

# Oral Testimony Before the CASAC Ozone Review Panel on the First Draft Ozone REA

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Thank you for the opportunity to speak on behalf of the American Forest and Paper Association. My comments this afternoon are focused on the characterization of health risks based on controlled human exposure studies in the first draft ozone REA (US EPA, 2012).

EPA developed exposure-response functions (ERFs) for lung function decrements (as measured by changes in forced expiratory volume in one second, FEV<sub>1</sub>) from several controlled human exposure studies. It did this based on two models, one that was used in the 2007 ozone NAAQS review and an alternative model by McDonnell *et al.* (2010). The quantitative results of these risk assessments were recently released in an update to the first draft REA. EPA said it is planning to update the ERF using new data presented in the third draft Integrated Science Assessment (ISA), including those from the Hazucha *et al.* (1992), Kim *et al.* (2011), and Schelegle *et al.* (2009) studies.

EPA should consider more recent models by Schelegle *et al.* (2012) and McDonnell *et al.* (2012) that supersede the models used in the REA. McDonnell *et al.* (2012) updated their original exposure-response model (McDonnell *et al.*, 2007, 2010) with additional data and the inclusion of a threshold dose. The authors considered data from 23 human controlled exposure studies and, in some models, used a threshold defined as 59 parts per million (ppm)-liters of inhaled air, thus accounting for both the level of exercise and the ozone concentration. McDonnell *et al.* (2012) reported a better fit with the threshold model compared to previous models, particularly for the early time points at the lowest exposure levels. Because these exposures are more relevant to the NAAQS, the threshold model presented by McDonnell *et al.* (2012) provides a more accurate estimate of risk for the general population.

Rather than using a model based on group mean FEV<sub>1</sub> decrements, EPA used a model based on the percentage of people with lung function decrements over a certain value (*i.e.*, 10, 15, or 20%). This is inappropriate; it overestimates the significance of individual responses, particularly at lower ozone exposure levels, due to the individual variability of FEV<sub>1</sub> when repeatedly measured by diagnostic spirometry. Because there is only one measurement per person at a given exposure time, the studies included in these models are designed to characterize a group mean response rather than individual responses. For example, in a study where repeated FEV<sub>1</sub> measurements were made on a single healthy individual exposed to clean air, the observed variation in FEV<sub>1</sub> was up to  $\pm 5\%$  in some subjects (Lefohn *et al.*, 2010). Based on this range, a substantial segment of the low-exposure individuals included as responders in the EPA assessment may simply fall within the experimental variability. Also, FEV<sub>1</sub> is only one measure of respiratory impacts, and other endpoints (*e.g.*, symptoms) are generally required to determine if someone is experiencing an adverse effect. For example, the American Thoracic Society (2000) guidelines for identifying adverse effects includes both pulmonary changes with respiratory symptoms. In a key clinical study, Schelegle *et al.* (2009) reported significant changes in both FEV<sub>1</sub> and symptom scores only after over 6 hrs of exposures to an ozone levels of 80 ppb, and following a rigorous

exercise protocol. Thus, while FEV<sub>1</sub> may be used as a biomarker, by itself, it likely overestimates the number of individuals experiencing adverse effects.

Finally, EPA stated that it assumed that asthmatic school-aged children are more susceptible to ozone exposures than non-asthmatic children. CASAC recently indicated that overall the evidence that asthmatics are more sensitive to the respiratory effects of ozone is weak, and we came to the same conclusion based on a review of epidemiology, controlled human exposure, and toxicity studies (see Appendix A). It is noteworthy that in Figures 6-8 to 6-15 of the REA, the risks in asthmatic school-aged children differ little, if at all, from risks in all school-aged children in four urban areas.

In conclusion, EPA should rely on a model that incorporates a threshold for calculating risk, such as the one by McDonnell *et al.* (2012), and should use the absolute level of FEV<sub>1</sub> rather than a level above or below a cutoff value. EPA should also reconsider the evidence which indicates that asthmatics are not more sensitive to ozone. On behalf of the American Forest and Paper Association, thanks for your consideration of these comments.

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# Appendix A

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## Asthma as an "at-risk" factor

Despite previous comments from CASAC (US EPA, 2012a) indicating that the overall evidence that asthmatics are more sensitive to the respiratory effects of ozone is weak, in the third draft ISA, EPA retained its conclusion that there is "adequate evidence" that asthma is a risk factor for increased susceptibility to ozone (US EPA, 2012b). Although EPA cited data from epidemiology, controlled human exposure, and toxicology studies to support its conclusion, a review of the data indicate that there is no consistent evidence that asthmatics are at increased risk of effects from ambient ozone exposure.

The reported findings in the epidemiology studies on which EPA relied were inconsistent, with some studies reporting statistically significant effects in asthmatics and others reporting no difference in reported effects for asthmatics and non-asthmatics. For example, in studies of respiratory morbidity [*i.e.*, lung function changes, respiratory symptoms, airway hyper-responsiveness (AHR), and inflammation], some studies reported effects only in asthmatics (Escamilla-Nuñez *et al.*, 2008) or greater effects in asthmatics (Alexeeff *et al.*, 2007; Thaller *et al.*, 2008). Other studies, however, reported no differences in response between asthmatics and non-asthmatics (Barraza-Villarreal *et al.*, 2008; Berhane *et al.*, 2011; Khatri *et al.*, 2009). EPA also argued that recent studies of behavioral responses do not take into account individual behavioral adaptations to forecasted air pollution levels (such as avoidance or reduced time outdoors), which may underestimate the observed associations in studies that examined the effect of ozone exposure on respiratory health (Neidell and Kinney, 2010, as cited in US EPA, 2012b). In fact, exposure misclassification can bias results in either direction.

EPA also examined the association between ozone exposure and altered lung function by asthma medication use. In studies that examined effect measure modification of the relationship between short-term ozone exposure and altered lung function by corticosteroid use, there is limited and inconsistent evidence of ozone-related health effects and medication use. Lewis *et al.* (2005) reported a greater association between short-term ozone and lung function for corticosteroid users compared with noncorticosteroid users in children with asthma living in Detroit, but this association was only significant in a two-pollutant model of diurnal variability in FEV<sub>1</sub> with a lag of 3 to 5 days (3.76, 95% CI: 0.27-7.26, *p* <0.04; note that the CI is very wide). Hernández-Cadena *et al.* (2009) reported the opposite effect – decreased lung function among noncorticosteroid users compared with corticosteroid users. Qian *et al.* (2009, as cited in US EPA, 2012b) reported a counterintuitive inverse association of airway inflammation with ozone of similar magnitude for all groups of corticosteroid users and non-users, and Liu *et al.* (2009) found no association between lung function corticosteroid users and non-users in a study conducted in Canada during the winter. These findings do not support an increased risk for ozone-related effects in asthmatics.

Human controlled exposure studies reported inconsistent results in asthmatics at high ozone exposure concentrations (160 to 400 ppb). In studies that reported statistically significant effects, the effects were mild, transient, and reversible. Also, sample sizes were generally very small and asthmatics that had higher lung function decrements also had lower baseline airway measurements. Effects were also inconsistent within studies, with some effects being significant and others showing no associations with exposure. For example, Kreit *et al.* (1989, as cited in US EPA, 2012b) reported a significant decrease in FEV<sub>1</sub> in asthmatics compared with healthy controls following exposure to 400 ppb ozone for two hours with moderate-heavy exercise, but FVC did not differ between the groups. Another two studies found

increased markers of inflammation but no differences in lung function or symptoms between asthmatic and non-asthmatics (Basha *et al.*, 1994; Scannell *et al.*, 1996). In recent studies, no-effects lung function were observed in asthmatics compared to non-asthmatics after exposures to 400 ppb for two hours (Alexis *et al.*, 2000) and 200 ppb for two hours (Mudway *et al.*, 2001). Inconsistent findings within and among the human controlled high-exposure studies do not provide adequate evidence of an increased risk for asthmatics at ambient ozone concentrations.

EPA also evaluated studies that investigated the effects of ozone in animals with asthma or AHR. In these studies, an asthmatic phenotype is modeled by allergic sensitization of the respiratory tract. In the third draft ISA, EPA stated:

[N]umerous toxicological studies have demonstrated that ozone-induced airway hyperresponsiveness occurs in guinea pigs, rats, and mice after either acute or repeated exposure to relevant concentrations of ozone. (p. 6-74)

The majority of animal study results on which EPA relied used high ozone concentrations and do not reflect relevant human exposures to ambient ozone. There are only a limited number of studies that have observed airway hyper-reponsiveness in rodents and guinea pigs at less than 300 ppb. Depuydt *et al.* (1999) reported that after exposure to 0.05 ppm ozone for four hours, two (BDII and Long-Evans) of the nine strains of rats tested experienced AHR as measured by inflammatory cells and markers in bronchial lavage fluid (BALF). This concentration is lower than in any other studies that reported AHR, and EPA concluded it "warrants verification in other species." More recent studies comparing ovalbumin-sensitized rodents to non-sensitized rodents showed that responses occurred in sensitized animals at levels of 0.12 ppm (Chhabra *et al.*, 2010) and 0.1 to 0.25 ppm (Larsen *et al.*, 2010). The endpoints indicating AHR included lipid peroxidation, superoxide anion generation in the bronchial lavage cells, red cell superoxide dismutase and glutathione peroxidase, and goblet-cell metaplasia. It is unclear from these studies whether these biomarkers were clinically significant or whether they were transient and reversible effects. Other studies discussed in the third draft ISA included Funabashi *et al.* (2004, as cited in US EPA, 2012b), who demonstrated changes in pulmonary function (increased respiratory resistance and decreased dynamic compliance) in mice exposed to 1,000 ppb ozone, and Wagner *et al.* (2007), who reported enhanced inflammatory responses (such as intraepithelial mucosubstances, subepithelial eosinophils, and IL-6 production in BALF) in rats exposed to 1,000 ppb ozone in the mice sensitized to allergen. Again, these concentrations were extremely high and not relevant to ambient exposures, and it was unclear if these effects were transient or clinically relevant.

The species differences in airway morphology in rodents compared with humans leads to uncertainty regarding the relevance of these rodent studies to humans. In addition, although three other studies in more biologically relevant species (non-human primates; Schlegele *et al.*, 2003; Joad *et al.*, 2006, both as cited in US EPA, 2012b; Fanucchi *et al.*, 2006) found that cyclic episodes of ozone exposure (at 500 ppb) produced alterations in airways that could lead to chronic airway disease and decreased lung function, it is unclear if long-term, environmentally relevant exposures could cause similar changes.

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