March 13, 2014

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Dr. H. Christopher Frey
Chair, Clean Air Scientific Advisory Committee
Science Advisory Board
US Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, DC 20460

Re: Comments on EPA's Health Risk and Exposure Assessment and Policy Assessment for Ozone

Dear Dr. Frey:

In its 2013 Integrated Science Assessment (ISA) for ozone, EPA concluded that the available evidence supports a likely causal relationship between long-term ozone exposure and respiratory effects, including respiratory mortality. EPA also concluded that the evidence supports a likely causal relationship between short-term exposure and mortality (US EPA, 2013). EPA evaluated these endpoints in the ozone Health Risk and Exposure Assessment (REA). Based on this evaluation, EPA made recommendations in the ozone Policy Assessment (PA) regarding proposed alternative standards (US EPA, 2014a,b).

At the request of the trade associations listed below, Gradient has performed independent reviews of the studies that EPA cited in support of its conclusions (see attached). Gradient has found that the epidemiology evidence, in conjunction with other relevant data, does not support a causal link between ozone exposure and mortality or morbidity. We present a summary of Gradient's findings below.

Long-term Exposure and Respiratory Effects

In 2006, EPA concluded that the evidence indicated a suggestive but inconclusive relationship between long-term ozone exposure and respiratory effects (US EPA, 2006). In 2013, EPA concluded that the evidence was likely causal (US EPA, 2013), citing stronger evidence than was available in 2006. However, evidence available since 2006 is not stronger, nor does it support a causal link.

EPA based its 2013 conclusion primarily on epidemiology studies, particularly those evaluating asthma incidence (new-onset asthma), asthma prevalence and symptoms, asthma hospital admissions and emergency department (ED) visits, pulmonary structure and function, and pulmonary inflammation, injury, and oxidative stress. The majority of the analyses that focus on the impacts of long-term air pollution exposure on new-onset asthma in children demonstrate a lack of respiratory effects (including asthma) associated with long-term ozone exposure, even in areas with high levels of

ozone (*e.g.*, Peters *et al*., 1999; Gauderman *et al*., 2000, 2002, 2004; McConnell *et al*., 2002, 2010; Berhane *et al*., 2004). One analysis reported a positive association between playing three or more sports in a high-ozone exposure community and anincreased risk of developing asthma (McConnell *et al*., 2002), while other studies indicated children that may be more genetically susceptible to respiratory inflammation also have an increased risk of asthma (Li *et al*., 2006; Islam *et al*., 2008, 2009). It is unclear, however, whether ozone actually played a role in any of these associations.

Long-term studies evaluating the association between ozone and asthma prevalence or asthma symptoms at a single time point (*e.g.*, in a given year), as well as those evaluating long-term exposure to ozone and asthma hospital admissions and ED visits, have shown largely mixed results, with most showing no effects on these outcomes. Many of these studies did not account for co-pollutant exposure, other factors that could have led to asthma hospital admissions and ED visits, or the fact that, generally, people spend most of their time indoors. Similarly, when considered together, the three studies EPA cited that reported a possible link between long-term ozone exposure and allergies or respiratory-related illness are likely unreliable, both because of study limitations (such as not accounting for potential allergens (Parker *et al*., 2009; Rage *et al*., 2009)) and the lack of observed statistical differences for children living in high- *vs.* low-exposure communities (Wenten *et al*., 2009).

Epidemiology studies have also evaluated effects of long-term ozone exposure on pulmonary structure and lung function. As with those evaluating the association with asthma incidence or symptoms, the majority of these studies found no association between long-term ozone exposure and lung function (Peters *et al*., 1999; Mortimer *et al*., 2008a,b; Latzin *et al*., 2009; Forbes *et al*., 2009). In fact, Gauderman *et al*. (2000, 2002) reported that, in following children as they grew, there was no evidence that ozone affected lung function in any way to compromise children's respiratory health later in life. Only one study, conducted in Mexico City, reported ozone exposures that correlated with a decline in lung function in children (Rojas-Martinez *et al*., 2007). However, this study relied on crude measures of ozone exposure and did not account for confounding factors.

EPA also noted that new epidemiology evidence of other pulmonary effects from long-term exposure to ozone, such as inflammation, injury, and oxidative stress, is too limited to draw conclusions. Considering this conclusion and the lack of support for causation demonstrated above, the new evidence does not support a likely causal association between long-term ozone exposure and respiratory effects.

Long-term Exposure and Mortality

In 2013, EPA also strengthened its 2006 conclusion that evidence was suggestive of a causal link between long-term exposure and premature mortality (US EPA, 2013). However, as with respiratory effects, the evidence is not stronger now than it was in 2006. Much of the newly available studies that evaluate this relationship were re-analyses of existing data rather than new data. For example, three of the five newly available studies since 2006 used different statistical analyses to reanalyze previously

analyzed data. Importantly, the previous studies of these data reported no links between ozone and mortality. While small risks were observed for all-cause and cause-specific mortality in some of the re-analyses, results were not consistent within or across the studies, which does not support causality. Of the other two new studies EPA identified, one reported a link between ozone exposure and mortality in populations with specific health conditions (Zanobetti and Schwartz, 2011). The other reported no link between ozone and mortality at ozone concentrations typically seen in the US today (Wang *et al*., 2009).

Of these five new studies, EPA relied most heavily on Jerrett *et al*. (2009), which reported a link between ozone exposure and respiratory mortality. However, these findings are not consistent with other risk estimates reported in this study, such as the lack of association between ozone and all-cause or cardiovascular (CV) related mortality, which would be expected if ozone truly impacted respiratory mortality. The positive findings are also not supported by other studies that did not show statistically significant associations between ozone and respiratory deaths (Abbey *et al*., 1999; Lipsett *et al*., 2011).

Short-term Exposure and Mortality

In 2013, EPA modified its 2006 conclusion from a suggestive to likely causal relationship between short-term exposure and premature all-cause and CV mortality (US EPA, 2013). It also maintained its conclusion that short-term ozone exposure causes respiratory effects, including mortality. Numerous multi-city studies have evaluated all-cause and cause-specific mortality from air pollution in specific cities around the world. Many of these studies are re-analyses of data evaluated in prior studies. These studies generally reported small average mortality risks across cities that ranged from about a 1-6% increase in all-cause mortality with an increase in ozone concentration. However, these estimates varied greatly between cities and depended on the choice of statistical model and model assumptions, sometimes showing a link and sometimes not. For a large number of cities, in any given study there was no association between increased ozone and mortality or associations showed a significant deficit (indicating a benefit of ozone); this casts doubt on the overall average risk estimates. Associations between respiratory or CV mortality and short-term ozone exposure are even more variable; the majority of available analyses, including the large study, Air Pollution and Health: A European Approach (APHENA), by Katsouyanni *et al*. (2009) on which EPA relied heavily, does not demonstrate statistically significant associations.

Finally, the assessment of both short- and long-term ozone exposure and mortality suffer from many of the same uncertainties and shortcomings. These include not fully considering factors that may account for statistical links between ozone and mortality (*e.g.*, meteorological factors such as temperature, lifestyle factors such as smoking) and the use of crude exposure measurements utilized in epidemiology studies (*e.g.*, from a few outdoor monitors located in populated areas) that do not accurately reflect people's exposure to ozone. In addition, the link between ozone exposure and mortality is not supported by animal toxicity or mechanistic studies. In fact, a biologically plausible

mechanism has yet to be discovered by which ozone exposure at levels typically found in the US today can cause death.

Short- and Long-term Exposure and Cardiovascular Effects

Gradient recently conducted a weight-of-evidence (WoE) analysis to determine whether evidence supports an association between short- and long-term ozone exposures and CV effects using a novel WoE framework adapted from the US EPA's National Ambient Air Quality Standards causality framework (Goodman *et al*., 2014; Prueitt *et al*., 2014). Specifically, Gradient synthesized and critically evaluated the relevant epidemiology, controlled human exposure, experimental animal, and mechanistic data and made a causal determination using the same categories proposed by the Institute of Medicine report *Improving the Presumptive Disability Decision-making Process for Veterans* (IOM, 2008). Gradient found that the totality of the data indicates that the results for CV effects are largely null across human, experimental animal, and mechanistic studies. The few statistically significant associations reported in epidemiology studies of CV morbidity and mortality are very small in magnitude and likely attributable to confounding, bias, or chance. In experimental animal studies, the reported statistically significant effects at high exposures are not observed at lower exposures and are, thus, not likely relevant to humans exposed to current ambient ozone exposures. Mode-of-action data also do not support a biologically plausible mechanism for CV effects of ozone. Overall, the limitations of the available studies preclude definitive conclusions regarding causation or a lack thereof. Still, taken together, the WoE indicates that a causal relationship between short-term exposure to ambient ozone levels and adverse effects on the CV system is not likely in humans.

Conclusions

Overall, EPA's conclusions regarding long-term ozone-related respiratory effects (including mortality), short-term ozone-related all-cause mortality, and short- and long-term ozone-related cardiovascular morbidity and mortality are not supported by the available evidence. For all of these endpoints, there is a lack of definitive evidence supporting an effect of ozone (as opposed to other factors). In addition, there is a lack of consistency and coherence within and across studies that calls into question a causal link. Furthermore, the evidence of causality for these endpoints is no stronger today than it was in 2006, with epidemiology studies mostly indicating a lack of association and other evidence (*e.g.*, animal and mechanistic studies) providing little, if any, additional support. Therefore, EPA's causal determinations for these endpoints should not be stronger than in its 2006 review.

Based on Gradient's assessments, the evidence does not support a causal or even likely causal association at ozone levels at or below the current National Ambient Air Quality Standards. In particular, short-term ozone-related all-cause mortality and long-term ozone-related respiratory mortality endpoints should not be considered in the REA, and none of these endpoints should be used to inform policy decisions in the PA.

If you have any questions about these comments, please contact Timothy Hunt, Senior Director for Air Quality Programs at the American Forest & Paper Association and American Wood Council at 202-463-2588 or by email at tim_hunt@afandpa.org or thunt@awc.org. Thank you in advance for your consideration of these comments.

Submitted on Behalf of,

American Chemistry Council
American Forest & Paper Association
American Iron and Steel Institute
Amerian Petroleum Institute
American Wood Council
Corn Refiners Association
Council of Industrial Boiler Owners
National Oilseed Processors Association
Portland Cement Association
Rubber Manufacturers Association
Treated Wood Council
U.S. Chamber of Commerce
Utility Air Regulatory Group

Attachments:
Gradient report on Long-Term Ozone Expsosure and Mortality – April 26, 2013
Gradient report on Short-term Ozone Exposure and Mortality – December 20, 2013
Gradient report on Long-Term Ozone Exposure and Respiratory Morbidity – December 20, 2013

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