

September 24, 2008

**By e-Mail (jenkins.scott@epa.gov)**

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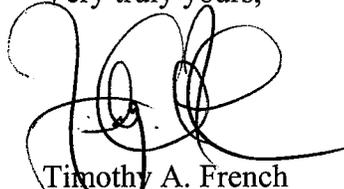
**Re: Comments on Draft Risk and Exposure  
Assessment for Nitrogen Dioxide (NO<sub>x</sub>)  
Docket I.D. No. EPA-HQ-OAR-2006-0922**

Dear Dr. Jenkins:

Enclosed for filing and submission to Docket ID No. EPA-HQ-OAR-2006-0922 are the Comments of the Engine Manufacturers Association (as prepared by Jon M. Heuss of Air Improvement Resource, Inc.) regarding EPA's Draft Risk and Exposure Assessment Report for Nitrogen Dioxide (NO<sub>x</sub>), the notice of which was published in the Federal Register on September 2, 2008. (See 73 FR 51297, Sept. 2, 2008.) Please ensure that these comments are duly filed, and also ensure that copies are circulated to the members of the Clean Air Scientific Advisory Committee (CASAC).

Thank you for your assistance in this matter, and please contact me if you have any questions.

Very truly yours,



Timothy A. French  
General Counsel

cc: EPA Docket I.D. No. EPA-HQ-OAR-2006-0922 ([a-and-r-docket@epa.gov](mailto:a-and-r-docket@epa.gov))  
Dr. Angela Nugent ([nugent.angela@epa.gov](mailto:nugent.angela@epa.gov))  
EMA Environmental Activities Committee

EMADOCS: 33725.1

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**Review and Critique of the EPA's "Risk and Exposure Assessment to Support the Review of the NO<sub>2</sub> Primary National Ambient Air Quality Standard: Second Draft"**

**Prepared for  
Engine Manufacturers Association**

**By  
Jon M. Heuss  
Air Improvement Resource, Inc.**

**September 24, 2008**

As part of the U. S. EPA review of the National Ambient Air Quality Standard (NAAQS) for Nitrogen Dioxide (NO<sub>2</sub>) standard, the second draft Risk and Exposure Assessment (REA)<sup>1</sup> was released for public comment in August. The draft Risk and Exposure Assessment underwent Clean Air Scientific Advisory Committee (CASAC) review on September 9-10, 2008. The REA together with the Integrated Science Assessment (ISA)<sup>2</sup> will feed into the Advanced Notice of Proposed Rules (ANPR) that essentially replaces the Staff Paper in the old NAAQS review process. As noted in the following comments, interested parties are compromised in their ability to provide timely comments because (1) a key chapter (Chapter 8) was not available at the time of the CASAC meeting, and (2) EPA staff inserted new material (an unpublished meta-analysis) in the final ISA that impacts significantly on its analysis in the REA without any opportunity for public or CASAC comment.

The REA uses three approaches to characterize health risks from ambient nitrogen dioxide. The first involves comparing NO<sub>2</sub> ambient monitoring data with potential health effect benchmark levels, using the monitoring data as a surrogate for potential human exposures. The second approach uses modeled estimates of actual human exposures to compare with the health benchmarks. The third approach uses selected epidemiological associations to estimate health impacts. As documented below, there is substantial evidence that the risk estimates from the first and third approaches significantly overestimate actual risks. Unfortunately, the chapter of the REA that presents the results of the second approach, Chapter 8 – Exposure Assessment and Health Risk Characterization, was not included in the draft released for public and CASAC review. It will undergo separate review when available.

In the following, we provide comments on the utility of the three approaches, on the choice of health benchmarks, and on the staff's preliminary choices for the indicator,

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<sup>1</sup> U. S. Environmental Protection Agency, "Risk and Exposure Assessment to Support the Review of the NO<sub>2</sub> Primary National Ambient Air Quality Standard: Second Draft," EPA-452/P-08-004a, August 2008.

<sup>2</sup> U.S. Environmental Protection Agency, "Integrated Science Assessment for Oxides of Nitrogen – Health Criteria," EPA/600/R-08-071, June 2008.

averaging time, form, and level of the NO<sub>2</sub> air quality standard.

**The results for the first approach are known to overestimate the distribution of actual human exposures**

The first approach, comparing monitoring data with potential health benchmarks, is based on the assumption that the monitor reflects people's actual exposure. However, people spend the bulk of their time indoors, where there is ample evidence that indoor NO<sub>2</sub> concentrations are approximately half of that measured outdoors. Therefore, it is important to use the results of detailed modeling of population exposures to provide realistic estimates of health risks. For example, the preliminary exposure results for Philadelphia in the first draft REA<sup>3</sup> using the second approach demonstrated that actual human exposures to NO<sub>2</sub> of ambient origin are substantially below that estimated from ambient monitoring. Figure 7 of the first draft REA showed that the annual exposures to NO<sub>2</sub> of ambient origin are generally in the 0.007 to 0.015 ppm range whereas the ambient data indicate annual means of 0.024 to 0.029 ppm. The importance of indoor sources was also shown in this figure with an additional annual exposure increment of from 0.002 to 0.005 ppm from indoor sources. Figure 8 showed that at current ambient levels well over 90 % of the population does not have a maximum 1-hour NO<sub>2</sub> exposure over 0.20 ppm from NO<sub>2</sub> of ambient origin. Estimates of the number of repeated exposures above the benchmarks showed that that only a very small portion of the population has repeated exposures in a year due to NO<sub>2</sub> of ambient origin.

Since the results of the first approach overestimate personal exposures, any risk estimates should be discounted as compared to the results from the second approach. As noted above, Chapter 8 of the second draft REA which includes the detailed modeling of population exposures, is not available yet. Since Chapter 8 uses a sophisticated modeling approach to estimate the distribution of actual human exposures, it will be particularly important. The public and CASAC will need time to evaluate these models and their underlying assumptions.

**The results of the third approach – estimating risk based on epidemiological associations – also overestimates the risk from NO<sub>2</sub>**

The AIR, Inc. comments<sup>4</sup> on the second draft ISA documented many issues with the epidemiological literature for nitrogen dioxide. For example, 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. In addition, the review of epidemiology in the ISA focused on single pollutant model results rather than evaluating

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<sup>3</sup> U. S. Environmental Protection Agency, "Risk and Exposure Assessment to Support the Review of the NO<sub>2</sub> Primary National Ambient Air Quality Standard: First Draft," EPA-452/P-08-001, April 2008.

<sup>4</sup> J. M. Heuss, Air Improvement Resource, Inc. Comments on March 2008 Second External Review Draft of "Integrated Science Assessment of Oxides of Nitrogen –Health Criteria." Prepared for the Alliance of Automobile Manufacturers, April 22, 2008.

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.

Further, issues of publication bias, model selection uncertainty, and confounding hinder interpretation of air pollution epidemiological studies. During the ozone review, CASAC pointed out, where systematic analyses have been carried out, as in NMMAPS, 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 Agency 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 documented variability 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.

The first draft REA did not include any quantitative risk estimates based on epidemiological studies and was criticized by several epidemiologists on the CASAC panel during the May 2 review for this omission. The second draft does include an estimate of increased emergency room visits for respiratory disease using single-pollutant and multi-pollutant associations reported by Tolbert et al. 2007 for Atlanta. The draft indicates that staff has chosen to focus on the Atlanta studies of Peel et al. 2005 and Tolbert et al. 2007 for the epidemiology-based risk assessment. However, a careful analysis of the risk characterization in Chapter 9 and the Peel et al. 2005 and Tolbert et al. 2007 papers reveals that the estimated risk cannot be distinguished from zero.

First, the risk assessment evaluated all respiratory-related ED visits rather than asthma-related visits. The human clinical evidence points strongly to exacerbation of asthma as the endpoint that would be affected at the lowest concentrations. Therefore, if there is a causal association between NO<sub>2</sub> and emergency department visits or hospital admissions, it is expected to occur with asthmatics at much lower concentrations than with non-asthmatics. However, Peel et al. 2005 report stronger associations of NO<sub>2</sub> with either all emergency department visits for respiratory disease or with specific disease categories other than asthma than with asthma visits. In fact, the single-pollutant association for 1-hr NO<sub>2</sub> with asthma visits using a three-day moving average was not statistically significant in Peel et al. 2005.

Second, both Peel et al. and Tolbert et al. report small positive associations of a number of pollutants with all respiratory disease in single-pollutant models. Neither study implicates NO<sub>2</sub> over the other pollutants based on the pattern of single-pollutant results.

Third, based on multi-pollutant models, Tolbert et al. concluded that PM10 and ozone persisted as predictors with NO<sub>2</sub> associations becoming non-significant. Thus, the results in Tables 9-1 through 9-3 show that the confidence intervals for multi-pollutant models include zero or “no effect.”

Fourth, the REA notes several important uncertainties and limitations associated with the risk assessment. The most important uncertainty relates to the extent that the associations between NO<sub>2</sub> and ED visits for respiratory causes actually reflect causal relationships.

Given the many concerns over how to interpret positive NO<sub>2</sub> associations in epidemiological studies acknowledged in the ISA and REA, given that the pattern of associations in Peel et al. and Tolbert et al. does not implicate NO<sub>2</sub>, per se, over other pollutants, given that the association with asthma visits, the end-point expected to be affected based on controlled studies, is smaller and less significant than the association with all respiratory visits in Atlanta, and given that the risk of an emergency department visit based on multi-pollutant models is not distinguishable from zero, the results of the epidemiological risk assessment should be highly discounted in the REA and in the Administrator’s decision-making.

**Between the first and second draft REAs, the staff inappropriately added a potential health benchmark at 0.10 ppm**

The first draft REA included a detailed set of exposure calculations that were compared to short-term exposure benchmarks that were chosen by staff based on the clinical studies of effects of NO<sub>2</sub> on airways responsiveness. The first draft referred to the 1-hour concentrations of 0.20 ppm, 0.25 ppm, and 0.30 ppm as potential health benchmark levels. The first draft characterized these levels as the lowest levels at which controlled human studies have provided sufficient evidence for the occurrence of nitrogen dioxide-related airway responsiveness. However, the second draft, referring to the final ISA, added a benchmark at 0.10 ppm. A careful review of the changes between the second draft ISA and the final ISA demonstrates that there is no new data reporting effects on airway responsiveness at 0.10 ppm. Therefore, the addition of a 0.10 ppm benchmark is not scientifically defensible.

The final ISA includes the results of a meta-analysis that was not vetted in the first or second draft ISAs. The final ISA includes Table 3.1-2 that summarizes relevant studies and Table 3.1-3 that presents the results of the meta-analysis that is described on page 3-16. The text indicates a number of changes from the meta-analysis reported in Folinsbee 1992 that was influential in the 1995/6 review of the standard. The most important issue with the new analysis is that it relies on the Orehek, et al. 1976 study of airway responsiveness that has never been replicated. The large effect reported by Orehek et al. is the reason there is a significant effect at 0.10 ppm in the 50 subjects included in the analysis. However, the Orehek study was fully evaluated and considered during previous NO<sub>2</sub> reviews and discounted because it has never been replicated. For example, the 1995 Staff Paper explicitly concluded “Several controlled exposure studies (Ahmed et al.,

1983a,b; Bylin et al., 1985; Hazucha et al., 1982, 1983; Koenig et al., 1985; Orehek et al., 1981) of asthmatics showed no significant effect on responsiveness at very low NO<sub>2</sub> concentrations of 0.1 to 0.12 ppm.”<sup>5</sup> There is no new data to change this conclusion.

Reliance on the Orehek et al. 1976 study in an unpublished meta-analysis to claim an effect at 0.10 ppm is scientifically unsound. The Orehek paper was not included in the second draft ISA and was used for this critical change but not discussed in the final ISA. The summary of the conclusions regarding airway responsiveness in the current review and in the past review in Table 5.3-1 of the second draft ISA are remarkably similar, noting that this is the most sensitive indicator of response, with effects in the range of 0.20 to 0.30 ppm. In the final ISA, these conclusions were re-written to imply new information showing effects now at 0.10 ppm. This change cannot be scientifically supported.

A number of key details related to the change have not had sufficient CASAC review. The REA includes (as Table 4-1) Table 3.1-3 from the ISA that reports the results of the new meta-analysis but excludes Table 3.1-2 from the ISA that identifies the Orehek et al. 1976 paper and the two other papers that are included in the analysis of effects at 0.10 ppm. Table 1 in the first draft REA was a listing and summary of the key controlled human exposure studies of airways responsiveness. It included 19 studies, but not one of the three studies used in the new meta-analysis evaluating effects at 0.10 ppm was listed as a key study in the first draft REA.

**The public health significance of any clinical effects identified in the 0.20 to 0.30 ppm range needs to be fully discussed in order to put the public health impact of the various exposure scenarios in the REA in perspective**

The airway hyperresponsiveness identified in the human clinical studies of allergen and nonspecific bronchial challenges in asthmatics needs to be put into perspective. The REA notes that transient increases in airway responsiveness have the potential to increase symptoms and worsen asthma control. However, the REA also notes that the allergen-induced effects were not accompanied by any changes in pulmonary function or subjective symptoms. The authors of these studies note that these are subclinical effects from repeated short-term exposures that might be of clinical importance (Barck et al. 2002, 2005a). The recent California review of that state’s NO<sub>2</sub> air quality standard noted that these are subclinical effects, that the various endpoints were not consistently seen across studies with very similar protocols, and that dose-response information is lacking. Furthermore, Folinsbee 1992 noted that the NO<sub>2</sub> exposures in the studies in his meta-analysis did not lead to clinical asthma exacerbation. The lack of clinically important responses in the now numerous human exposure studies needs to be acknowledged in the REA.

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<sup>5</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 37.

**The staff's preliminary discussion of the appropriate indicator, averaging time, form, and range for the level of the primary standard is incomplete and overly-conservative**

Chapter 5 identifies potential alternative standards for analysis. Because the ISA concluded that the only area where there was information sufficient to infer a likely causal relationship was for effects of short-term exposure to NO<sub>2</sub> on respiratory morbidity, the REA focuses on short-term endpoints and a potential short-term standard. However, a decision regarding the current annual standard, which was set to guard against long-term effects and limit short-term exposures to guard against short-term effects, will need to be made during the upcoming rulemaking. Therefore, the relationship between annual mean and peak 1-hour and 24-hour exposures should be evaluated in the REA. Such an analysis will also be valuable in judging the appropriateness of the roll-up and roll-down procedures used in the REA to simulate attainment of alternative standards.

**Indicator** Since the vast majority of information on the health effects of various oxides of nitrogen relates to nitrogen dioxide, we agree that NO<sub>2</sub> remains the appropriate indicator. However, the ISA notes that current monitoring overestimates the ambient concentrations of NO<sub>2</sub> due to interferences from other gaseous species. Some sensitivity analyses of the impact of the overestimation should be included in the final REA.

**Averaging time** Staff has chosen to evaluate standards with a 1-hour averaging time. Given the evidence from controlled studies of respiratory effects from short-term exposures, this is reasonable. However, implementing a 1-hour standard may be very difficult given the limitations of current atmospheric models. Therefore, consideration should be given to alternative standards and approaches that can provide equal protection but can be implemented in a practical manner. The Agency appears poised to change from its long-standing annual standard to a 1-hr standard. As in the 1995/96 review, EPA should evaluate the extent to which a long-term standard will protect against short-term exposures of concern.

**Form** Staff recognizes the need for a stable and robust regulatory target and so recommends a 98<sup>th</sup> or 99<sup>th</sup> percentile form averaged over three years akin to the judgment made in the recent PM NAAQS review. Apparently this would be a 98<sup>th</sup> or 99<sup>th</sup> percentile of the 1-hour daily maximum NO<sub>2</sub> concentrations at a site. We encourage the development of a stable and robust target that is linked both to effects of concern and a modeling system that can be used to develop a robust State Implementation Plan.

**Level** To determine a range of levels for a short-term standard Staff evaluated both the human clinical and epidemiological databases. The REA notes that only effect detected in controlled human studies that is expected at or near ambient levels is airway hyperresponsiveness in asthmatics. From epidemiology, there are various positive associations of NO<sub>2</sub> with respiratory endpoints in single-pollutant models but as indicated in footnote 4, referring to the staff's preferred studies in Figures 5-1 and 5-2, the effect estimates only retained statistical significance in one of the studies that evaluated multi-

pollutant models.

Based on the airway responsiveness results and the epidemiologic studies, staff indicated that an appropriate upper end of the range of potential standard levels is a daily maximum 1-hr concentration of 0.20 ppm. Since the evidence for causality is strong for the controlled studies but weak and controversial for the observational studies, we believe more weight should be put on the controlled studies in choosing an appropriate range. Since the effects at 0.20 ppm in controlled studies are subclinical, the choice of 0.20 ppm as the upper end of the range is already health conservative.

In identifying additional levels to analyze in the REA, staff considered observational studies reporting associations in areas with low NO<sub>2</sub> concentrations, the new meta-analysis referred to above that claims airway responsiveness effects at 0.10 ppm, and the lack of controlled studies of severe asthmatics who could experience increased effects compared to mild asthmatics. Based on these considerations, staff indicated that standard levels of 0.10 and 0.15 ppm would be considered. Finally, staff referred to the Delfino et al. 2002 study reporting an association with asthma symptoms in a location with low NO<sub>2</sub> (that became non-significant in a two-pollutant model with PM10) to support the choice of 0.05 ppm as the low end of the range.

Since the new meta-analysis is not scientifically sound, and there is no reason to alter the judgment in 1995 that there are no significant effects on responsiveness in asthmatics at 0.10 to 0.12 ppm, the choice of potential standards in the REA is overly conservative. The upper end of range could well be 0.30 ppm and still be health protective given the nature of the first subclinical effects of NO<sub>2</sub>. The lower end of the range could be 0.20 ppm or somewhat lower if a margin of safety is desired. However, it should also be borne in mind that the allowed frequency of occurrence of a short-term standard, by itself, provides a substantial margin of safety.

In evaluating the health risks from NO<sub>2</sub>, the Agency should take note of CASAC's advice regarding the second draft ISA that:

“The human clinical studies reviewed in the ISA need to be interpreted with caution. The lowest reported effect of NO<sub>2</sub> exposure was found in three Swedish studies of airway responses to antigen challenge in allergic asthmatics. However, other human clinical studies have shown mixed results with some studies failing to find biologically significant health effects at similar or higher levels of NO<sub>2</sub> exposure alone.”<sup>6</sup>

The use of epidemiological associations to choose potential standards is equivocal and misleading. Given the biologically implausible wide range of positive and negative associations in time-series studies of ambient pollutants in systematic analyses, the search for the epidemiological study that reports the strongest association with NO<sub>2</sub> (or with any other pollutant) at the lowest concentration of the pollutant will identify an outlier, not a

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<sup>6</sup> June 25, 2008 CASAC letter from Dr. Rogene Henderson to Administrator Johnson, EPA-CASAC-08-015, at page 4.

real effect.

In evaluating the risk to public health based on the totality of evidence, the Agency should take note of the qualifications in CASAC's statement that:

“In summary, the new scientific literature reviewed in the second draft of this ISA document provides a number of strong indications of possible NO<sub>2</sub> health effects, but confounding or exacerbating co-pollutants and variable findings in human clinical studies remain problematic.”<sup>7</sup>

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<sup>7</sup> June 25, 2008 CASAC letter, EPA-CASAC-08-015, at page 4.