost all the published literature, was on the positive associations, Ito's plot shows that there are many negative associations in the data. Although there may be somewhat more positive associations than negative associations, there is so much noise or variability in the data that identifying which positive associations may be real health effects and which are not is beyond the capability of current methods.

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[35] J. M. Heuss and J. J. Vostal, Comments on the Fourth External Review Draft of "Air Quality Criteria for Particulate Matter" EPA 600/P-99/002aD, June 2003, Prepared for General Motors Corporation. August 28, 2003.

[36] Stieb et al., J. Air & Waste Management Association, **52**, 470-484, 2002; Stieb et al., J. Air & Waste Management Association, **53**, 258-261, 2003.

[37] K. Ito, pages 143-156 in Health Effects Institute, Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health, May 5, 2003.

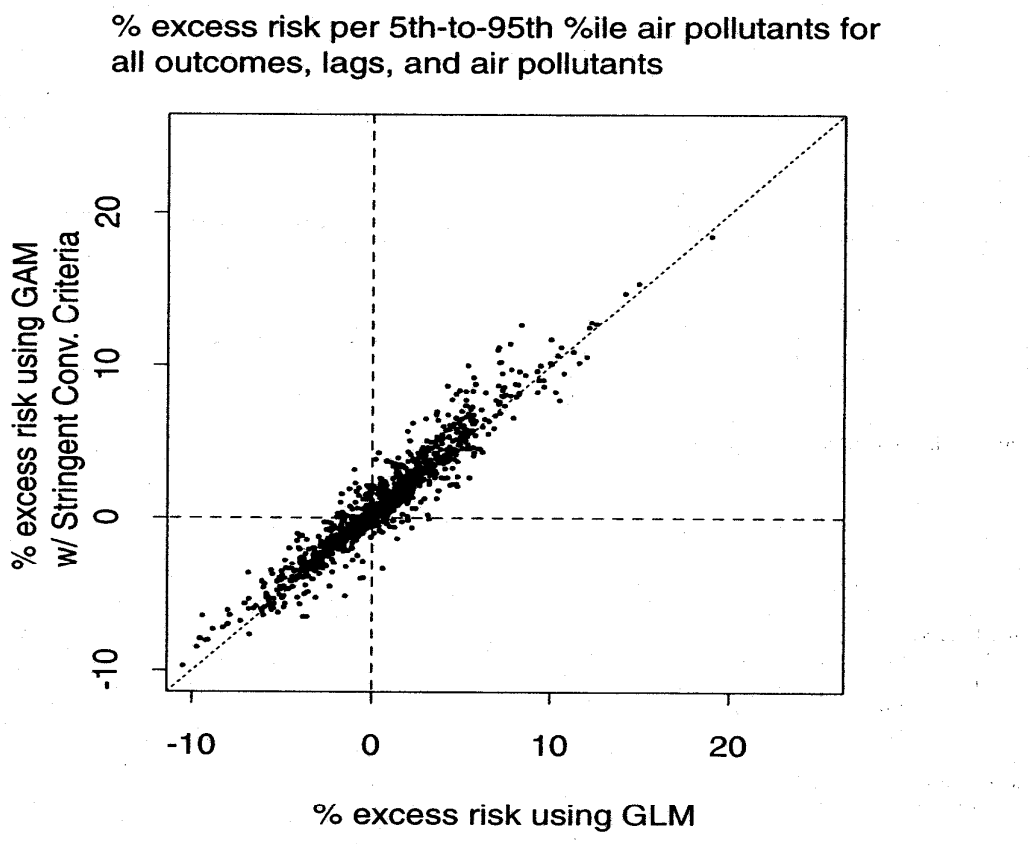

Figure 2 from Ito 2003

Comments on respiratory effects studies The OEHHA recommendation describes the respiratory effects database as robust. In particular, OEHHA notes that the studies of asthmatics are particularly important because they support the findings of the clinical studies. The time series studies of hospital admissions and emergency department visits for asthma are described as fairly consistent and robust.[38] At another point, these studies are described as consistent and robust.[39] In the section on the recommended level for the annual standard, these studies are described as particularly robust.[40] However, OEHHA also acknowledges that there is a real possibility that the NO_2 effects reported in both short- and long-term studies may be due to measured and unmeasured indoor or outdoor co-pollutants that are products of traffic and/or fuel combustion.[41]

In addition to the well-acknowledged issue of whether NO_2 is acting as a surrogate for some measured or unmeasured products of combustion, the recent FACES study in

[38] CalEPA, Technical Support Document, *supra* note 2, at pages A-25.
[39] CalEPA, Technical Support Document, *supra* note 2, at pages A-35.
[40] CalEPA, Technical Support Document, *supra* note 2, at pages A-36.
[41] CalEPA, Technical Support Document, *supra* note 2, at pages A-36.

California has found that both central monitoring site NO_2 and personal exposures to NO_2 were associated with concentrations of several bioaerosols - endotoxin, *Cladosporium* mold, and agricultural fungi.[42] Tager et al. report that it appears that NO_2 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.

A careful reading of the 11 studies that OEHHA includes in their Figure 1 demonstrates that the NO_2 associations with asthma and other respiratory endpoints are not as consistent or robust as suggested by OEHHA. In fact, none of the studies suggest that NO_2, 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_2 is robust to consideration of other pollutants in multi-pollutant models but, in others, the NO_2 association is reduced and non-significant. There is much less consistency than OEHHA indicates.

The first six studies noted in Figure 1 are time-series studies. For example, the Anderson, et al. 1998 study of asthma admissions in London from 1987-1992 concludes that ozone, SO_2, NO_2, 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 pollutant assessed and the proportions with significant findings for ozone, SO_2, NO_2, and particles were 7/14, 6/12, 2/9, and 7/15, respectively. Similar results were found for adults and children considered separately. They 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_2, 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_2. 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.

The pattern in the other time series studies noted by OEHHA is similar. All the studies reported positive NO_2 associations in single pollutant models which in some cases persisted in multiple pollutant models but in others did not. All the studies reported associations of asthma with some other pollutants, too. The authors of the studies did not focus on NO_2 as the causal agent but rather refer to their studies as implicating air pollution. When NO_2 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.

[42] I. Tager, et al., *supra* note 14, at page 5-6.

However, as noted above, the FACES report demonstrates that NO_2 might be a surrogate for non-anthropogenic as well as anthropogenic substances. In addition, the assumption that NO_2 is a good surrogate for traffic emissions is questionable since NO_2 formation occurs displaced in time and space from the point of NOx emission. The factors that determine the day-to-day differences in NO_2 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_2.

In contrast to the claim of consistency for NO_2 effects for respiratory endpoints included in the final OEHHA recommendation, the draft OEHHA recommendation summarized the available epidemiological literature differently. The draft OEHHA recommendation specifically discussed the fact that epidemiological studies have reported associations with air pollution, in general, with hospitalizations, emergency room visits, and calls to doctors for asthma in children.[43] The draft recommendation acknowledged that most of these studies indicated an effect of particulate matter and ozone. However, the text also indicates that in many studies NO_2 showed associations with hospital admissions or emergency room visits for asthma in single pollutant models and that "there are several instances" where the effect remained after adjustment for other pollutants.[44]

Studies 7 through 11 in Figure 1 evaluated either long-term effects or spatial differences in associations. As discussed above, the Gauderman 2004 study of lung function growth does not implicate NO_2, per se, but rather a number of possible pollutants. In the Kramer et al. 2004 study, there were associations of symptoms with outdoor NO_2 levels but not with personal NO_2 exposure measurements. This is not consistent with a NO_2 effect, per se, but is consistent with NO_2 acting as a surrogate for something else. In fact, Kramer et al. conclude that their study implicates traffic-related air pollution. The Kim et al. 2004 study also reports associations with a number of traffic-related pollutants. However, the associations are very weak and the associations of NO_2 with physician-confirmed asthma were not statistically significant in either all subjects or long-term residents. The Janssen et al. 2003 study reported a traffic effect on respiratory symptoms in atopic children but found no associations with car traffic. This result also suggests that something other than NO_2 is causing the effects. 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 but traffic counts in close proximity to the home did not. This pattern is similar to that reported by Janssen et al. and suggests that something other than NO_2 is the causal factor.

One candidate that has not received sufficient attention is allergic materials that are re-suspended by traffic. Miguel et al.[45] 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 the levels that would prevail

[43] CalEPA, draft Staff Report, *supra* note 4, at page A-23
[44] CalEPA, draft Staff Report, *supra* note 4, at page A-23.
[45] 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.

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.

When the limitations and inconsistencies of the time-series studies are considered together with the limitations of the long-term or spatial difference studies, it is clear that the scientific basis for the OEHHA recommendation for an annual standard is very weak. ARB staff acknowledges that it is difficult to distinguish the effects of NO_2 from other traffic-related pollutants due to high correlation with other measured or unmeasured pollutants. Staff goes on to indicate that it is prudent to regulate NO_2 since many of the other traffic-related pollutants are not regulated.[46] This is not logical. Reducing NO_2 may or may not reduce other traffic pollutants, depending on the technology chosen. In addition, to the extent other factors such as bioaerosols are involved in explaining the epidemiological associations, reducing NO_2 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.

Toxicological Studies

The AIR comments on the draft SR and TSD concentrated on the way the information was summarized in the draft SR. We noted that the SR summaries discussed effects with no mention of the level of exposure, length of exposure, or means of exposure. It omitted any qualifications that are found in the primary discussion of the material.

This material has now been revised to include information on the doses that are needed to elicit various effects in animals. The SR modified the blanket statement that the animal studies are consistent with and supportive of the epidemiological and controlled human studies presented elsewhere in the document. Instead, the SR now indicates that the toxicological studies provide support for the health effects information reported in clinical and epidemiologic studies. This statement is still too broad. The staff should carefully evaluate the extent to which the animal studies support the biologic plausibility (in terms of both the kinds of effects and the doses that may cause them) for the effects seen in controlled human studies and implicated by the associations reported in epidemiological studies. The low exposures to current ambient NO_2 noted above should be considered carefully as part of this analysis.

[46] CalEPA, Technical Support Document, *supra* note 2, at page 7-18 and 7-19.