Incorporating Mechanistic Evidence and Systematic Review Tools to Assess the Biological Plausibility of Cardiovascular Effects in Integrated Science Assessments

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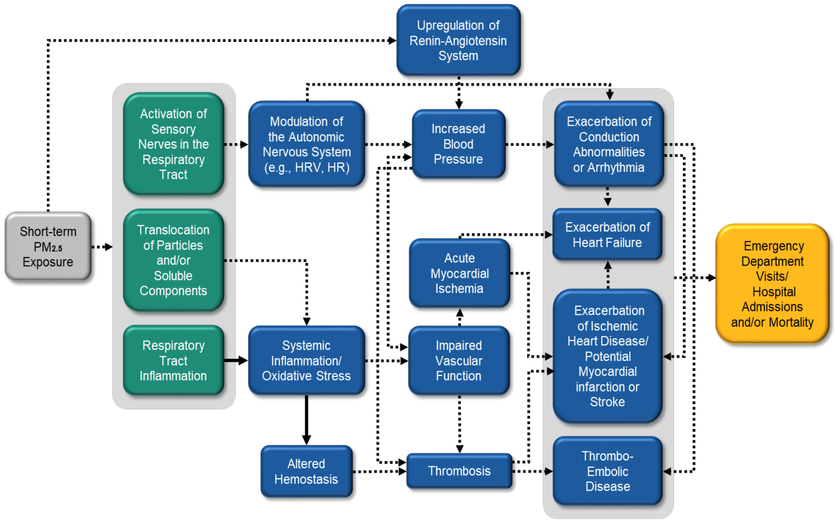
Background

National Ambient Air Quality Standards (NAAQS) are set for the six criteria pollutants: particulate matter (PM) ozone (O_3), oxides of sulfur, oxides of nitrogen, lead, and carbon monoxide. Primary NAAQS are set to protect public health- including sensitive populations such as children, older adults and people with chronic diseases. The Integrated Science Assessments (ISAs) identify, evaluate, and synthesize the best available and most policy-relevant exposure and health evidence, and communicate critical science judgments regarding the extent to which a specific health effect is related to exposure to a specific criteria pollutant. In making causality determinations, it is important to provide evidence that can plausibly link the inhalation of a criteria pollutant to downstream health effects that are systemic in nature. In the External Review Draft of the 2018 ISA for PM, a new and innovative approach was taken to systematically assess the biological plausibility for epidemiologic results indicating positive associations between ambient $PM_{2.5}$ concentrations and serious health outcomes such as ischemic heart disease (IHD), heart failure, and mortality. This approach leveraged mechanistic animal toxicology evidence along with human health endpoint data to identify biologically plausible pathways by which inhalation exposure to $PM_{2.5}$ could lead to these health outcomes. Here, we describe this approach and these biologically plausible pathways, placing emphasis on the role of mechanistic data in their construction. In addition, using the currently being developed 2018 draft O_3 ISA as an example, we briefly describe how this approach will be improved upon in future ISAs through the expanded use of systematic review tools and techniques.

Approach

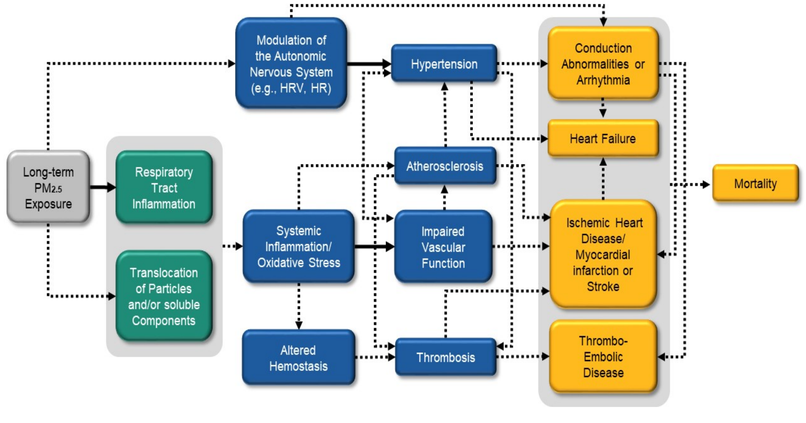
- Review the controlled human exposure, animal toxicological and epidemiologic literature examining the relationship between exposure to PM and endpoints ranging from changes in biomarker expression to associations with serious cardiovascular outcomes such as stroke, myocardial infarction and mortality
- Identify mechanistic studies in animals that used techniques such as pharmacological inhibitors, or knockout mice to elucidate the linkage between two or more endpoints
- Using the information above, construct a plausibility figure that depicts potential pathways leading from inhalation exposure of PM to an apical endpoint such as an emergency department visit for a cardiovascular-related event
- Separate figures are created for long- and short-term exposure to $PM_{2.5}$, $PM_{10-2.5}$ and ultrafine particles (see examples 1 and 2)
- Boxes are color coded:
  - Gray represents an exposure to a particular size fraction of PM
  - Green represent an initial event- often evidence of biomarker expression (e.g., cytokine expression in the respiratory tract),
  - Blue represents an intermediate event- may be evidence of biomarker expression (e.g., increased markers of coagulation) or be clinical in nature
  - Orange depicts apical associations reported in epidemiologic studies
- Figures are located at the beginning of each health chapter to serve as a roadmap for the health effects that are going to be discussed in more detail later in that chapter
- Figures are *not* developed using on a weight of evidence approach, as long as one study demonstrates an effect, it is included as a "box" on the figure. Dotted lines are proposed pathways between two boxes, while solid lines specifically link two boxes based on mechanistic studies using a pharmacological inhibitor or genetic knockout model following exposure to PM

Example 1: Potential biological pathways for cardiovascular effects following *short-term* exposure to $PM_{2.5}$



NOTE: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Solid arrows denote mechanistic evidence of the relationship as provided by an inhibitor of the pathway or a genetic knock out model. Progression of effects is depicted from left to right and color coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies

Example 2: Potential biological pathways for cardiovascular effects following *long-term* exposure to $PM_{2.5}$



*See NOTE under Example 1

Incorporating additional systematic review tools into future ISAs

- The 2018 O_3 ISA is under development and a draft has not been completed yet. However, the literature screening process has begun with the use additional systematic review tools
- Title abstract screening was done using SWIFT-ActiveScreener(AS), a software application employing machine learning in real-time based on inclusion/exclusion decisions to predict relevance of references
- Screening questions were used during title/abstract screening to "tag" references to disciplines/topics
- A "tag" for mechanistic studies was added within SWIFT-active to ensure these studies were reflected in the appropriate biological plausibility section
- Full text screening (conducted outside of SWIFT-AS), and decisions were recorded in Evidence Inventories (see below)

Sample Evidence Inventory

Study Details				Health Outcome Tags								Exp Dur Tags			Exp Conc Tags		Study Type Tags				Other Tags								
HERO ID	Author	Year	Title	Resp	CV	Reprod/Dev	Nervous	Met	Cancer	Dermal	Other	ST	LT	Unclear	Above	At or Below 1ppm	Other	Tox Human	Tox Animal	Chit	Other/Unclear	REVIEW/BACKGR	QUAL	SR	Potentially/Relevs	Mechanistic	Dosimetry	ATRISK	Other
4256321	Uludag, M	2017	Effects of ozone treatment in endotoxin induced shock model in rats	N	Y	N	N	Y	N	N	Y	N	N	Y	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N
4256695	Mason, R	2013	Biomarkers Of Oxidative Stress Study	Y	Y	N	N	N	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	Y	N	N	N	N	N	N
4256698	Mason, R	2014	Biomarkers of oxidative stress study																										
4251532	Kuz'mina,	2012	[The effect of ozone therapy on the level of blood cholesterol in cerebrovascular	N	Y	N	Y	Y	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	Y
4256780	Mason, R	2015	Biomarkers Of Oxidative Stress Study	Y	Y	N	N	N	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	Y	N	N	N	N	N	N
4251943	Wang, L; C	2014	Ozone oxidative preconditioning inhibits renal fibrosis induced by ischemia and reperfusion	N	Y	N	N	N	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N
4252568	Wagner, J	2013	channels in ozone-induced decreases in blood pressure and heart rate in rats on a high fructose diet	N	Y	N	N	N	N	N	N	N	Y	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N
4252569	Wagner, J	2014	exposure to a mixture of ozone and rural ambient fine particles (PM2.5) in rats on a high fructose diet	Y	Y	N	N	N	N	N	N	N	Y	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N
4253769	Lynch, H; S	2013	Weight-of-evidence evaluation of the cardiovascular effects of ozone exposure	N	Y	N	N	N	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	Y
4247395	Meng, W;	2017	reperfusion injury: A role for oxidative preconditioning in attenuating mitochondrial injury	N	Y	N	N	N	N	N	N	N	Y	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N

Summary

- The PM ISA incorporated a new and innovative approach for using mechanistic evidence to provide biological plausibility for the associations reported in epidemiologic studies
- This systematic approach results in a biological plausibility figure, as well as accompanying text that depicts the potential pathways leading from inhalation exposure of PM to an apical endpoint such as an emergency department visit for IHD or heart failure
- This approach will be improved upon in future ISAs by incorporating additional systematic review tools. This includes the use of software employing machine learning for literature screening and a "tag" for identifying mechanistic studies relevant to specific biological plausibility sections
- In addition to increasing transparency, the use of systematic review tools increases the efficiency of ISAs

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