Comments on US EPA's Proposed Revisions to the NO_2 NAAQS

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on behalf of the American Petroleum Institute
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EPA conducted a meta-analysis of controlled exposure studies in asthmatics and concluded that short-term exposure to 0.1 ppm NO_2 can cause increases in response to nonspecific airway challenges. Gradient conducted more rigorous meta-analyses and meta-regressions, including 10 additional studies, and using more current and appropriate meta-analysis techniques. Gradient found there is no evidence to suggest that NO_2 leads to significant adverse effects at any of the exposures tested, up to 0.6 ppm. Furthermore, according to the NO_2 REA, the current annual NO_2 NAAQS of 0.053 ppm protects against short term exposures of 0.4 ppm and higher and there are no nonattainment areas at the current annual standard. **Thus, the data do not support a short term standard for NO_2**.

One difference between our analysis and EPA's analysis is that EPA evaluated only the fraction affected in a limited number of available studies, but did not evaluate the dose-response or other measures of effect. We assessed dose-response in a number of ways. We conducted meta-analyses for 0.1 ppm exposure increments and conducted meta-regressions. We also did not limit our analysis to the fraction of subjects with effects, but looked at the difference of ΔFEV_1 ($\Delta\Delta FEV_1$) following and airway challenge and provocative dose (ΔPD) of and airway challenge with and without NO_2 exposure. In no case did the dose-response approach statistical significance. In addition, there is no indication that any effects could be considered adverse. For example, the changes in ΔFEV_1 for each study ranged from +1.5% to -5.3%, with the meta-effect of -1.6%. Although this slightly differs from 0, it is highly statistically significantly different from 15%, the ΔFEV_1 that is considered adverse.

While statistically significant effects were found in our meta-analysis, these are highly unlikely to be a result of NO_2 exposure for a few reasons. The associations didn't hold for high exposures, and it does not seem biologically plausible that lower exposures cause effects while higher exposures do not. We also assessed the associations in studies using chamber exposures only. With one exception, there were no statistically significant effects on fraction affected or $\Delta\Delta FEV_1$ at any exposure or overall, suggesting mouthpiece exposures could have contributed to some of the observed statistical significance in the main analyses. It should also be noted that the assumptions made in our analyses were biased

towards finding an effect. This also could have contributed to statistically significant results in the meta-analyses.

For EPA to conclude that the clinical studies show effects at 0.1 ppm NO_2 and perhaps lower, there would need to be significant dose-response associations. This is not the case. There is no dose-response whatsoever, suggesting any statistical significance observed at specific doses is not a result of NO_2, but rather chance or some other factor. In addition, epidemiology studies do not support associations at lower exposures, as they generally report statistically significant findings in single-pollutant, but not multi-pollutant, models, and no finding is large, robust, or consistent. **Together, these data do not support a short-term standard for NO_2**.

Figure 1. Association between NO_2 exposure and the fraction of asthmatics with greater airway hyper-responsiveness following NO_2 exposure

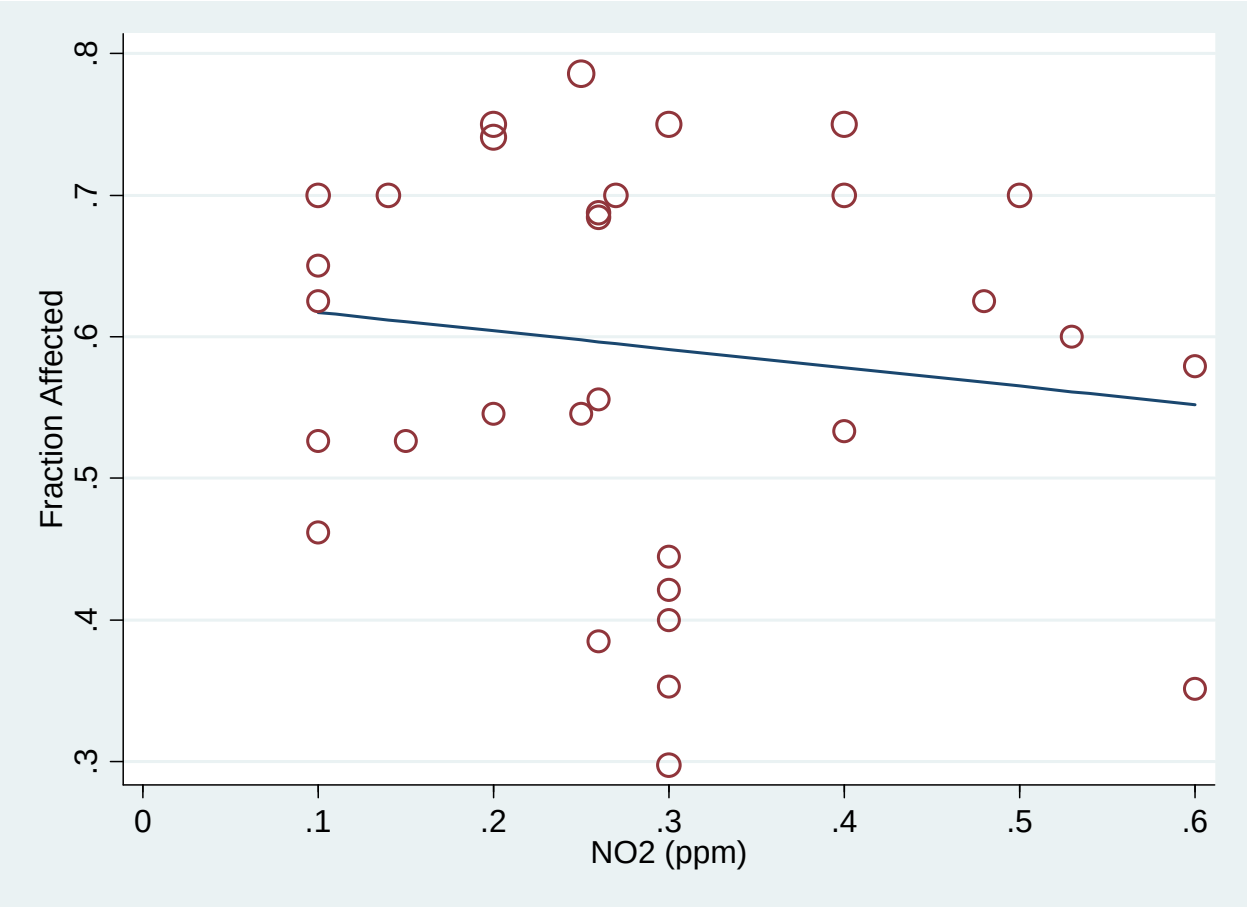

Figure 2. Association between NO_2 exposure and the difference between airway challenge provocative dose following exposure to NO_2 *vs.* air based on summary statistics (Δ PD_g)

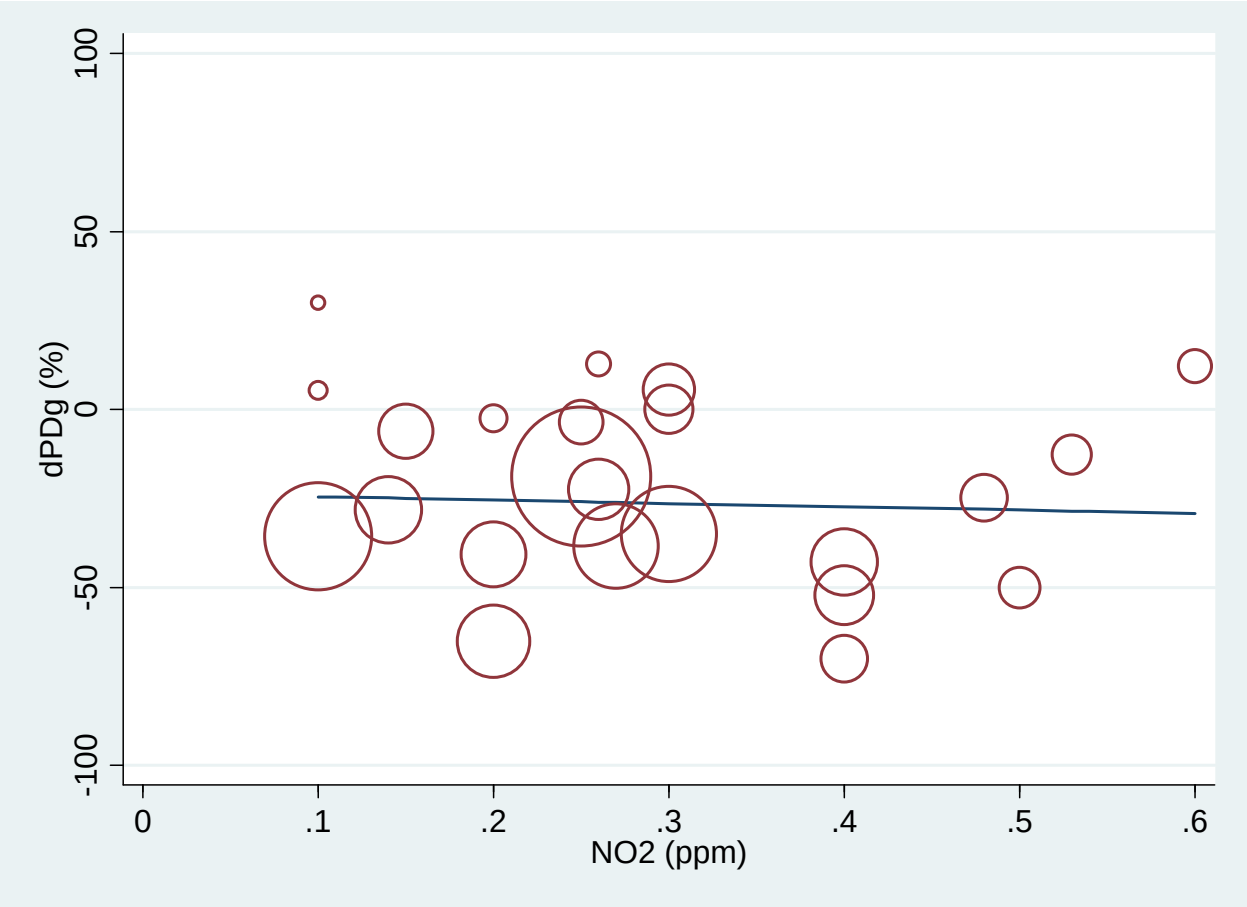

Figure 3. Association between NO_2 exposure and the difference between airway challenge provocative dose following exposure to NO_2 *vs.* air based on individual data (Δ PD_i)

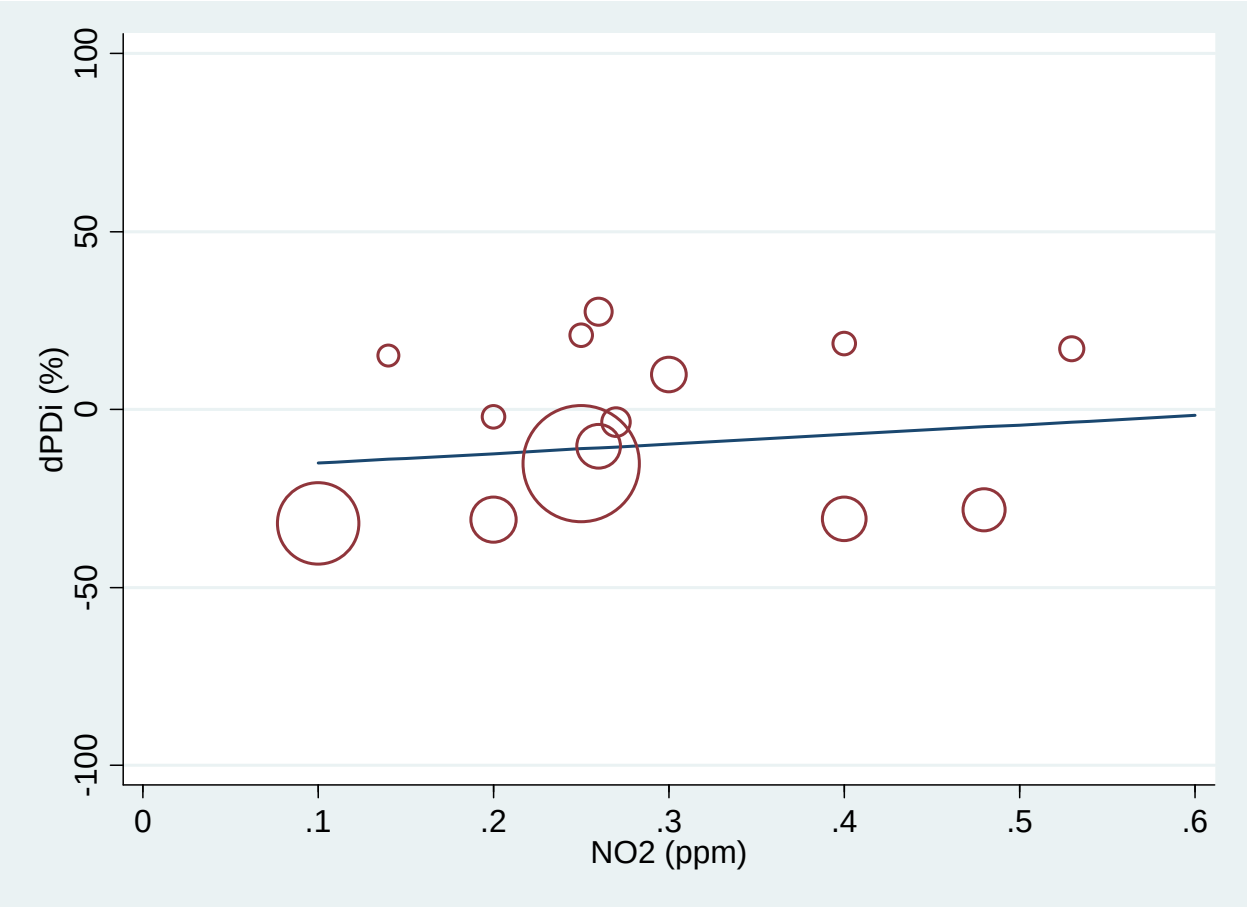
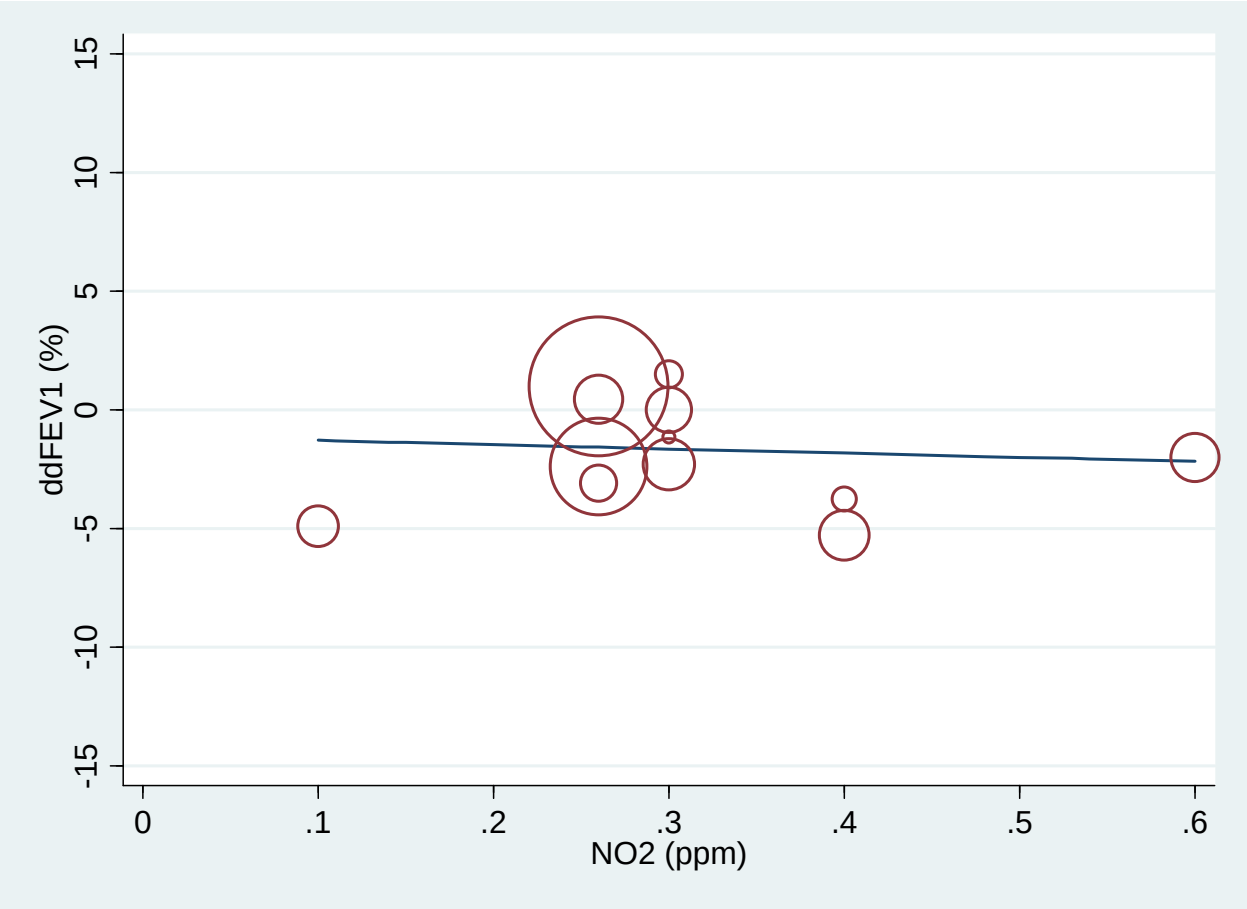
Figure 4. Association between NO_2 exposure and the differences between the change in FEV_1 induced by an airway challenge following exposure to NO_2 *vs.* air ($\Delta\Delta$ FEV_1)