

## **Comments on the Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards (Second External Review Draft)**

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Thank you for the opportunity to speak on behalf of the American Forest and Paper Association.

The second draft *Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards* (PA, US EPA, 2014) relied heavily on the health effects evaluated in the Integrated Science Assessment (ISA) for Ozone. In the 2013 ISA (US EPA, 2013), the United States Environmental Protection Agency (EPA) concluded that there is likely to be a causal relationship between short-term exposure to ozone and cardiovascular (CV) effects. This conclusion is based on an evaluation using the causal framework described in the ISA (US EPA, 2013). The framework does not include specific guidance for several aspects that are critical for a rigorous weight-of-evidence (WoE) evaluation, which led to an inconsistent evaluation of the evidence.

Using a framework incorporating best practices in WoE analyses (Rhomberg *et al.*, 2013), my colleagues and I critically reviewed the existing evidence regarding short-term and long-term ozone exposures and CV effects. These analyses have been submitted and are currently undergoing peer review (Goodman *et al.*, 2014; Prueitt *et al.*, 2014). Although the conclusions on short- and long-term ozone exposure and CV effects are similar, the data are much more limited for long-term exposure; thus, my comments today focus on the short-term effects of ozone on CV health outcomes.

We found that epidemiology studies of short-term ozone exposure and CV effects are generally of inadequate quality, resulting in considerable uncertainty. The majority of these studies have several common methodological limitations, including selection bias, exposure measurement error, outcome misclassification, and residual and unmeasured confounding. These limitations severely undermine the validity of the results, making it difficult to infer causality.

The effect estimates for ozone reported in epidemiology studies are very small and are often not statistically significant. Deviations from the null are more likely due to bias, confounding, or chance, than a causal relationship. Effects observed in controlled human exposure, experimental animal, and biomarker studies are also very small and are likely to indicate homeostatic processes.

EPA based its "likely causal" conclusion for short-term ozone primarily on epidemiology studies of CV mortality. However, these studies reported positive, null, and even negative associations, all of very small

magnitude. In addition, epidemiology studies mostly reported null associations between ozone and CV morbidity. Such a discrepancy between CV mortality and morbidity should considerably influence the causal determinations of ozone effects, as it is not biologically plausible that ozone could impact CV mortality but not morbidity. However, although this lack of coherence between studies of CV mortality and morbidity was acknowledged by EPA in the ISA, it was not given full consideration in EPA's causal determination.

Finally, there is a lack of a confirmed mode of action for ozone exposure to cause CV effects. Mechanisms such as changes in cardiac autonomic control and increased systemic inflammation and oxidative stress have been proposed and have played a role in EPA's causal determination. But data across scientific disciplines do not support either of these proposed modes of action.

In summary, we believe current evidence is not sufficient to determine a causal relationship between short-term exposure to ozone and CV effects. Therefore, CV effects should not be included in the PA (US EPA, 2014).

## References

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