

Comments on US EPA's Proposed Reconsideration of the 2008 NAAQS for Ozone

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February 2, 2009**

After careful analysis of EPA's rationale for the proposed reconsideration of the 2008 ozone standard, it is evident that the controlled human exposure and epidemiology studies relied on by EPA do not support a lowering of the ozone standard. At the time of the 2008 rulemaking, it was clear that there were many issues with these studies, and those issues still remain. Because the Administrator is basing the reconsideration on the scientific record from the last ozone review, our comments will only include these data; however, we must point out that more recent studies also do not support a further lowering of the standard.

Controlled human exposure studies do not support an association between ozone exposure and adverse respiratory effects below 0.08 ppm.

The studies by Adams (2002, 2006)¹ were the only controlled human exposure studies available for the 2008 rulemaking that examined respiratory effects in healthy subjects associated with six hours of near-continuous exercise at ozone exposures below 0.08 ppm. Adams (2002) examined face-mask exposures to filtered air and 0.04, 0.08, and 0.12 ppm ozone and reported no effects on lung function at 0.04 ppm. Adams (2006) examined hourly chamber exposure responses to filtered air and 0.04, 0.06, and 0.08 ppm ozone over 6.6 hours and reported a group mean decrement in FEV₁ of about 2.8% for the 0.06 ppm exposure groups compared to the control group. This small decrement was attributable to FEV₁ reductions of 10-15% in two of the 30 study subjects and was not statistically significantly different from the control group according to the author, who analyzed the data at all time points using an ANOVA test (see Figure 1, below). In contrast, EPA reported that this decrement was statistically significantly different based on a t-test EPA used to re-analyze the data at the final time point only. This re-analysis was not then published or peer-reviewed, and the use of a t-test to compare the final measurements

¹ Adams, WC. 2002. "Comparison of chamber and face-mask 6.6-hour exposures to ozone on pulmonary function and symptoms responses." *Inhal. Toxicol.* 14(7):745-764; Adams, WC. 2006. "Comparison of chamber 6.6-h exposures to 0.04-0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses." *Inhal. Toxicol.* 18(2):127-136.

between the control and treated groups is inappropriate because it ignores most of the data at the other time points and, thus, does not account for multiple comparisons as does an ANOVA test. It is more appropriate to compare the outcomes at all time points in order to determine whether there is statistically significant evidence of an effect. Even EPA investigators who perform human clinical studies of ozone do not routinely use the simple t-test to evaluate pulmonary function data, but instead use statistical procedures similar to those used by Adams.²

The small lung function changes measured in the Adams (2006) study are not adverse.

Even if the decrement in FEV₁ at exposure to 0.06 ppm ozone in the Adams (2006) study was statistically significant, it is a small group mean change and not an adverse effect according to the American Thoracic Society, which considers an individual decline of less than 15% FEV₁ to not be of clinical significance because of the large variability that is characteristic of FEV₁ measures, even in unexposed groups³. In addition, EPA's high reliance on FEV₁ decrements of >10% in only two individuals exposed to low ozone concentrations is not justified scientifically. EPA fails to consider the day-to-day variability in baseline pulmonary function and many other factors that could account for this small FEV₁ change in 2/30 measurements. This is evidenced by the fact that for a number of other individuals, a small increase in pulmonary function is reported. Again, this is not likely attributable to ozone exposure but rather results from the normal variability in both filtered air and test measurements that is attributed to factors other than low-level ozone exposure. Reliance on data from such a small number of subjects in a single study should not be used to support a NAAQS. During the public comment period of the March 5, 2007 CASAC teleconference, Dr. Adams himself expressed the view that the results of his study should not be interpreted as demonstrating respiratory effects at exposure to 0.06 ppm ozone⁴. Thus, the Adams (2006) data are too limited to support a decrease from 0.08 to 0.06 ppm for the

² For example, Liu, L; Leech, JA; Urch, RB; Poon, R; Zimmerman, B; Kubay, JM; Silverman, FS. 1999. "A comparison of biomarkers of ozone exposure in human plasma, nasal lavage and sputum." *Inhal. Toxicol.* 11(8):657-674; Gong, H; Wong, R; Sarma, RJ; Linn, WS; Sullivan, ED; Shamoo, DA; Anderson, KR; Prasad, SB. 1998. "Cardiovascular effects of ozone exposure in human volunteers." *Am. J. Respir. Crit. Care Med.* 158(2):538-546; Vincent, R; Bjarnason, SG; Adamson, IYR; Hedgecock, C; Kumarathasan, P; Guenette, J; Potvin, M; Goegan, P; Bouthillier, L. 1997. "Acute pulmonary toxicity of urban particulate matter and ozone." *Am. J. Pathol.* 151(6):1563-1570; Torres, A; Utell, MJ; Morow, PE; Voter, KZ; Whitlin, JC; Cox, C; Looney, RJ; Spers, DM; Tsai, Y; Frampton, MW. 1997. "Airway inflammation in smokers and nonsmokers with varying responsiveness to ozone." *Am. J. Respir. Crit. Care Med.* 156:728-736; Linn, WS; Shamoo, DA; Venet, TG; Spier, CE; Valencia, LM; Anzar, UT; Hackney, JD. 1983. "Response to ozone in volunteers with chronic obstructive pulmonary disease." *Arch. Environ. Health.* 38(5):278-283; Kulle, TJ; Sauder, LR; Hebel, JR; Chatham, MD. 1985. "Ozone response relationships in healthy nonsmokers." *Am. Rev. Respir. Dis.* 132(1):136-141.

³ Wang, ML; Petsonk, EL. 2004. "Repeated measures of FEV₁ over 6 to 12 months: what change is abnormal?" *J. Occup. Environ. Med.* 46(6):591-595.

⁴ Adams, WC. 2007. Public Comment to CASAC Ozone Review Panel Teleconference, March 5, 2007. Accessed at: [http://yosemite.epa.gov/sab/sabproduct.nsf/02C53E24812747E6852572C800568632/\\$File/pub_comments_03-05-07_dr_wm_adams_uc-davis.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/02C53E24812747E6852572C800568632/$File/pub_comments_03-05-07_dr_wm_adams_uc-davis.pdf)

LOAEL in controlled human exposure studies for lung function decrements and should not be used as positive evidence in a weight-of-evidence analysis to inform judgments on setting an ozone standard to any level below 0.08 ppm.

The epidemiological evidence for short-term health effects of ozone is weak and does not support causality at levels below 0.08 ppm.

The NMMAPS study by Bell *et al.* (2004)⁵ that EPA cites as a key study supporting the relationship between premature mortality and short-term exposure to ozone is an example of a weak and problematic study. This study reported substantial variability in mortality coefficients across 95 cities, and the vast majority (89 of 95) of these coefficients were not statistically significant (see Figure 2, below). Results were inappropriately combined across cities and summarized as an overall national average relative risk; however, this is of limited value in light of the substantial heterogeneity across cities and regions. This variability should be taken into account if these coefficients are going to be applied to risk analyses. Another issue is that the mortality coefficients were based on 24-hour average ozone levels, rather than the 8-hour averaging time used for past and current ozone standards.

Health effects are attributed to ozone exposure when PM-related associations are not accounted for.

Confounding by particulate matter is a common issue in studies of ozone health effects. Bell *et al.* (2004) computed estimates with and without adjustment for PM₁₀ and claimed that overall results were robust to inclusion of PM₁₀ or PM_{2.5}. A re-analysis of the data by Smith *et al.* (2009)⁶ demonstrated that when PM₁₀ is included in the model, the effect of ozone decreases by 22-33%, and that the ozone mortality effect is statistically significant only when PM₁₀ concentrations are above the median. Although the Smith *et al.* (2009) re-analysis was not published until 2009, EPA was aware of these data through public comments on the 2007 Proposed Rule for the ozone NAAQS⁷.

There are other examples of weak epidemiological evidence.

⁵ Bell, ML; McDermott, A; Zeger, SL; Samet, JM; Dominici, F. 2004. "Ozone and short-term mortality in 95 US urban communities, 1987-2000. *JAMA*. 292(19):2372-2378.

⁶ Smith, RL; Xu, B; Switzer, P. 2009. "Reassessing the relationship between ozone and short-term mortality in US urban communities." *Inhal. Toxicol.* 21(S2):37-61.

⁷ McClellan, RO. 2007. Public Comment on National Ambient Air Quality Standards for Ozone: Proposed Rule. Submitted to EPA Docket, ID No. EPA-HQ-OAR-2005-0172 on October 9, 2007.

There are three meta-analyses that EPA cites as evidence of a "robust" association between short-term ozone exposure and mortality (Bell *et al.*, 2005; Ito *et al.*, 2005; Levy *et al.*, 2005)⁸. All three sets of authors stress the high degree of heterogeneity in the estimates from individual cities and the fact that the results for many of the cities were not statistically significant. The meta-analysis approach assumes homogeneity in the data from across cities, and high variability results in uncertainty in the risk estimates. The authors of all three meta-analyses reported evidence of publication bias, where authors tend to publish only positive results. Model selection bias, where authors tend to choose only models yielding positive results, was also evident in each analysis, as different studies using data from the same city showed a marked contrast in results. Despite this evidence, which should high-bias risk estimates, each meta-analysis reported extremely weak risks. Thus, these analyses do not provide robust evidence of a causal relationship between ozone and mortality at ambient exposures as EPA suggests.

There are many issues with EPA's scientific method.

In addition to the weak epidemiological evidence for short-term effects of ozone exposure, EPA's assessment of this evidence is not scientifically appropriate. Risk estimates that are not statistically significant are used by EPA both as evidence for a positive association and in the risk assessment. The few statistically significant risk estimates reported in mortality studies are very weak and susceptible to confounding and bias. EPA did not base the "best" estimates for lag times on biological plausibility but rather on the largest positive association. EPA also ignored certain negative studies in favor of those with positive results. An example of this can be seen in the review of the panel studies. The key studies cited by EPA (Mortimer *et al.*, 2002; Gent *et al.*, 2003; Korrick *et al.*, 1998)⁹ reported small respiratory effects but other studies of similar design (Delfino *et al.*, 1997; Schildcrout *et al.*, 2006; Girardot *et al.*, 2006)¹⁰ reporting no association between ozone exposure and respiratory effects were not cited as key studies.

⁸ Bell, ML; Dominici, F; Samet, JM. 2005. "A meta-analysis of time-series studies of ozone and mortality with comparison to the National Morbidity, Mortality, and Air Pollution Study." *Epidemiology*. 16(4):436-445; Ito, K; De Leon, SF; Lippmann, M. 2005. "Associations between ozone and daily mortality: Analysis and meta-analysis." *Epidemiology*. 16(4):446-457; Levy, JI; Chemerynski, SM; Sarnat, JA. 2005. "Ozone exposure and mortality: An empiric Bayes metaregression analysis." *Epidemiology*. 16(4):458-468.

⁹ Mortimer, KM; Neas, LM; Dockery, DW; Redline, S; Tager, IB. 2002. "The effect of air pollution on inner-city children with asthma." *Eur. Respir. J.* 19:699-705; Gent, JF; Triche, EW; Holford, TR; Belanger, K; Bracken, MB; Beckett, WS; Leaderer, BP. 2003. "Association of low-level ozone and fine particles with respiratory symptoms in children with asthma." *JAMA*. 290(14):1859-1867; Korrick, SA; Neas, LM; Dockery, DW; Gold, DR; Allen, GA; Hill, LB; Kimball, KD; Rosner, BA; Speizer, FE. 1998. "Effects of ozone and other pollutants on the pulmonary function of adult hikers." *Environ. Health Perspect.* 106(2):93-99.

¹⁰ Delfino, RJ; Zeiger, RS; Seltzer, JM; Street, DH; Matteucci, RM; Anderson, PR; Koutrakis, P. 1997. "The effect of outdoor fungal spore concentration on daily asthma severity." *Environ. Health Perspect.* 105(6):622-635; Schildcrout, JS; Sheppard, L; Lumley, T; Slaughter, JC; Koenig, JQ; Shapiro, GG. 2006. "Ambient air pollution and asthma exacerbations in children: An eight-city analysis." *Am. J. Epidemiol.* 164(5):505-517; Girardot, SP; Ryan, PB; Smith, SM; Davis, WT; Hamilton, CB; Obenour, RA; Renfro, JR; Tromatore, KA; Reed, GD. 2006. "Ozone and PM_{2.5} exposure and acute pulmonary health effects: A study of hikers in the Great Smoky Mountains National Park." *Environ. Health Perspect.* 114(7):1044-1052.

EPA also did not appropriately take into consideration the flaws in the time-series and panel studies, such as their use of ambient monitors as surrogates of personal ozone exposures in spite of the weak correlation between ambient and personal ozone exposures. In addition, many of the panel studies including the study by Mortimer *et al.* (2002), which EPA places high reliance on, used self-reported peak expiratory flow (PEF) rate measurements which have been demonstrated to be highly unreliable (Kamps *et al.*, 2001)¹¹.

In conclusion, the many issues inherent to human clinical and epidemiology studies relied on by EPA as evidence for the 2008 rulemaking still remain in the proposed reconsideration. The human chamber data are too limited to support an ozone standard at any level below 0.08 ppm. The epidemiological evidence for short-term health effects of ozone is weak, methodologically flawed, and not appropriately assessed by EPA. Both the controlled human exposure and epidemiological studies do not support an association between short-term exposure to ozone and adverse effects at levels below 0.08 ppm.

¹¹ Kamps, AWA; Roorda, RJ; Brand, PLP. 2001. "Peak flow diaries in childhood asthma are unreliable." *Thorax*. 56:180-182.

Figures

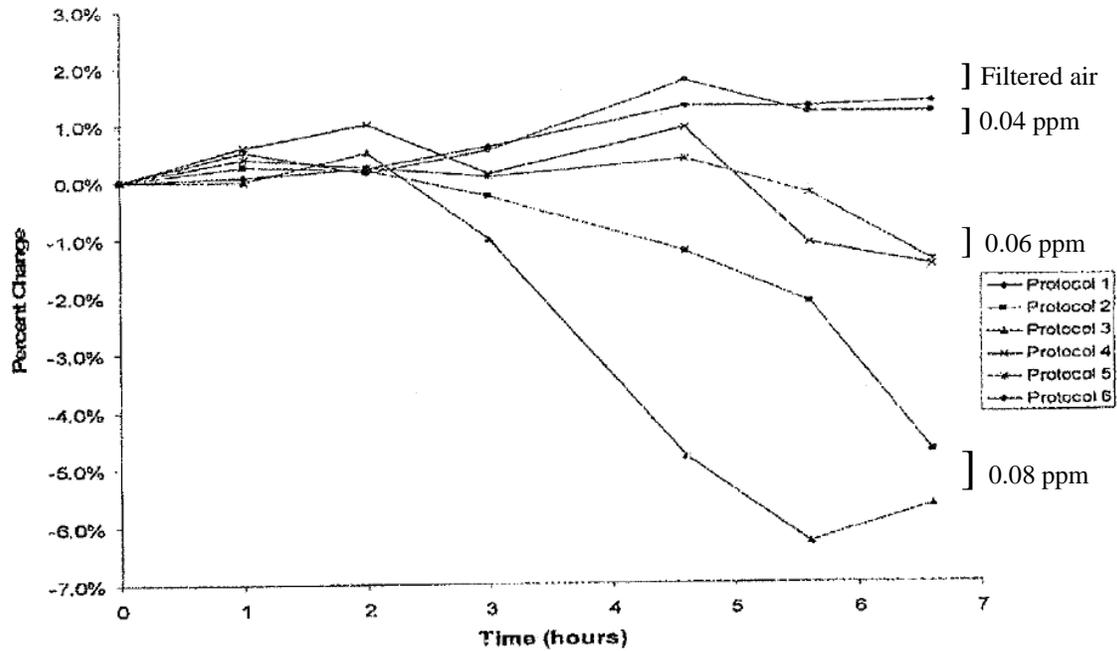


Figure 1. Hour by hour percent change in group means of FEV₁ in the Adams (2006) study. Decrements in FEV₁ for the constant and variable 0.06 ppm ozone groups are only observed after 5 to 6 hours of nearly continuous exercise and are small in magnitude. An appropriate statistical test (*i.e.*, ANOVA) indicates no statistically significant differences in group mean FEV₁ decrements between the 0.06 ppm exposure groups and the filtered air control group (Adapted from Figure 1 of Adams, 2006).



Figure 2. Ninety-five percent posterior intervals for the community-specific ozone mortality estimates from Bell *et al.* (2004). The heterogeneity among the estimates across cities is evident, and the vast majority of cities had coefficients that were not statistically significant (Figure 2 of Bell *et al.*, 2004).