Comments on Chapter 10 of the Final Risk and Exposure Assessment to Support the Review of the NO_2 Primary National Ambient Air Quality Standard (Docket ID. No. EPA-HQ-2006-0922)

Julie E. Goodman, PhD, DABT
Gradient Corporation, Cambridge, MA

on behalf of the American Petroleum Institute

December 1, 2008

Chapter 10 of the *Risk and Exposure Assessment to Support the Review of the NO_2 Primary National Ambient Air Quality Standard* (hereafter referred to as the "REA") assesses the adequacy of the current nitrogen dioxide (NO_2) primary National Ambient Air Quality Standard (NAAQS) of 0.053 ppm (annual average) and alternative primary NO_2 standards (US EPA, 2008a). This assessment is based on the scientific evidence provided in the NO_2 *Integrated Science Assessment for Oxides of Nitrogen* (hereafter referred to as the "ISA") and the exposure and risk characterization data presented in the REA (US EPA, 2008a,b). US EPA concluded that "the scientific evidence reasonably supports a range of standard levels from 50 ppb to 200 ppb, with strong support for a level at or below 100 ppb" based on fewer NO_2-related emergency department (ED) visits, on average, than those associated with just meeting the current standard. US EPA based this conclusion on epidemiology studies focused on these concentrations, and noted that this is also supported by "1) evidence from controlled human exposure studies of airway hyper-responsiveness in asthmatics, 2) controlled human exposure and animal toxicological studies of impaired host-defense systems and increased risk of susceptibility to viral and bacterial infection, and 3) controlled human exposure and animal toxicological studies of airway inflammation" (US EPA, 2008a). The REA fails to consider several issues, discussed below, which suggest that clinical and epidemiology studies do not provide a sufficient scientific basis for establishing a 1-hr standard of 0.05 to 0.1 ppm NO_2.

1. Studies assessing the association between 1-h daily maximum levels of NO_2 close to 0.1 ppm or 0.2 ppm and respiratory morbidity do not support causation.

US EPA (2008a) primarily relies on six studies to support an appropriate upper end of the range of the 1-h daily maximum NO_2 standard. Four of these focused on maximum 1-h NO_2 levels of approximately 0.1 ppm (Peel *et al.*, 2005; NYDOH, 2006; Ito *et al.*, 2007; Tolbert *et al.*, 2007). The REA reports:

> Positive and statistically-significant associations were observed in several key US epidemiologic studies associated with 1-h daily maximum levels of NO_2 close to 0.1 ppm (Peel *et al.*, 2005; NYDOH, 2006; Ito *et al.*, 2007; Tolbert *et al.*, 2007) (see Figure 5-1). In multi-pollutant models, effect estimates remained statistically-significant in the study by Ito and positive, but non-significant, in the other studies.

This statement is misleading. There were several single-pollutant models in these studies that did not produce statistically significant effects. For example, the association between NO_2 and ED visits for asthma in the Peel *et al*. (2005) study was not statistically significant. In addition, there was a "key" study identified in Chapter 5 (Jaffe *et al.*, 2003) for which there were no statistically significant risks based on single-pollutant models that was not discussed in Chapter 10. Also, the risk estimates that were statistically significant in the studies noted above were not robust; that is, they were small in magnitude and their lower 95% confidence intervals (95% CIs) were close to 1. Both null results and the strength of significant associations should be considered in a proper weight-of-evidence analysis, but the REA does not do this. It should also be noted that statistical significance in these models did not fully account for all uncertainties, such as measurement error and exposure misclassification. Had these uncertainties been accounted for, it is possible that the risk estimates would not have been statistically significant. Finally, and perhaps most importantly, Chapter 10 of the REA does not give appropriate weight to the correlation of NO_2 with other co-pollutants, or that the study by Ito *et al*. (2007) was the only study reporting statistically significant effects in multi-pollutant models. Moreover, despite reporting significant effects using a multi-pollutant model, Ito *et al*. stated: "NO_2 may be a good indicator of more air pollution from local combustion sources. NO_2 is sometimes referred to as a surrogate marker of traffic-related air pollution." They suggested that it may be a surrogate for ultrafine particles or an agent "that may or may not be measured regularly and yet has some potential health effects."

In addition to the studies assessing health effect at NO_2 concentrations around 0.1 ppm, the REA relies on two studies with the highest 1-h NO_2 concentrations. Regarding these studies, US EPA (2008a) states:

> Positive and statistically-significant NO_2 effect estimates were also observed in the two key US studies associated with the highest 1-h NO_2 concentrations (Linn *et al.*, 2000; Ostro *et al.*, 2001). These studies were associated with 98th and 99th percentile 1-h daily maximum NO_2 concentrations from 0.18 ppm to 0.21 ppm. These studies did not evaluate multi-pollutant models. Therefore, they do not provide additional support for an

> independent association between NO_2 and respiratory morbidity beyond that provided by the studies noted above.

It is notable that the REA acknowledges that these studies are not useful for assessing the causal association between short-term NO_2 exposure and respiratory morbidity because effects were not evaluated in multi-pollutant models. This is not consistent with their evaluation of studies assessing 1-h daily maximum levels of NO_2 close to 0.1 ppm, for which statistically significant effects were not found in multi-pollutant models except those described by Ito *et al*. (2007), but for which US EPA still considered to provide evidence of positive associations with NO_2. The REA should put more emphasis on multi-pollutant models, particularly when results differ from single pollutant models.

In sum, there is no weight-of-evidence assessment in Chapter 10 of the REA. US EPA (2008a) does not consider all data (statistically significant and not) equally, nor does it consider the uncertainties associated with exposure measurements and the likelihood that associations between respiratory morbidity and short-term NO_2 may actually be attributable to other factors. Thus, these epidemiology studies do not provide sufficient evidence for an upper end of the range of the 1-h daily maximum NO_2 standard.

2. The study by Delfino *et al*. (2002) does not provide sufficient evidence for determining an appropriate lower end of the range of levels for a standard.

One of two primary factors US EPA (2008a) considered for determining the lower end of the range of levels for the standard that are supported by the evidence was the study by Delfino *et al*. (2002). Regarding this study, US EPA states:

> [T]he study by Delfino *et al*., (2002) provides evidence for associations between short-term ambient NO_2 concentrations and respiratory morbidity in a location where NO_2 concentrations were well below levels in most other key US epidemiologic studies. This study reports positive associations between 1-h and 8-h (only 8-h associations were statistically-significant) levels of NO_2 and asthma symptoms in a location where the 98th and 99th percentile 1-h daily maximum NO_2 concentrations were 0.05 and 0.053 ppm, respectively.

In fact, the study by Delfino *et al*. (2002) does *not* provide sufficient evidence for determining the lower end of the range for several reasons. There were only 22 asthmatic children in this study and analyses stratified by medication use (on/off) were conducted using only 10 and 12 children, respectively. These small numbers could have lead to unstable estimates and spurious results. As with several other

studies, Delfino *et al*. (2002) relied on fixed site monitors to determine levels in individuals, and this could have lead to exposure misclassification, also leading to spurious results (and at the very least, led to a higher degree of uncertainty that was not accounted for). Eight-h max NO_2 was statistically significantly correlated with every other independent variable assessed in this study (*i.e.*, 8-h max O_3, 1-h max PM_{10}, 24-h mean PM_{10}, 1-h max NO_2, 12-h daytime fungi, 24-h pollen, max temperature, and 24-h mean relative humidity) and 1-h max NO_2 was statistically significantly correlated with all of these except 8-h max O_3 (see Table 3, Delfino *et al*., 2002). Any statistically significant associations observed between 8-h NO_2 and asthma symptoms may have been attributable to one of these other factors. Finally, Delfino *et al*. (2002) stated that their sensitivity analysis "identified the need for both a greater amount of data to model the shape of the exposure-response curve and better modeling strategies to determine that shape." Given this high level of uncertainty, the Delfino *et al*. (2002) study is not appropriate for determining the lower end of the range of the standard.

3. Clinical studies do not support a causal association between short-term NO_2 exposure and increased airway hyper-responsiveness.

Overall, results from the clinical, controlled-exposure studies do not provide clear evidence that there is a causal association between short-term (*i.e.*, less than 2 hours) exposure to NO_2 and increased airway hyper-responsiveness in individuals with asthma. US EPA's determination that increased airway hyper-responsiveness to non-specific bronchial challenges occurs at near ambient concentrations (0.1 – 0.3 ppm) relies primarily on US EPA's unpublished meta-analysis of controlled exposure studies (Section 3.1.3.2 of the ISA, US EPA, 2008b). US EPA's analysis is based on a meta-analysis published by Folinsbee (1992), and excludes studies that used specific allergen challenges, but includes an additional, more recent study that used a non-specific bronchial challenge. US EPA's meta-analysis also focuses on results involving resting exposures to NO_2, for which the response was greater than for studies that involved NO_2 exposures during exercise. US EPA's determination is questionable in that there is no clear relationship between NO_2 concentration and airway hyper-responsiveness for concentrations up to 1.0 ppm; the majority of the studies included in the meta-analysis do not show any statistically significant or biologically meaningful effect due to NO_2 exposure; the greater response for subjects at rest contradicts results from other studies and does not have a readily explainable biological basis; and the weight-of-evidence from more recent studies does not indicate that NO_2 exposure up to a concentration of at least 0.4 ppm has a significant effect on airway hyper-responsiveness either for individuals with or without asthma.

A key tenet in establishing a causal relationship between an exposure and a subsequent response is that the magnitude of the response should increase as exposure increases. Yet, as shown in Figure 1, there is no clear relationship between NO_2 concentration and non-specific airway hyper-responsiveness for the studies included in the Folinsbee (1992) meta-analysis.

Figure 1a

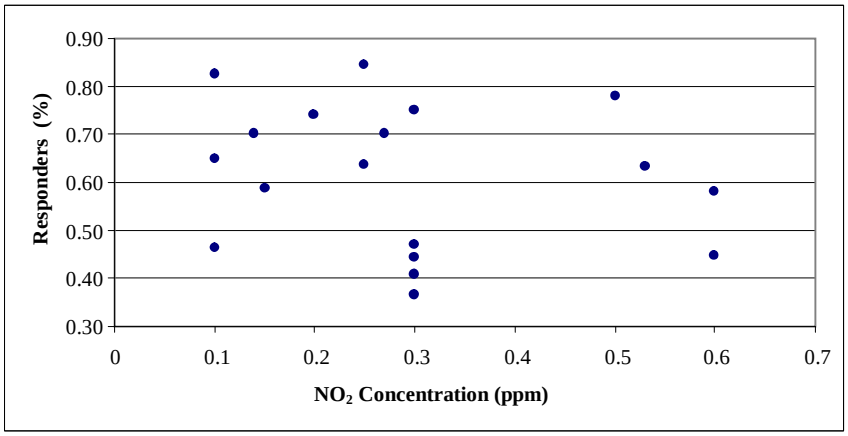

Figure 1b

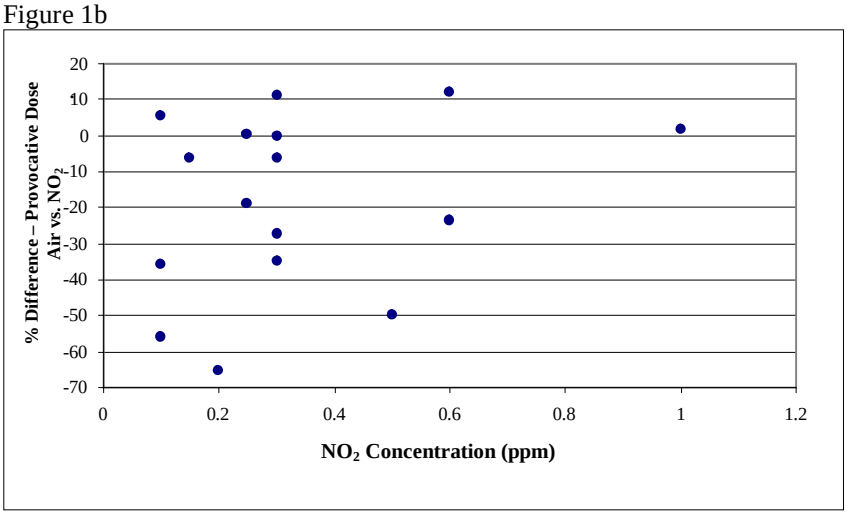

Figure 1. Top panel (a) shows the percent of study subjects who responded to NO_2 exposure with increased airway hyper-responsiveness (relative to the number of subjects who responded with both increased and decreased airway hyper-responsiveness but excluding those with no change) as a function of NO_2 concentration. Bottom panel (b) shows the percent difference in the provocative dose required for an airway response following exposure to either air or NO_2, as a function of NO_2 concentration. Data from individual studies are plotted as individual circles, based on Folinsbee (1992). Note that in Figure 1a, the percent of positive responders is overestimated because subjects whose airway response did not differ between air and NO_2 were excluded, and because it likely includes subjects whose change in responsiveness was within the range of normal intra-individual variability. Figure 1b excludes results from two studies, at 0.2 and 0.8 ppm, with a difference between air and NO_2 of 0.02 and -0.06, respectively, because Folinsbee did not provide data on the magnitude of the response.

Importantly, the lack of a concentration-response relationship for the studies included in the Folinsbee (1992) meta-analysis is similarly borne out in individual studies from the Folinsbee analysis that have evaluated more than one NO_2 concentration, none of which show a concentration-response between NO_2 exposure and airway hyper-responsiveness (*e.g.*, Avol *et al.*, 1988; Bylin *et al.*, 1988; Jorres and Magnussen, 1990; Linn *et al.*, 1986; Rasmussen *et al.*, 1990, as cited in Folinsbee, 1992; Roger *et al.*, 1990). Further, the lack of a concentration-response for the studies included in the Folinsbee meta-analysis is understandable when evaluating the individual studies, the majority (15 of 20) of which did not show differences in response that were either statistically significant or biologically meaningful.

In the Folinsbee (1992) meta-analysis, a statistically significant relationship between NO_2 and airway hyper-responsiveness is observed only for subjects who were exposed at rest, but not while exercising. This counter-intuitive observation contradicts results from many controlled exposure studies which find that exercise enhances airway response to inhaled pollutants (*e.g.*, Bauer *et al.*, 1986; Linn *et al.*, 1985; Rubinstein *et al.*, 1990; Sheppard *et al.*, 1981). To explain the inconsistency between the meta-analysis and results from other studies, Folinsbee cites a study by Inman *et al.* (1990), in which responsiveness to methacholine is reduced *during* exercise; as well as a study by Freedman *et al.* (1988, as cited in Folinsbee), in which methacholine-induced bronchoconstriction is reduced more rapidly with exercise. However, in the studies cited by Folinsbee, exercise *preceded* the methacholine challenge (*i.e.*, Jorres and Magnussen, 1991; Kleinman *et al.*, 1983; Roger *et al.*, 1990; Strand *et al.*, 1996). Hence, the studies by Inman *et al.* and Freedman *et al.* that Folinsbee cites do not necessarily explain the paradox observed by Folinsbee of a greater effect on airway responsiveness at rest *vs.* with exercise.

As with many of the studies included in the Folinsbee analysis, more recent studies similarly do not indicate that short-term exposure (30 minutes to 6 hours) to NO_2, at levels ranging from 0.2 to 0.4 ppm, affects airway hyper-responsiveness (*e.g.*, Barck *et al.*, 2005; Jenkins *et al.*, 1999; Strand *et al.*, 1998; Witten *et al.*, 2005). These more recent studies evaluated airway response to naturally occurring allergens, including plant allergens (*e.g.*, birch, grass, timothy) and house dust mites.

Taken together, the clinical studies do not support a causal association between short-term NO_2 exposure and increased airway hyper-responsiveness.

4. US EPA overestimated the percentage of asthmatics who may experience NO_2-related airway hyper-responsiveness.

US EPA estimated the percentage of asthmatics who may be sensitive to NO_2-induced hyper-responsiveness based on the percentage of positive responders (*i.e.* individuals with increased airway hyper-responsiveness following exposure to NO_2) relative to the number of positive responders plus the number of negative responders (*i.e.*, individuals with decreased airway hyper-responsiveness following NO_2 exposure), as reported by Folinsbee (1992). However, the studies in the Folinsbee meta-analysis also included data for individuals whose response did not differ between NO_2 and air, and who presumably would not be sensitive to NO_2-induced hyper-responsiveness. For example, the study by Orehek *et al*. (1976) included data for three individuals whose response did not differ between NO_2 and air. By excluding this data, US EPA overestimated the percentage of individuals with asthma who may be susceptible to NO_2-related airway hyper-responsiveness.

A second way in which US EPA may have overestimated the number of individuals potentially sensitive to NO_2-induced hyper-responsiveness is by classifying as positive responders individuals whose response was within normal range of intra-individual variability. As US EPA correctly notes in the REA (US EPA, 2008a), the Folinsbee meta-analysis does not account for the magnitude of response. Yet it is important to distinguish responses which may be due to normal day-to-day variability from responses which are truly due to NO_2 exposure. Potential intra-individual variability can be estimated roughly based on responses of subject number 16 in the study by Orehek *et al*. (1976), who was exposed twice to air and twice to NO_2. Using this estimate of intra-individual variability, there at least six individuals classified as positive responders whose responses may have been due to normal variability rather than to any effect of NO_2.

A third way in which US EPA may have overestimated the number of individuals potentially susceptible to NO_2-induced hyper-responsiveness is by limiting their analysis to non-specific airway hyper-responsiveness, following challenge with pharmacological agents such as methacholine and carbochol, high concentrations of sulfur dioxide (SO_2), or cold air. In their own, unpublished meta-analysis, US EPA (2008b) has excluded studies from the Folinsbee (1992) analysis that used specific challenges (*i.e.*, allergens, such as ragweed), and has added a more recent study by Strand *et al*. (1996) that used a non-specific histamine challenge. Moreover, both of the studies that used SO_2 challenges assessed responsiveness to SO_2 using hyperventilation, which by itself can increase airway hyper-responsiveness

(discussed in US EPA, 1993). Non-specific challenges to methacholine, carbachol, and high concentrations of SO_2 may overestimate responses to relevant challenges, such as ragweed, grass, and cold air, that individuals may actually be exposed to in their daily lives. Among studies that used specific allergen challenges (*i.e.*, ragweed, grass) or cold, which are more relevant than challenges with carbachol, methacholine, or hyperventilated SO_2, a significant effect of NO_2 on hyper-responsiveness was observed only in the study by Bauer *et al*. (1986). The enhanced response to NO_2 in the study by Bauer *et al*. may be at least partly due to use of a mouthpiece for exposing subjects to NO_2. As discussed by Sheppard *et al*. (1984), mouthpiece exposures tend to over-estimate responses relative to exposures involving more natural, oronasal breathing.

By excluding individuals whose responses did not differ between NO_2 and air, by not accounting for intra-individual variability, and by limiting their analysis to non-specific airway hyper-responsiveness, US EPA overestimated the percentage of asthmatics who may experience NO_2-related airway hyper-responsiveness.

5. Evidence from epidemiological and clinical studies does not consistently support a linear no-threshold dose-response association between short-term NO_2 exposure and respiratory morbidity.

With regard to the epidemiological evidence, US EPA (2008a) primarily relies on section 5.3.2.9 (p. 5-15) of the ISA, which concludes that the NO_2 epidemiologic studies provide "little evidence of any effect threshold." In Chapter 4 of the ISA, US EPA (2008b) states:

> [O]f the epidemiology studies that attempted to look at the shape of the concentration-response below 50 ppb, one indicated that effects were weaker at lower levels (Hajat *et al*. 1999), and one showed a steeper log-linear relationship at lower doses (Burnett *et al*. 1997c). The remainder found that a linear function best described the data (Burnett *et al*. 1997a,b; Jaffe *et al*. 2003; Tenias *et al*., 1998; Castellsague *et al*., 1995). These results do not provide adequate evidence to suggest that nonlinear departures exist along any part of this range of NO_2 exposure concentrations.

US EPA (2008b) suggests several reasons why "it is difficult to identify any threshold that may exist." These are described in Chapter 5 of the ISA ,where US EPA (2008b) states:

> Factors that made it difficult to identify any threshold that may exist included: interindividual variation; additivity of pollutant-induced effects to the naturally occurring

> background disease processes; additivity to health effects due to other environmental insults having a mode of action similar to that of NO_2; exposure error; and response measurement error. Low data density in the lower concentration range as a result of limited monitoring is a particular problem in terms of measurement error. Additionally, if the concentration-response relationship was shallow, identification of any threshold that may exist will be more difficult to discern.

This statement is only partially correct. Some of these factors, such as a shallow concentration-response curve and low data density, may mask a threshold if one exists, as the ISA correctly notes. The other factors will not confound the identification of a threshold, but may change the shape of the concentration-response curve. It is conceivable that US EPA is implying that these other factors will lead to a linear low-dose concentration-response curve which, by definition, has no threshold. This view was recently put forth by White *et al*. (2008), who suggested that interindividual variation, exposure misclassification, and additivity-to-background will "tend to smooth and linearize the dose-response relationship." In reality, however, this is not always the case (Rhomberg, 2008). Interindividual variation may broaden the concentration-response curve, but it will not linearize it (as suggested by White *et al*., 2008). Exposure misclassification may also flatten a concentration-response curve, and may mask what may in fact be a steeper curve. Additivity-to-background may support a linear model, but only under certain situations. It is incorrect to assume it will always do so, and the REA has not assessed whether it does or does not in this situation.

Although several studies cited in the ISA reported that a linear model provided the best fit to the data, these data have many uncertainties (*e.g.*, exposure misclassification, measurement error), few of which are accounted for in statistical models. Even if a linear model best describes the reported data, it is plausible that a non-linear model would have better described the data were these uncertainties taken into account. Because of the many uncertainties, the currently-available NO_2 epidemiology data are simply not robust enough to determine whether a linear no-threshold dose-response model describes the association between short-term NO_2 exposure and respiratory morbidity.

While it may be difficult to discern whether or not the epidemiology data support a linear, no threshold concentration-response relationship between NO_2 and morbidity, the clinical data do not support a linear relationship between NO_2 exposure and airway hyper-responsiveness, as discussed in Section 3. Because some of the uncertainties in epidemiology studies, such as exposure misclassification, are controlled in the clinical studies, it is much easier to discern the nature of concentration-response

relationship for clinical studies. As noted, neither a meta-analysis of the Folinsbee studies, nor individual studies that evaluated more than one NO_2 exposure concentration, provide evidence that the NO_2 concentration-response relationship is linear, with no threshold. Jenkins *et al.* (1999), who evaluated NO_2-induced airway hyper-responsiveness following a specific allergen challenge with house dust mite, similarly concluded that there may be a threshold for the effects of NO_2 on airway responses:

> These results suggest that the pollutant-induced changes in airway response of mild atopic asthmatics to allergen may be dependent on a threshold concentration, rather than the total amount of inhaled over a period of time.

Taken together, the evidence from epidemiological and clinical studies does not consistently support a linear no-threshold dose-response association between short-term NO_2 exposure and respiratory morbidity.

6. Conclusion

In conclusion, neither epidemiology nor clinical studies provide a sufficient scientific basis for establishing a 1-hr standard of 0.05 to 0.1 ppm NO_2. Although statistically significant associations were observed between NO_2 concentrations of approximately 0.1 ppm and ED visits in some (but not all) studies, this association remained significant when exposure to other pollutants was accounted for in only the study by Ito *et al*. (2007), who nonetheless concluded that NO_2 may be a surrogate for some other pollutant with potential health effects, rather than actually causing adverse health effects. The study by Delfino *et al*. (2002), which US EPA relies on for establishing the lower end of potential 1-hour standards at 0.05, is quite small (n = 22) and subject to similar limitations as those studies measuring risks at approximately 0.1 ppm. Thus, it is too uncertain to identify the nature of the concentration-response relationship with any confidence. Although increased airway hyper-responsiveness has been observed in some of the clinical studies at NO_2 concentrations of 0.1 ppm, the majority of clinical studies show no associations with airway hyper-responsiveness at this concentration, and no concentration-response association up to at least 0.4 ppm NO_2. Moreover, we determined that US EPA overestimated the percentage of asthmatics who may experience NO_2-related airway hyper-responsiveness. Finally, neither epidemiological or clinical studies consistently support a linear no-threshold dose-response association between short-term NO_2 exposure and respiratory morbidity. Taken together, the weight of evidence does not support changing the current NAAQS to a 1-hr standard of 0.05 to 0.1 ppm NO_2.

7. References

Avol, EL; Navidi, WC; Rappaport, EB; Peters, JM. May 1998. "Acute effects of ambient ozone on asthmatic, wheezy, and healthy children." Health Effects Institute (Cambridge, MA) Health Effects Institute Research Report No. 82. 30p.

Barck, C; Lundahl, J; Hallden, G; Bylin, G. 2005. "Brief exposures to NO_2 augment the allergic inflammation in asthmatics." *Environ. Res.* 97:58-66.

Bauer, MA; Utell, MJ; Morrow, PE; Speers, DM; Gibb, FR. 1986. "Inhalation of 0.30 ppm nitrogen dioxide potentiates exercise-induced bronchospasm in asthmatics." *Am. Rev. Respir. Dis.* 134:1203-1208.

Bylin, G; Hedenstierna, G; Lindvall, T; Sundin, B. 1988. "Ambient nitrogen dioxide concentrations increase bronchial responsiveness in subjects with mild asthma." *Eur. Respir. J.* 1 (7):606-612.

Delfino, RJ; Zeiger, RS; Seltzer, JM; Street, DH; McLaren, CE. 2002. "Association of asthma symptoms with peak particulate air pollution and effect modification with anti-inflammatory medication use." *Environ. Health Perspect.* 110(10):A607-617.

Folinsbee, LJ. 1992. "Does nitrogen dioxide exposure increase airways responsiveness?" *Toxicol. Ind. Health* 8 :273-283.

Inman, MD; Watson, RM; Killian, KJ; O'Byrne, PM. 1990. "Methacholine airway responsiveness decreases during exercise in asthmatic subjects." *Am. Rev. Respir. Dis.* 141:1414-1417.

Ito, K; Thurston, GD; Silverman, RA. 2007. "Characterization of PM2.5, gaseous pollutants, and meteorological interactions in the context of time-series health effects models." *J. Expo. Sci. Environ. Epidemiol.* 17(Suppl. 2):S45-S60.

Jaffe, DH; Singer, ME; Rimm, AA. 2003. "Air pollution and emergency department visits for asthma among Ohio Medicaid recipients, 1991-1996." *Environ. Res.* 91 :21-28.

Jenkins, HS; Devalia, JL; Mister, RL; Bevan, AM; Rusznak, C; Davies, RJ. 1999. "The effect of exposure to ozone and nitrogen dioxide on the airway response of atopic asthmatics to inhaled allergens." *Am J Respir Crit Care Med.* 160:33-39.

Jorres, R; Magnussen, H. 1990. "Airways response of asthmatics after a 30 minute exposure, at resting ventilation, to 0.25 ppm NO2 or 0.5 ppm SO2." *Eur. Respir. J.* 3(2):132-137.

Jorres, R; Magnussen, H. 1991. "Effect of 0.25 ppm nitrogen dioxide on the airway response to methacholine in asymptomatic asthmatic patients." *Lung* 169:77-85.

Kleinman, MT; Bailey, RM; Linn, WS; Anderson, KR; Whynot, JD; Shamoo, DA; Hackney, JD. 1983. "Effects of 0.2 ppm nitrogen dioxide on pulmonary function and response to bronchoprovocation in asthmatics." *J. Toxicol. Environ. Health* 12 (4-6) :815-826.

Linn, WS; Shamoo, DA; Avol, EL; Whynot, JD; Anderson, KR; Venet, TG; Hackney, JD. 1986. "Dose-response study of asthmatic volunteers exposed to nitrogen dioxide during intermittent exercise." *Arch. Environ. Health* 41(5):292-296.

Linn, WS; Solomon, JC; Trim, SC; Spier, CE; Shamoo, DA; Venet, TG; Avol, EL; Hackney, JD. 1985. "Effects of exposure to 4 ppm nitrogen dioxide in healthy and asthmatic volunteers." *Arch. Environ. Health* 40 (4) :234-239.

New York State, Dept. of Health (NYDOH) July 2006. "A Study of Ambient Air Contaminants and Asthma in New York City. Part A: A Comparison of Ambient Air Quality in the Bronx and Manhattan. Part B: Air Contaminants and Emergency Department Visits for Asthma in the Bronx and Manhattan." Report to Agency for Toxic Substances and Disease Registry (ATSDR); New York State, Energy Research and Development Authority. NTIS PB2006-113523. 260p.

Orehek, J; Massari, JP; Gayrard, P; Grimaud, C; Charpin, J. 1976. "Effect of short-term, low lwvel nitrogen dioxide exposure on bronchial sensitivity of asthmatic patients." *J. Clin. Invest.* 57:301-307.

Peel, JL; Tolbert, PE; Klein, M; Metzger, KB; Flanders, WD; Todd, K; Mulholland, JA; Ryan, PB; Frumkin, H. 2005. "Ambient air pollution and respiratory emergency department visits." *Epidemiology* 16(2):164-174.

Rhomberg, LR. 2008 "Linear low-dose extrapolation for non-cancer responses is not generally appropriate." *Environ. Health Perspect.* In press.

Roger, LJ; Horstman, DH; McDonnell, W; Kehrl, H; Ives, PJ; Seal, E; Chapman, R; Massaro, E. 1990. "Pulmonary function, airway responsiveness, and respiratory symptoms in asthmatics following exercise in NO(2)." *Toxicol. Ind. Health* 6(1):155-171.

Rubinstein, I; Bigby, BG; Reiss, TF; Boushey, HA. 1990 "Short-term exposure to 0.3 ppm nitrogen dioxide does not potentiate airway responsiveness to sulfur dioxide in asthmatic subjects." *Am. Rev. Respir. Dis.* 141:381-385.

Sheppard, D; Eschenbacher, WL; Boushey, HA; Bethel, RA. 1984. "Magnitude of the interaction between the bronchomotor effects of sulfur dioxide and those of dry (cold) air." *Am. Rev. Respir. Dis.* 130:52-55.

Sheppard, D; Saisho, A; Nadel, JA; Boushey, HA. 1981. "Exercise increases sulfur dioxide-induced bronchoconstriction in asthmatic subjects." *Am. Rev. Respir. Dis.* 123:486-491.

Strand, V; Salomonsson, P; Lundahl, J; Bylin, G. 1996. "Immediate and delayed effects of nitrogen dioxide exposure at an ambient level on bronchial responsiveness to histamine in subjects with asthma." *Eur. Respir. J.* 9:733-740.

Strand, V; Svartengren, M; Rak, S; Barck, C; Bylin, G. 1998. "Repeated exposure to an ambient level of NO2 enhances asthmatic response to a nonsymptomatic allergen dose." *Eur Respir J.* 12:6-12.

Tolbert, PE; Klein, M; Peel, JL; Sarnat, SE; Sarnat, JA. 2007. "Multipollutant modeling issues in a study of ambient air quality and emergency department visits in Atlanta." *J. Expo. Sci. Environ. Epidemiol.* 17:S29-S35.

US EPA. 2008a. "Risk and Exposure Assessment to Support the Review of the NO2 Primary National Ambient Air Quality Standard." Office of Air Quality Planning and Standards (Research Triangle Park, NC), US EPA-452/R-08-008a. 968p., November.

US EPA. 2008b. "Integrated Science Assessment for Oxides of Nitrogen." National Center for Environmental Assessment (NCEA) - RTP Division, US EPA/600/R-08/071, 260p., July.

US EPA. 1993. "Air Quality Criteria Document for the Oxides of Nitrogen." National Center for Environmental Assessment, Research Triangle Park, NC, EPA-600/8-91/049F.

White, RH; Cote, I; Zeise, L; Fox, M; Dominici, F; Burke, TA; White, PD; Hattis, DB; Samet, JM. 2008. "State-of-the-Science Workshop Report: Issues and Approaches in Low Dose–Response Extrapolation for Environmental Health Risk Assessment." Accessed online at http://www.ehponline.org/members/2008/11502/11502.pdf. doi: 10.1289/ehp.11502.

Witten, A; Solomon, C; Abbritti, E; Arjomandi, M; Zhai, W; Kleinman, M; Balmes, J. 2005. "Effects of nitrogen dioxide on allergic airway responses in subjects with asthma." *J Occup Environ Med.* 47:1250-1259.