Weight-of-Evidence Evaluation of Short-term Ozone Exposure and Cardiovascular Effects

ABSTRACT

There is a relatively large body of research on the potential cardiovascular (CV) effects associated with short-term ozone exposure. We conducted a weight-of-evidence (WoE) analysis to determine whether it supports the association using a novel WoE framework adapted from the US EPA’s National Ambient Air Quality Standards (NAAQS) causality framework. Specifically, we synthesized and critically evaluated the relevant epidemiology, controlled human exposure, experimental animal, and mechanistic data and made a causal determination using the same exposure, experimental animal, and mechanistic data that were used by the US EPA’s National Air Toxics Assessment (NAAQS) causality framework. The few statistically significant associations reported in epidemiology studies of CV mortality 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 current ambient ozone exposures in humans. 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.

Weight-of-Evidence Best Practices

Phase 1: Causal Question and Study Criteria

- Causal Question: Is short-term ozone exposure below the current NAAQS associated with adverse CV-related health effects?
- Study Selection Criteria: Evaluated short-term ozone exposures (i.e., < 90 days) provided ozone-specific results, all dose/exposure levels.
- Studies Identified: 56 Tier I studies, 26 biomarker studies

Phase 2: Individual Ozone Study Quality and Relevance

- Controlled Human Experiments
- Experimental Animal Studies
- Epidemiology Studies

Qualitative Evaluation

- Study design, sample size, selection, exposure assessment, and reproducibility of results

Quantitative Evaluation

- All of Adequate Quality

Phase 3: Integrating and Evaluating Ozone Evidence

- Considered several aspects to aid in our judgments regarding the WoE for a causal relationship between short-term ozone exposure and CV effects, including most of the Bradford Hald (1966) criteria.

Phase 4: Conclusions

- Relatively large number of studies of short-term ozone exposure and CV effects, but evidence is too limited to evaluate causality.

Table 1 Study Quality Scoring Matrix

- Score ≤0: Tier II
- Score >0: Tier I

Results from epidemiology studies largely null; few positive results not likely clinically significant.

Controlled exposure studies largely null; few positive results not likely clinically significant.

Results from animal studies cannot be extrapolated to humans; high exposures and hypothermic response.

Biomarker studies inconsistent and did not support a mode of action for CV effects.