Evidence Integration in Integrated Science Assessments (ISAs): A Case Study from the Draft Particulate Matter ISA

Michael J. Stewart, Ellen Kirrane, Thomas J. Luben, Jason Sacks, Barbara Buckley, Jennifer Nichols

National Center for Environmental Assessment | Environmental Media Assessment Group

Michael J. Stewart | stewart.michael@epa.gov | 919-541-7524

Background:

The National Center for Environmental Assessment (NCEA) develops Integrated Science Assessments (ISAs) as a key part of the Clean Air Act mandated reviews of the National Ambient Air Quality Standards (NAAQS), which are set for six criteria pollutants: particulate matter (PM), ozone, oxides of nitrogen, sulfur oxides, lead, and carbon monoxide. EPA establishes primary NAAQS to protect public health, including sensitive lifestages or populations, such as children or people with pre-existing disease. Secondary standards are established to protect against adverse ecological and other welfare effects. The ISAs identify, evaluate, integrate, and synthesize the comprehensive body of scientific evidence. This generally includes hundreds to thousands of studies spanning epidemiology, controlled human exposure, animal toxicology, dosimetry, exposure science, atmospheric science, welfare effects, and ecology. NCEA employs a weight of evidence framework in developing ISAs, integrating findings from the various lines of evidence and drawing conclusions on causality. More specifically, ISAs use a five-level hierarchical causal framework, incorporating aspects of the Hill criteria to assess causality (e.g., consistency, coherence, biological plausibility, temporality, etc.) and classify whether evidence is sufficient to conclude a "causal relationship", "likely to be a causal relationship", "suggestive of, but not sufficient to infer, a causal relationship", "inadequate to infer a causal relationship", or "not likely to be a causal relationship." Each level of the hierarchy represents the extent to which we can rule out chance, confounding or other biases. In ISAs, these causality determinations are presented both in a narrative form and in summary tables delineating the rationales and key evidence supporting the conclusion, reflecting the application of the framework and characterization of the evidence. In this case poster, an example from the draft PM ISA is presented, demonstrating the evaluation and integration of multiple lines of evidence underlying the conclusion that there is a "causal relationship" between short-term $PM_{2.5}$ exposure and cardiovascular effects.

ISA Development [1]

Literature Search and Study Selection
(See Figure III)

Evaluation of Individual Study Quality
After study selection, the quality of individual studies is evaluated by U.S. EPA or outside experts in the fields of atmospheric science, exposure assessment, dosimetry, animal toxicology, controlled human exposure, epidemiology, biogeochemistry, terrestrial and aquatic ecology, and other welfare effects, considering the design, methods, conduct, and documentation of each study. Strengths and limitations of individual studies that may affect the interpretation of the study are considered.

Develop Initial Sections
Review and summarize conclusions from previous assessments and new study results and findings by discipline and category of outcome/effect (e.g., toxicological studies of lung function or biogeochemical studies of forests)

Peer Input Consultation
Review of initial draft materials by scientists from both outside and within the U.S. EPA in public meeting or public teleconference.

Evaluation, Synthesis, and Integration of Evidence
Integrate evidence from scientific disciplines. Evaluate evidence for related groups of endpoints or outcomes to draw conclusions for specific health or welfare effect categories, integrating health or welfare effects evidence with information on mode of action and exposure assessment.

Development of Scientific Conclusions and Causal Determinations
Characterize weight of evidence and develop judgments regarding causality for health or welfare effect categories. Develop conclusions regarding concentration- or dose-response relationships, potentially at-risk populations, lifestages, or ecosystems.

Draft Integrated Science Assessment
Evaluation and integration of newly published studies

Clean Air Scientific Advisory Committee
Independent review of draft documents for scientific quality and sound implementation of causal framework during public meetings.

Public Comments
Comments on draft ISA solicited by the U.S. EPA

Final Integrated Science Assessment

U.S. Environmental Protection Agency
Office of Research and Development

This poster contains results from the external review Draft PM ISA. This information has been distributed solely for the purpose of predissemination peer review under applicable information quality guidelines. It has not been formally disseminated by EPA. It does not represent and should not be construed to represent any Agency determination or policy.

Aspects of Causality[1]

Aspect	Description
Consistency	An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. Statistical significance is not the sole criterion by which the presence or absence of an effect is determined. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.
Coherence	An inference of causality from one line of evidence (e.g., epidemiologic, controlled human exposure, animal, or ecological studies) may be strengthened by other lines of evidence that support a cause-and-effect interpretation of the association. There may be coherence in demonstrating effects from evidence across various fields and/or across multiple study designs or related health endpoints within one scientific line of evidence. For example, evidence on welfare effects may be drawn from a variety of experimental approaches (e.g., greenhouse, laboratory, and field) and subdisciplines of ecology (e.g., community ecology, biogeochemistry, and paleontological/historical reconstructions).
Biological plausibility	An inference of causality is strengthened by results from experimental studies or other sources demonstrating biologically plausible mechanisms. A proposed mechanism, which is based on experimental evidence and which links exposure to an agent to a given effect, is an important source of support for causality.
Biological gradient (exposure-response relationship)	A well-characterized exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times).
Strength of the observed association	The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. However, it is noted that a small magnitude in an effect estimate may or may not represent a substantial effect in a population.
Experimental evidence	Strong evidence for causality can be provided through "natural experiments" when a change in exposure is found to result in a change in occurrence or frequency of health or welfare effects.
Temporality of the observed association	Evidence of a temporal sequence between the introduction of an agent and appearance of the effect constitutes another argument in favor of causality.
Specificity of the observed association	Evidence linking a specific outcome to an exposure can provide a strong argument for causation. However, it must be recognized that rarely, if ever, does exposure to a pollutant invariably predict the occurrence of an outcome, and that a given outcome may have multiple causes.
Analogy	Structure activity relationships and information on the agent's structural analogs can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogs, can inform decisions regarding likely causality.

ISAs Causality Framework[1]

WEIGHT OF EVIDENCE FOR CAUSAL DETERMINATION

	Health Effects	Ecological and Other Welfare Effects
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (e.g., doses or exposures generally within one to two orders of magnitude of recent concentrations). That is, the pollutant has been shown to result in health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies that demonstrate consistent effects, or (2) observational studies that cannot be explained by plausible alternatives or that are supported by other lines of evidence (e.g., animal studies or mode of action information). Generally, the determination is based on multiple high-quality studies conducted by multiple research groups.	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. Controlled exposure studies (laboratory or small- to medium-scale field studies) provide the strongest evidence for causality, but the scope of inference may be limited. Generally, the determination is based on multiple studies conducted by multiple research groups, and evidence that is considered sufficient to infer a causal relationship is usually obtained from the joint consideration of many lines of evidence that reinforce each other.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. For example: (1) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent, or (2) animal toxicological evidence from multiple studies from different laboratories demonstrate effects, but limited or no human data are available. Generally, the determination is based on multiple high-quality studies.	Evidence is sufficient to conclude that there is a likely causal association with relevant pollutant exposures. That is, an association has been observed between the pollutant and the outcome in studies in which chance, confounding, and other biases are minimized but uncertainties remain. For example, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Generally, the determination is based on multiple studies by multiple research groups.
Suggestive of, but not sufficient to infer, a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures but is limited, and chance, confounding, and other biases cannot be ruled out. For example: (1) when the body of evidence is relatively small, at least one high-quality epidemiologic study shows an association with a given health outcome and/or at least one high-quality toxicological study shows effects relevant to humans in animal species, or (2) when the body of evidence is relatively large, evidence from studies of varying quality is generally supportive but not entirely consistent, and there may be coherence across lines of evidence (e.g., animal studies or mode of action information) to support the determination.	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but chance, confounding, and other biases cannot be ruled out. For example, at least one high-quality study shows an effect, but the results of other studies are inconsistent.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations and lifestages, are mutually consistent in not showing an effect at any level of exposure.	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies examining relationships with relevant exposures are consistent in failing to show an effect at any level of exposure.

Sample Causality Text: Short-term Exposure to $PM_{2.5}$ and Cardiovascular Effects[2]

A large body of recent evidence confirms and extends the evidence from the previous ISA indicating that there is a "causal relationship" between short term $PM_{2.5}$ exposure and cardiovascular effects. In the current review, evidence supporting the causality determination includes generally positive associations reported from epidemiologic studies of hospital admissions and emergency department (ED) visits for cardiovascular related effects, and in particular, for ischemic heart disease and heart failure. Results from these observational studies are in agreement with experimental evidence from controlled human exposure and animal toxicological studies of endothelial dysfunction, as well as with endpoints indicating impaired cardiac function, increased risk of arrhythmia, changes in heart rate variability (HRV), increases in blood pressure (BP), and increases in indicators of systemic inflammation, oxidative stress, and coagulation. Results from observational panel studies, though not entirely consistent, also provide some evidence of increased risk of arrhythmia, decreases in HRV, increases in BP, and changes in cardiac electrophysiology. Thus, the combination of evidence from experimental and epidemiologic panel studies provides coherence and biological plausibility for the results from observational epidemiologic studies. Finally, epidemiologic studies of cardiovascular-related mortality provide additional evidence and contributes to the continuum of effects from biomarkers of inflammation and coagulation, subclinical endpoints (HRV, BP, endothelial dysfunction), ED visits and hospital admissions for outcomes such as ischemic heart disease (IHD) and congestive heart failure (CHF), and eventually death. The current body of evidence also reduces uncertainties from the previous review related to the potential for copollutant confounding and biological plausibility for cardiovascular effects following short term $PM_{2.5}$ exposure.

Sample Causality Table: Short-term Exposure to $PM_{2.5}$ and Cardiovascular Effects[2]

Rationale for Causal Determination	Key Evidence
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Increases in ED visits and hospital admissions for IHD and CHF in multicity studies conducted in the U.S., Canada, Europe, and Asia Increases in cardiovascular mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia.
Consistent evidence from controlled human exposure studies at relevant $PM_{2.5}$ concentrations	Consistent changes in measures of endothelial dysfunction Generally consistent evidence for small increases in measures of blood pressure following CAPs exposure Additional evidence of conduction abnormalities, heart rate variability, impaired heart function, systemic inflammation/oxidative stress
Consistent evidence from animal toxicological studies at relevant $PM_{2.5}$ concentrations	Consistent changes in indicators of endothelial dysfunction. Additional evidence of changes in impaired heart function, conduction abnormalities/arrhythmia, heart rate variability, blood pressure, systemic inflammation/oxidative stress
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{2.5}$ association	The magnitude of $PM_{2.5}$ associations remain positive, but in some cases are reduced with larger confidence intervals in copollutant models with gaseous pollutants. Further support from copollutant analyses indicating positive associations for cardiovascular mortality. Recent studies that examined potential copollutant confounding are limited to studies conducted in Europe and Asia. When reported, correlations with gaseous copollutants were primarily in the low to moderate range ($r < 0.7$).
Consistent positive epidemiologic evidence for associations between $PM_{2.5}$ exposure and CVD ED visits and hospital admissions across exposure measurement metrics	Positive associations consistently observed across studies that used ground-based (i.e., monitors), model (e.g., CMAQ, dispersion models) and remote sensing (e.g., AOD measurements from satellites) methods, including hybrid methods that combine two or more of these methods.
Epidemiologic evidence supports a log-linear, no-threshold concentration-response (*C-R*) relationship	
Generally consistent evidence for biological plausibility of cardiovascular effects	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to short-term $PM_{2.5}$ exposure. Includes evidence for reduced myocardial blood flow, altered vascular reactivity, and ST segment depression.
Uncertainty regarding geographic heterogeneity in $PM_{2.5}$ associations	Multicity U.S. studies demonstrate city-to-city and regional heterogeneity in $PM_{2.5}$-CVD ED visit and hospital admission associations. Evidence supports that a combination of factors including composition and exposure factors may contribute to the observed heterogeneity.

* CMAQ= Community Multiscale Air Quality Modeling System; AOD= Aerosol Optical Depth; CAPs = Concentrated Ambient Particles

References:

1. Preamble to the ISA: https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244
2. ISA for PM (External Review Draft): http://cfint.rtpnc.epa.gov/ncea/prod/recordisplay.cfm?deid=341593