

A Conceptual Model for Assessing Criteria Air Pollutants in a Multipollutant Context: A modified adverse outcome pathway approach

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Alternative Approaches for Acute Inhalation Toxicity to Address Global Regulatory and Non-regulatory Data Requirements

PETA International Science Consortium (PISC), Ltd.

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

Webinar Series

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Adverse Outcome Pathways (AOPs) and the National Ambient Air Quality Standards (NAAQS)

- *NAAQS*
- *Multipollutant context*
- *Need for a conceptual model*
- *Possible frameworks*
- *AOP approach illustrated with case reports*

National Ambient Air Quality Standard Review Process

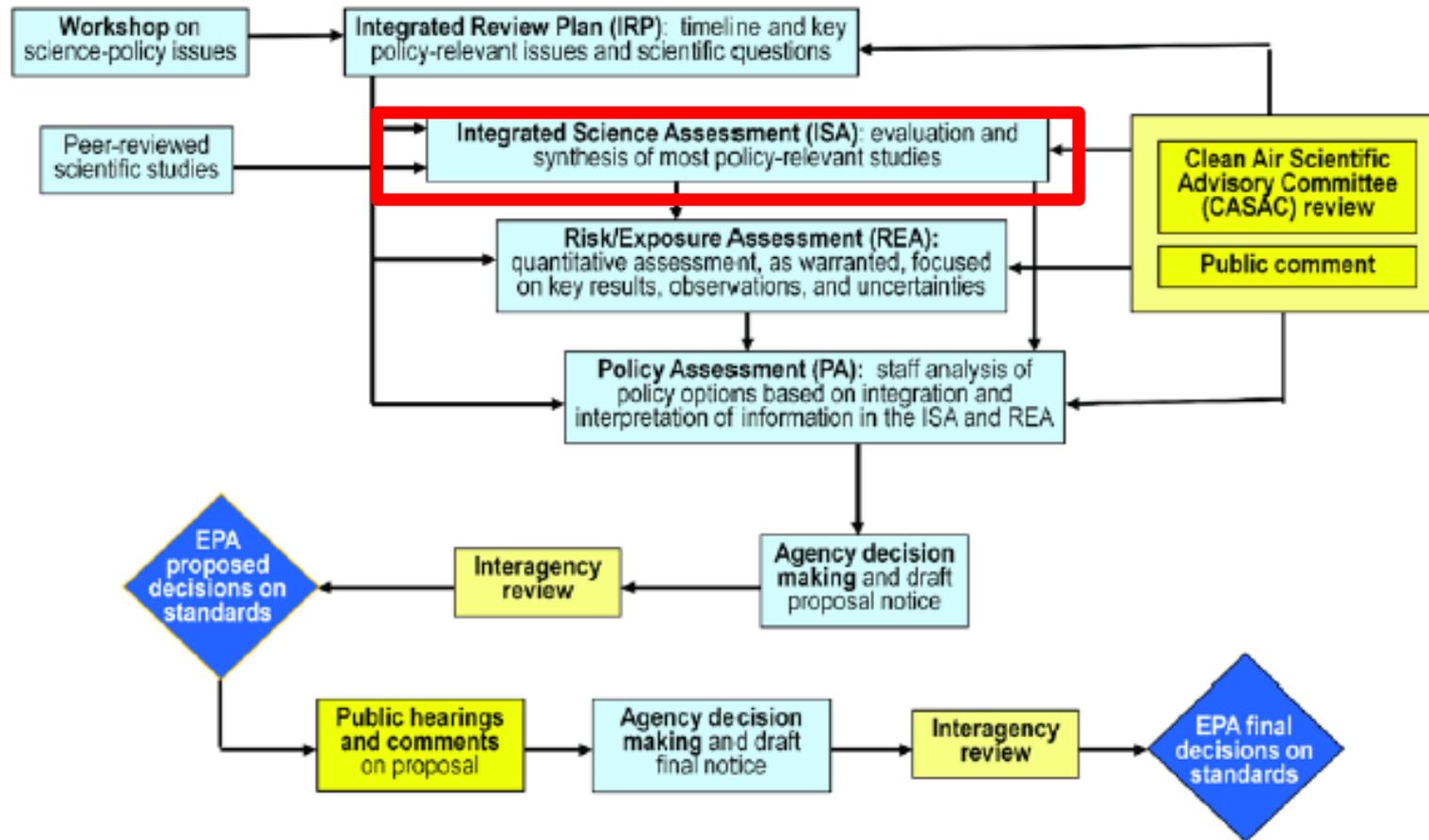


Figure 1 Schematic of the key steps in review of the National Ambient Air Quality Standards.

Figure from the U.S. EPA. Preamble to the Integrated Science Assessments. U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-15/067, 2015, available at <http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244>

- ***NAAQS are promulgated for individual criteria pollutants:***
 - *particulate matter (PM)*
 - *ozone (O₃)*
 - *oxides of nitrogen (NO_x)*
 - *sulfur oxides (SO_x)*
 - *carbon monoxide (CO)*
 - *lead (Pb)*
- ***There are two sets of standards:***
 - *Primary – based on health effects*
 - *Secondary – based on welfare effects*
- ***One of the criteria pollutants (PM) is a mixture***
- ***Currently, NO_x and SO_x are being reviewed together for the secondary NAAQS***

2004 NAS Report: “Air Quality Management in the United States”

Recommendation:

Address multiple pollutants in the NAAQS review and standard setting process

“Although the committee does not believe that the science has evolved to a sufficient extent to permit the development of multipollutant NAAQS, it would be scientifically prudent to begin to review and develop NAAQS for related pollutants in parallel and simultaneously”

NOTE: There are Currently no Plans to Attempt the Development of Multipollutant Primary NAAQS

Practical Advancement of Multipollutant Scientific and Risk Assessment Approaches for Ambient Air Pollution

Douglas O. Johns,¹ Lindsay Wichers Stanek,¹ Katherine Walker,² Souad Benromdhane,³ Bryan Hubbell,³ Mary Ross,¹ Robert B. Devlin,⁴ Daniel L. Costa,⁵ and Daniel S. Greenbaum²

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OBJECTIVES: The U.S. Environmental Protection Agency is working toward gaining a better understanding of the human health impacts of exposure to complex air pollutant mixtures and the key features that drive the toxicity of these mixtures, which can then be used for future scientific and risk assessments.

DATA SOURCES: A public workshop was held in Chapel Hill, North Carolina, 22–24 February 2011, to discuss scientific issues and data gaps related to adopting multipollutant science and risk assessment approaches, with a particular focus on the criteria air pollutants. Expert panelists in the fields of epidemiology, toxicology, and atmospheric and exposure sciences led open discussions to encourage workshop participants to think broadly about available and emerging scientific evidence related to multipollutant approaches to evaluating the health effects of air pollution.

SYNTHESIS: Although there is clearly a need for novel research and analytical approaches to better characterize the health effects of multipollutant exposures, much progress can be made by using existing scientific information and statistical methods to evaluate the effects of single pollutants in a multipollutant context. This work will have a direct impact on the development of a multipollutant science assessment and a conceptual framework for conducting multipollutant risk assessments.

CONCLUSIONS: Transitioning to a multipollutant paradigm can be aided through the adoption of a framework for multipollutant science and risk assessment that encompasses well-studied and ubiquitous air pollutants. Successfully advancing methods for conducting these assessments will require collaborative and parallel efforts between the scientific and environmental regulatory and policy communities.

KEY WORDS: air pollution, exposure, human health, multipollutant, risk assessment. *Environ Health Perspect* 120:1238–1242 (2012). <http://dx.doi.org/10.1289/ehp.1204939> [Online 29 May 2012]

health effects. As additional evidence of its commitment to this new thinking, scientists within the U.S. EPA's National Center for Environmental Assessment (NCEA), which is responsible for evaluating and synthesizing the scientific information related to the effects of exposure to criteria air pollutants as a part of the National Ambient Air Quality Standards (NAAQS) review process, are currently developing plans for conducting a formal multipollutant science assessment (MSA) of the health effects of exposure to air pollutant mixtures. As an initial step in the development of this proposed human health MSA, the U.S. EPA is preparing a framework describing the purpose and scope of the MSA, along with plans for conducting multipollutant analyses using existing data and information that will provide scientific support to the development of the MSA. The MSA is intended to serve as a companion document to single-pollutant Integrated Science Assessments (ISAs) of the criteria air pollutants (i.e., particulate matter,

Groupings of Pollutants and their Effects

By fundamental biological reactivity

- Oxidative injury
- Affinity for neural receptors
- Recognition by immune cells
- Covalent binding to DNA or proteins

(Mauderly, et al., Inhalation Toxicology 22(S1):1, 2010)

By surrogate marker

- Endothelial function
- Endothelial progenitor cells
- Blood pressure
- ANS measures
- Systemic inflammation
- Insulin resistance

(S. Rajagopalan, AAAR March 2010)

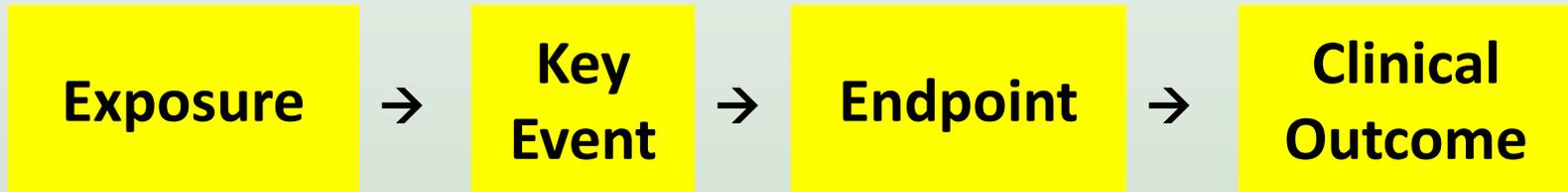
Characterization of Common Modes of Action and Toxicity Pathways

(Lead: Barbara Buckley)

***Do multiple criteria pollutants act
through similar pathways to induce
health effects?***

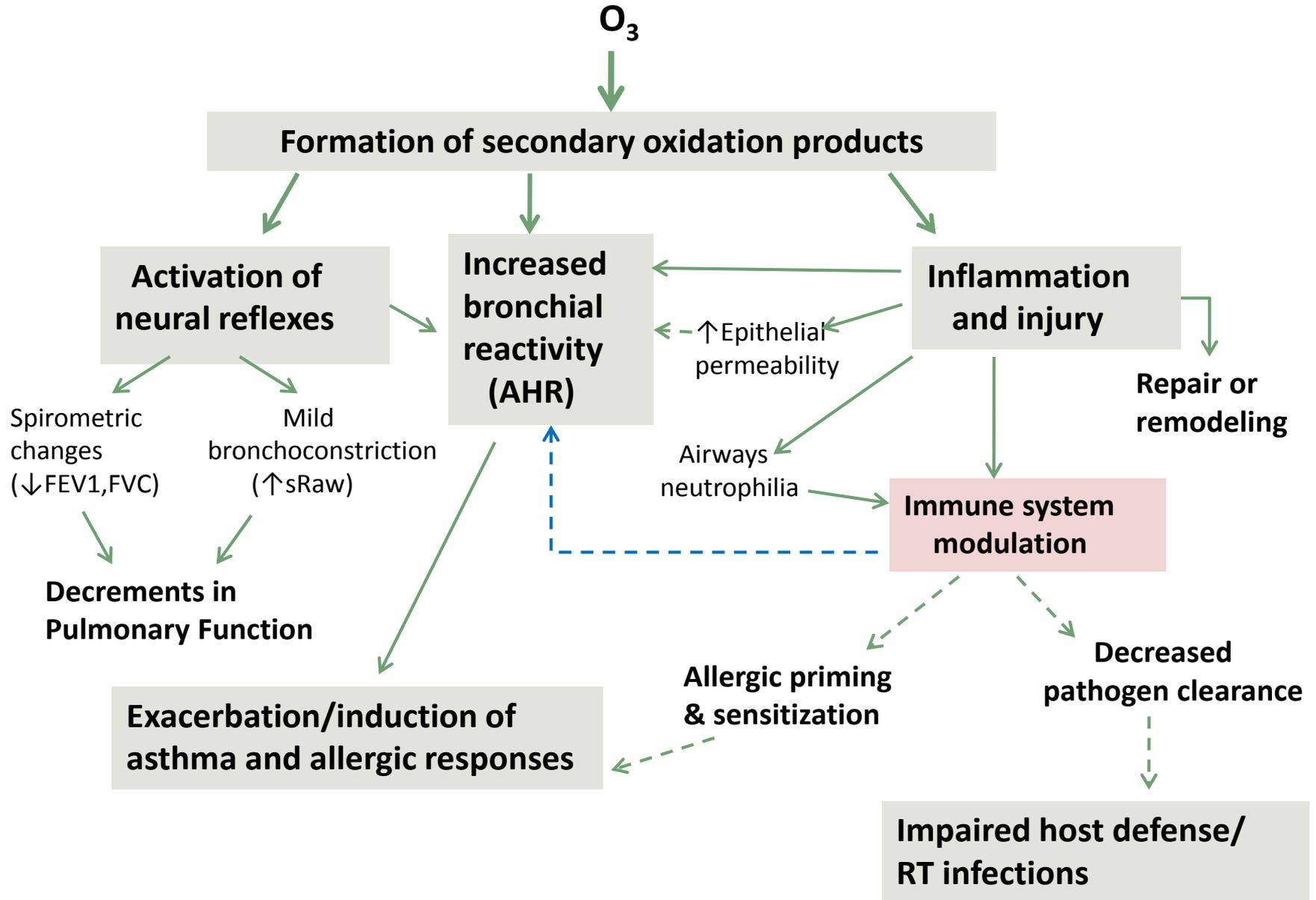
- *Develop framework*
- *Fit existing information for single pollutants into framework*
- *Provide case studies illustrating converging effects/converging pathways for multiple pollutants*

MOA Paradigm

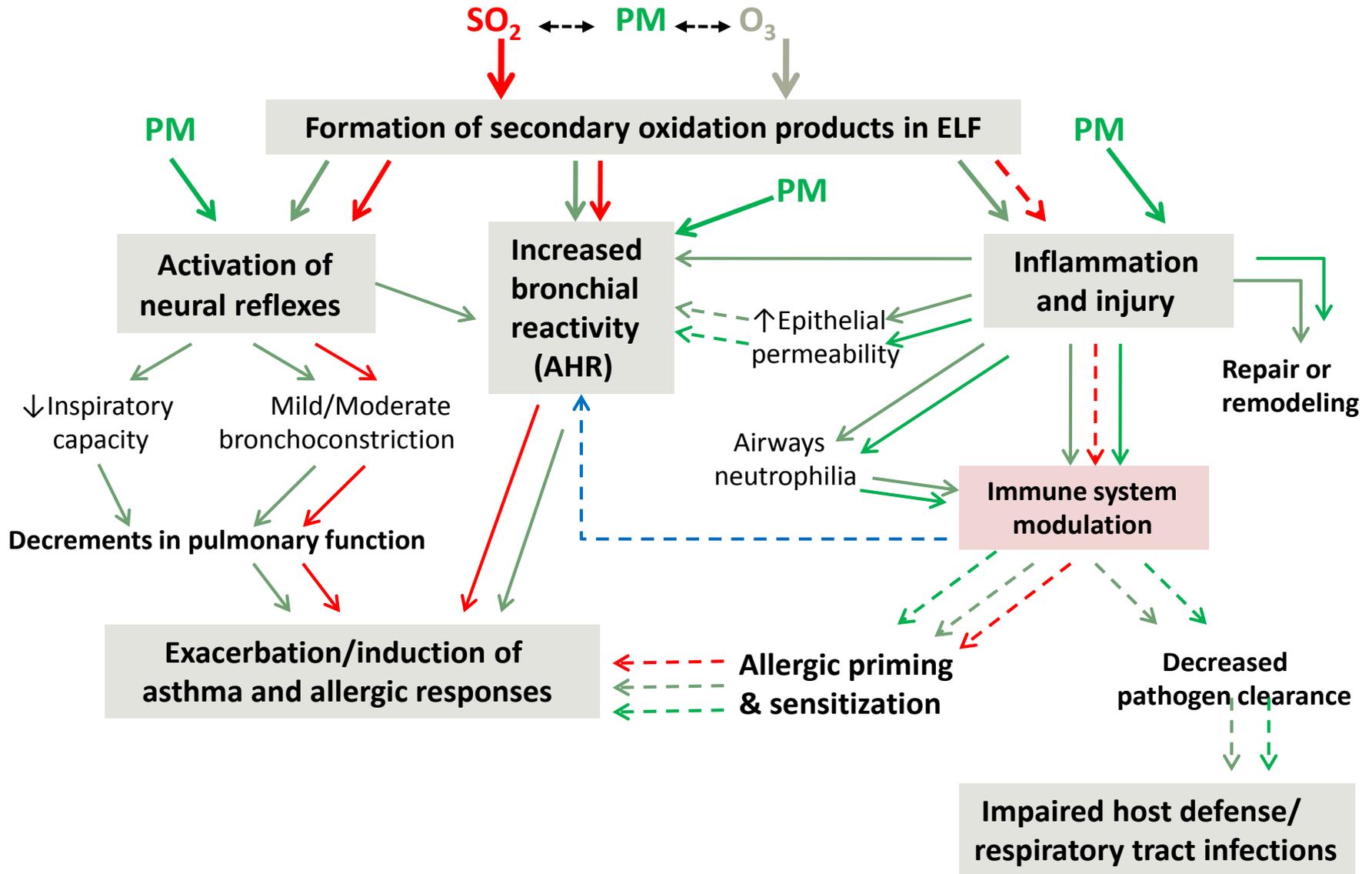


- Sequence of precursor steps necessary for end result
- Measureable key events or markers of key events
- Toxicokinetic/Toxicodynamics ???

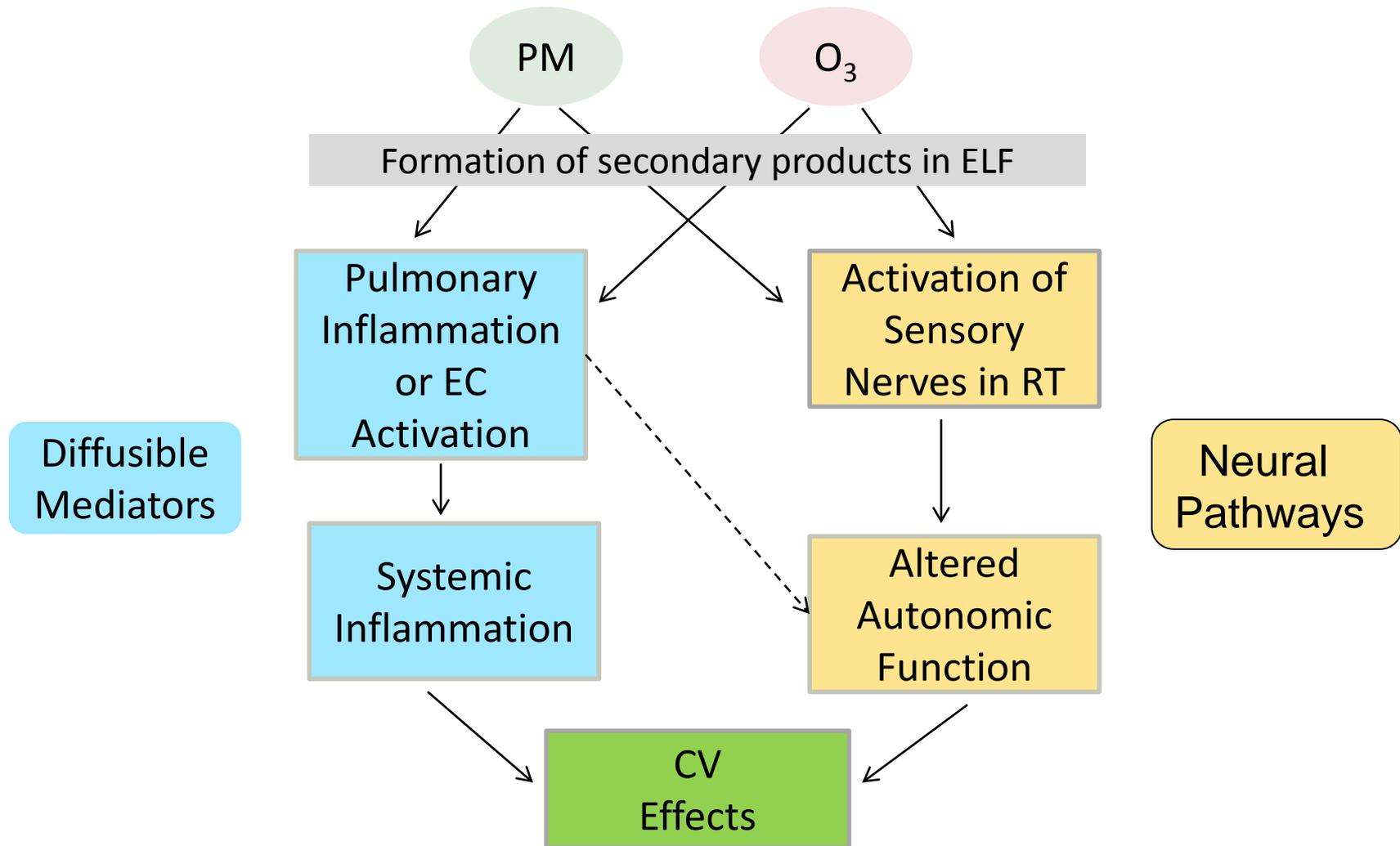
O₃ MOA: Respiratory Effects



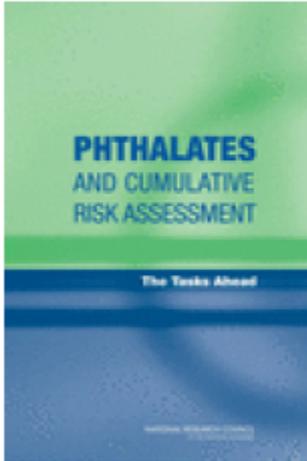
Multipollutant MOAs: Respiratory Effects



Multipollutant MOA: Cardiovascular (CV) Effects



Common Adverse Outcome Paradigm



Phthalates and Cumulative Risk Assessment The Task Ahead

ISBN: 0-309-12842-0, 0 pages, . ()

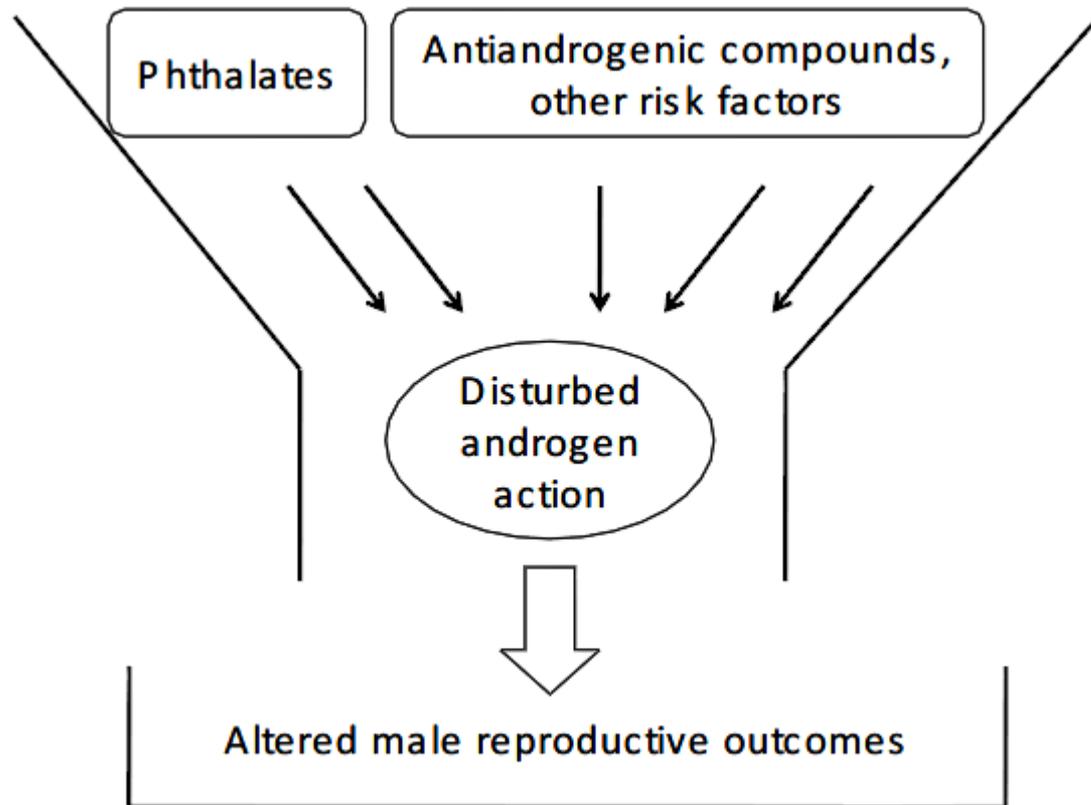
This free PDF was downloaded from:

<http://www.nap.edu/catalog/12528.html>

Developed by NRC to guide U.S. EPA in conducting a cumulative risk assessment of a class of chemicals (i.e., phthalate esters) which share a common health outcome rather than a common mechanism/mode of action

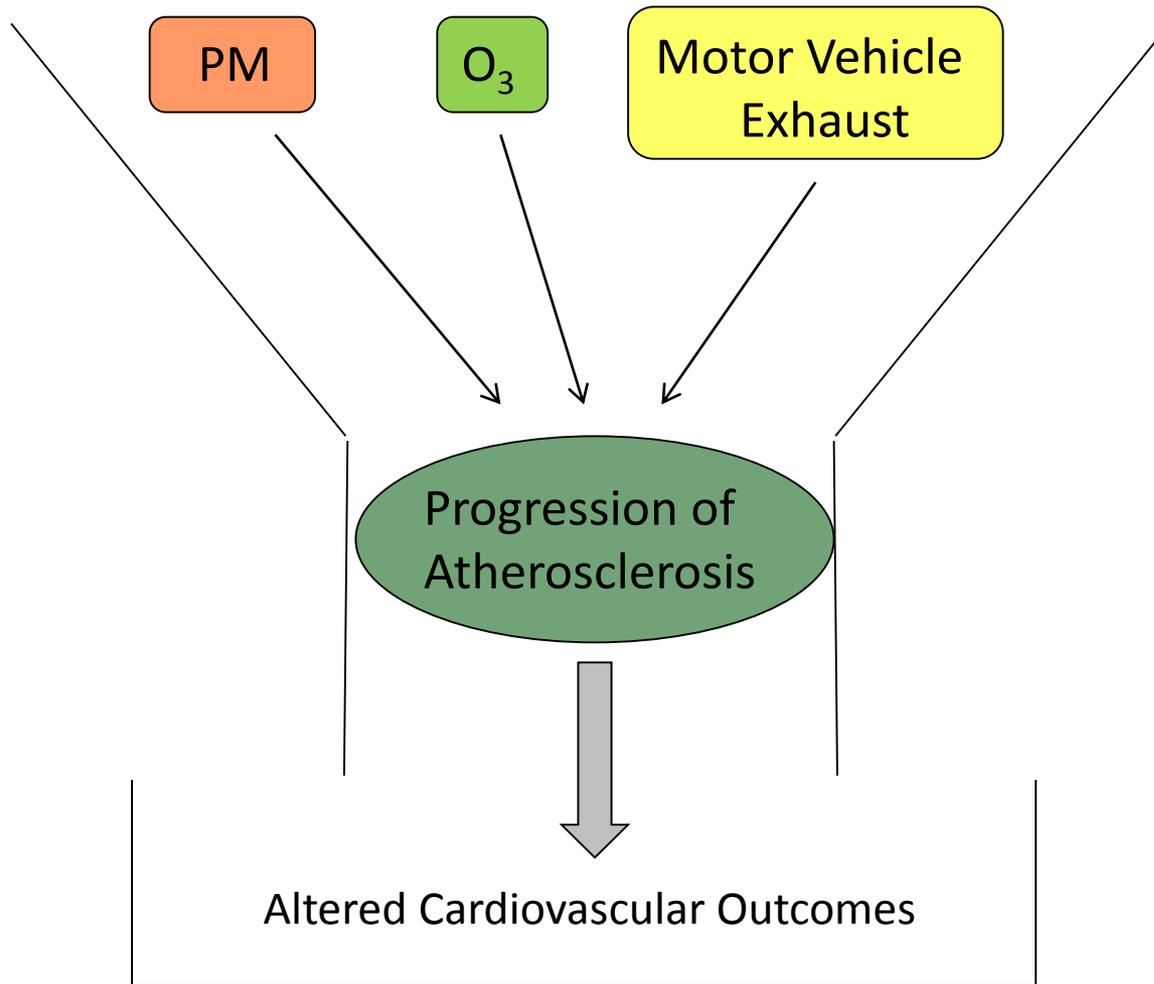
It broadened the focus to include contributions to the common health outcome resulting from stressors other than phthalates

Common Adverse Outcome Paradigm

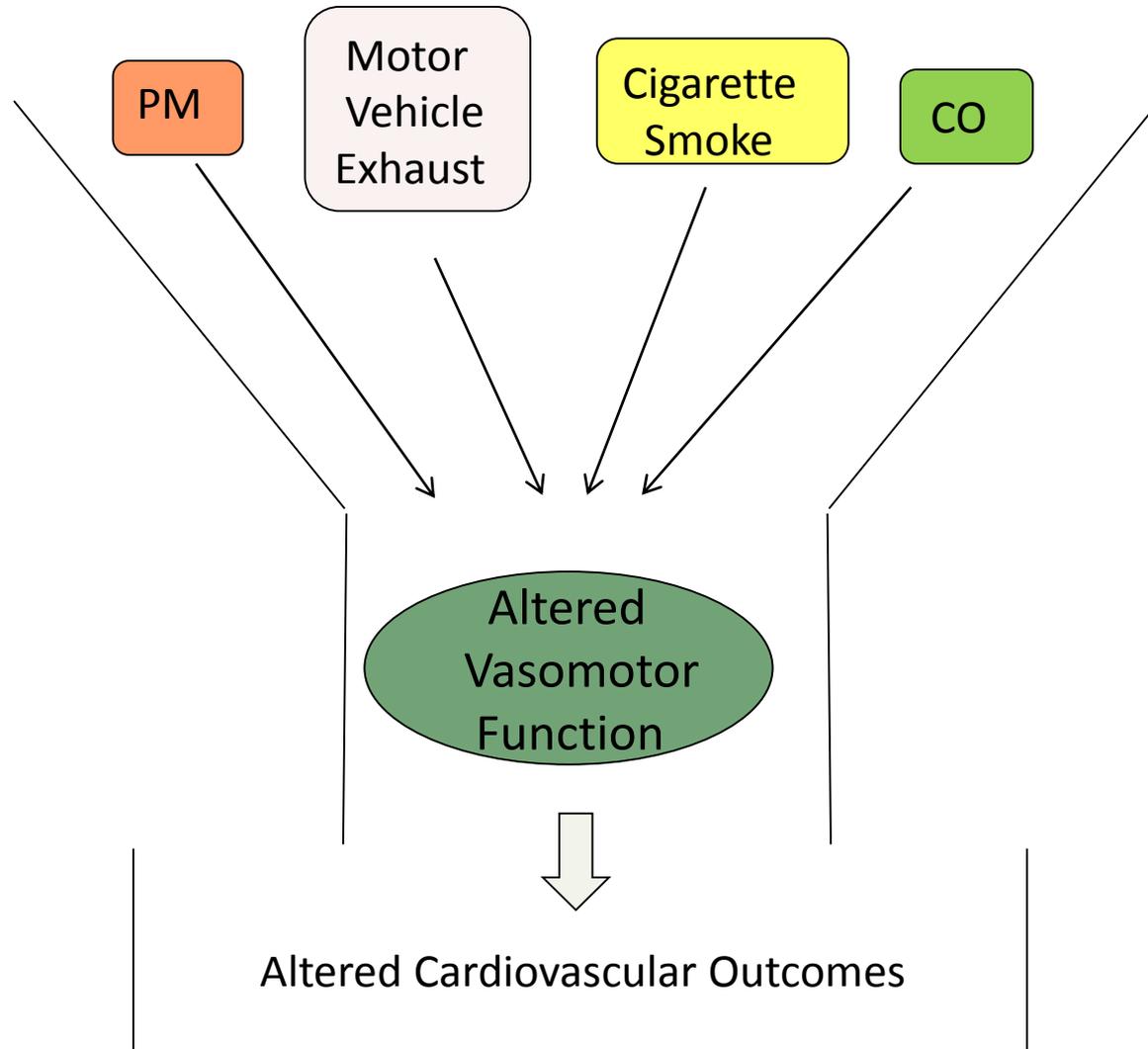


NRC 2008 Phthalates and Cumulative Risk Assessment - The Task Ahead

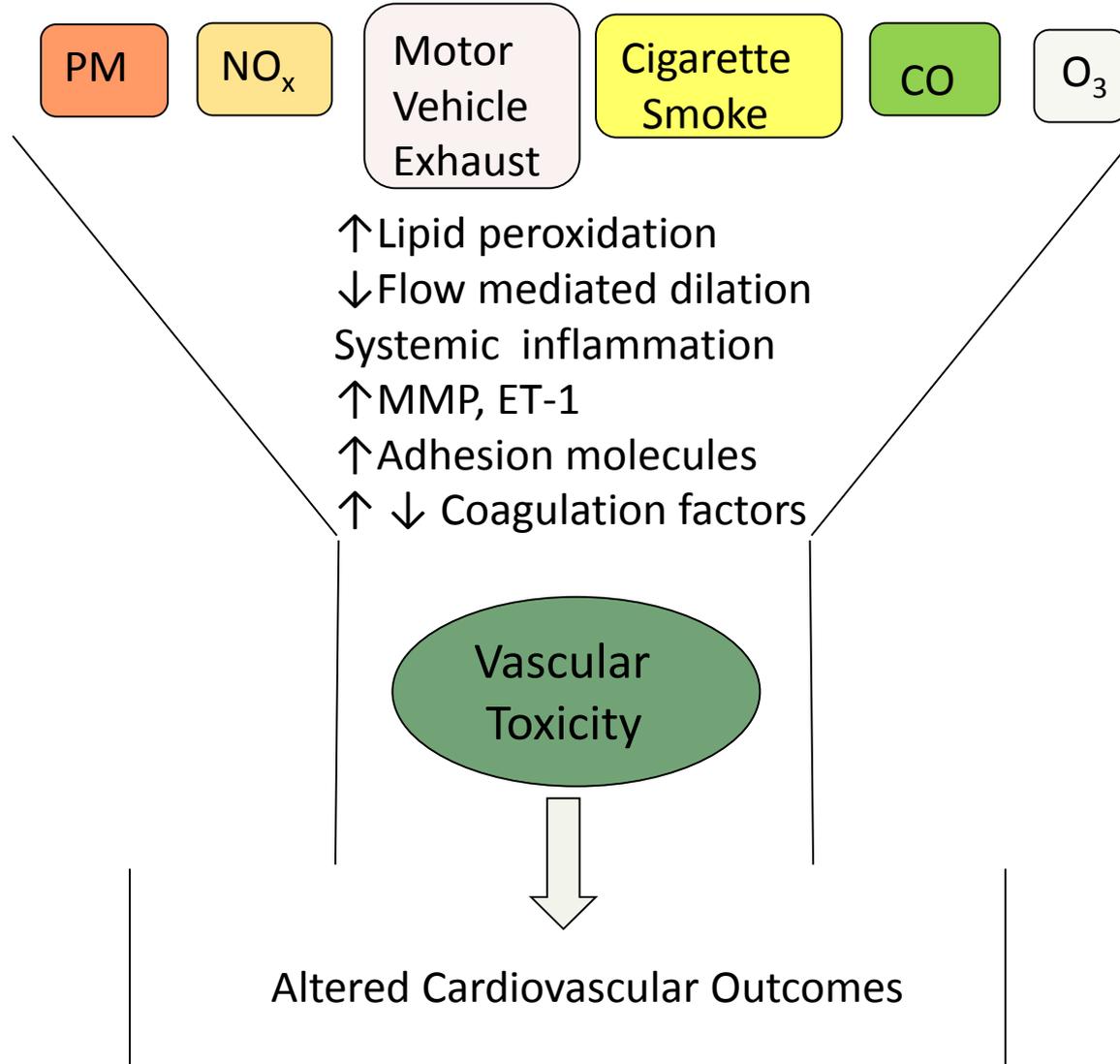
Common Adverse Outcome: Air Pollutants



Common Adverse Outcome: Air Pollutants

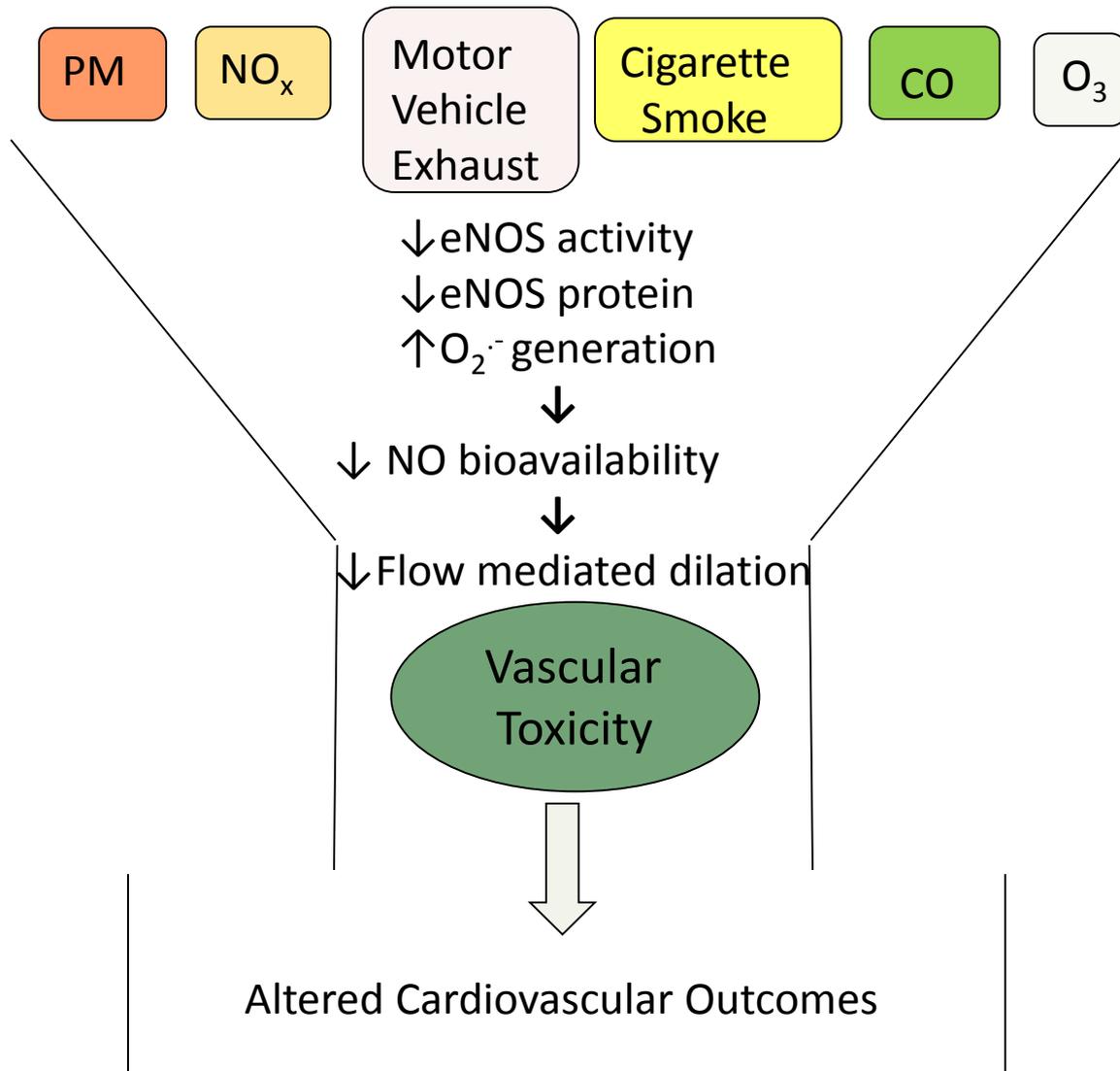


Common Adverse Outcome: Air Pollutants



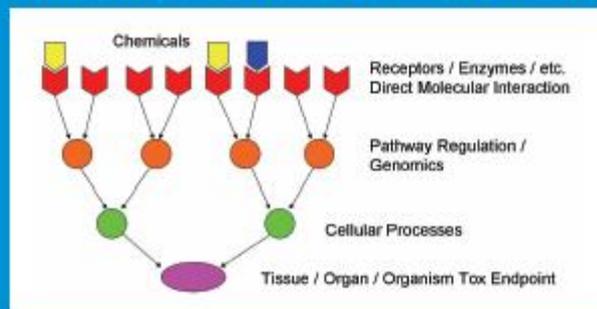
MMP: matrix metalloproteinase; ET-1: endothelin-1

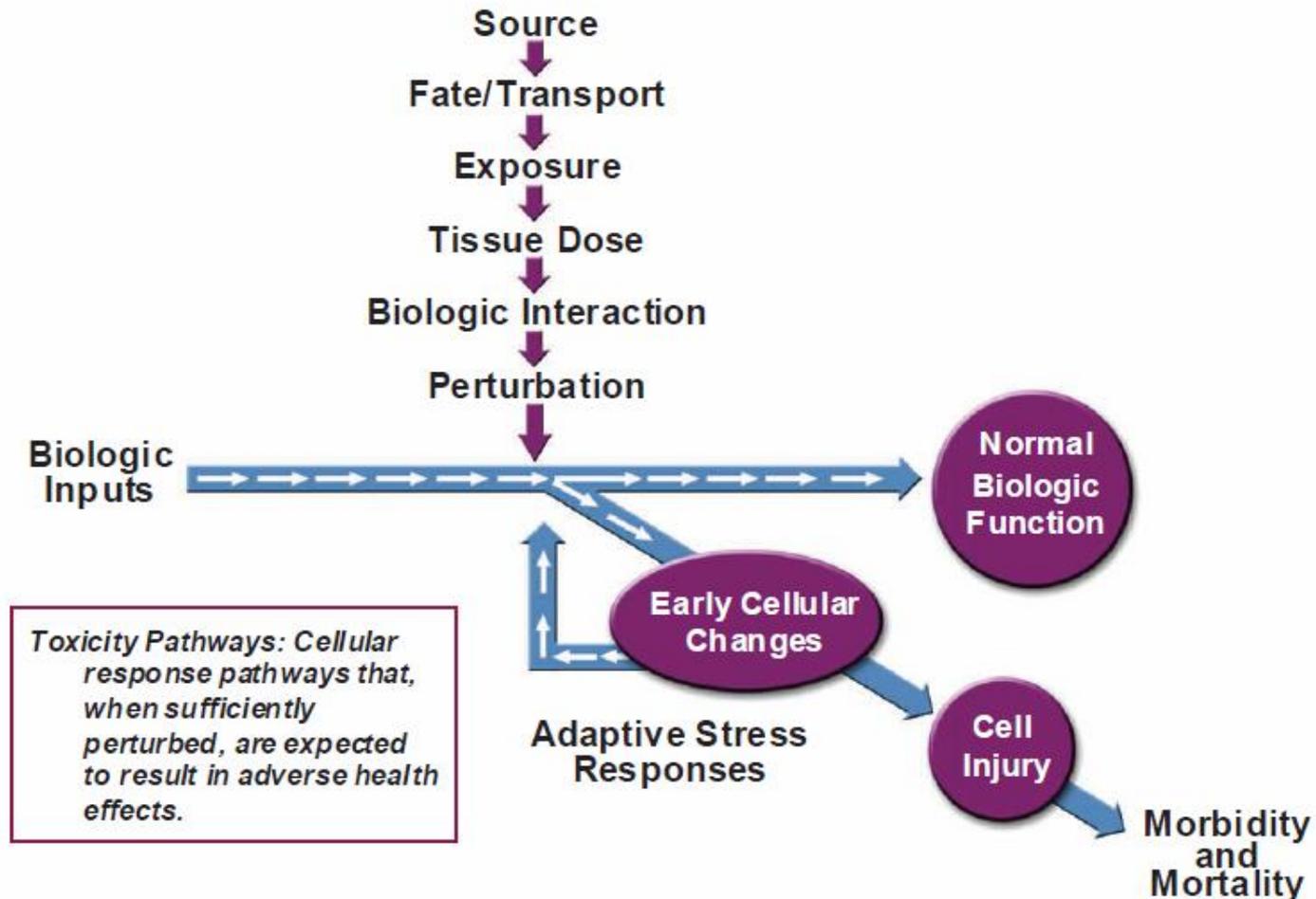
Common Adverse Outcome: Air Pollutants



O₂^{·-} : superoxide; NO: nitric oxide; eNOS: endothelial nitric oxide synthase

The U.S. Environmental Protection Agency's Strategic Plan for Evaluating the Toxicity of Chemicals

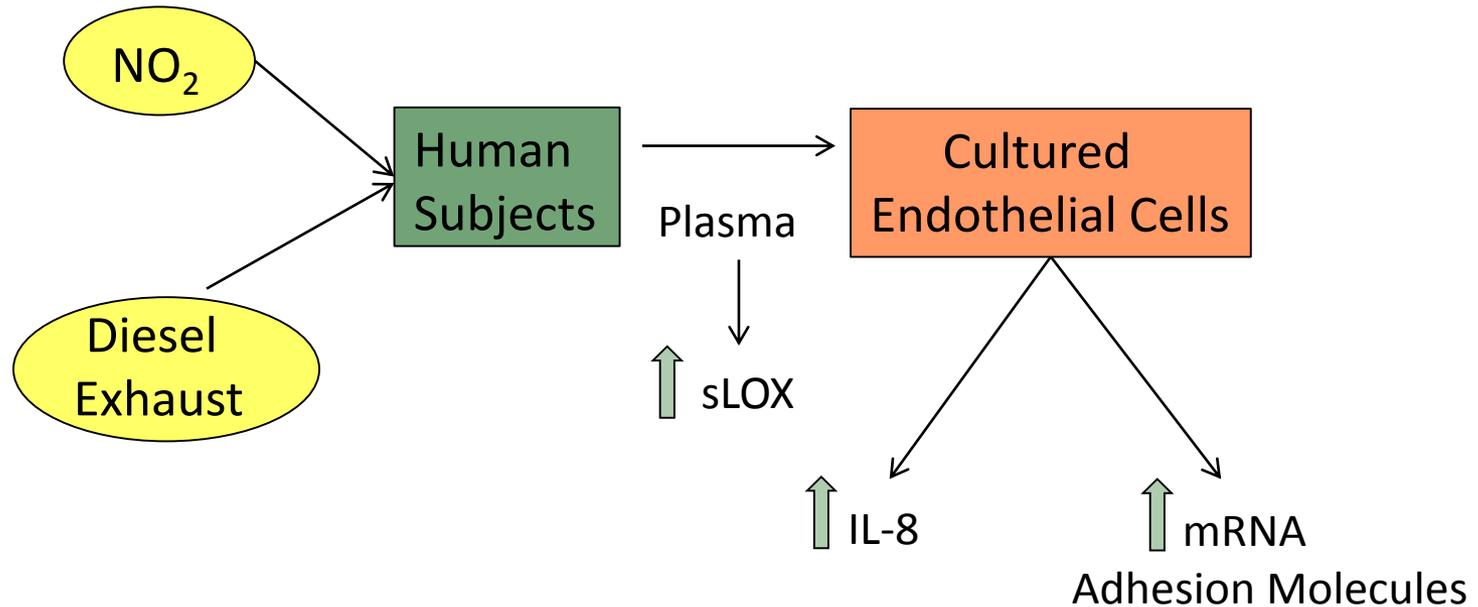




Modified from NRC, 2007

Figure 1. Toxicity Pathways. Toxicity pathways describe the processes by which perturbations of normal biological processes due to exposure to a stressor (e.g., chemical) produce changes sufficient to lead to cell injury and subsequent events (modified from NRC, 2007).

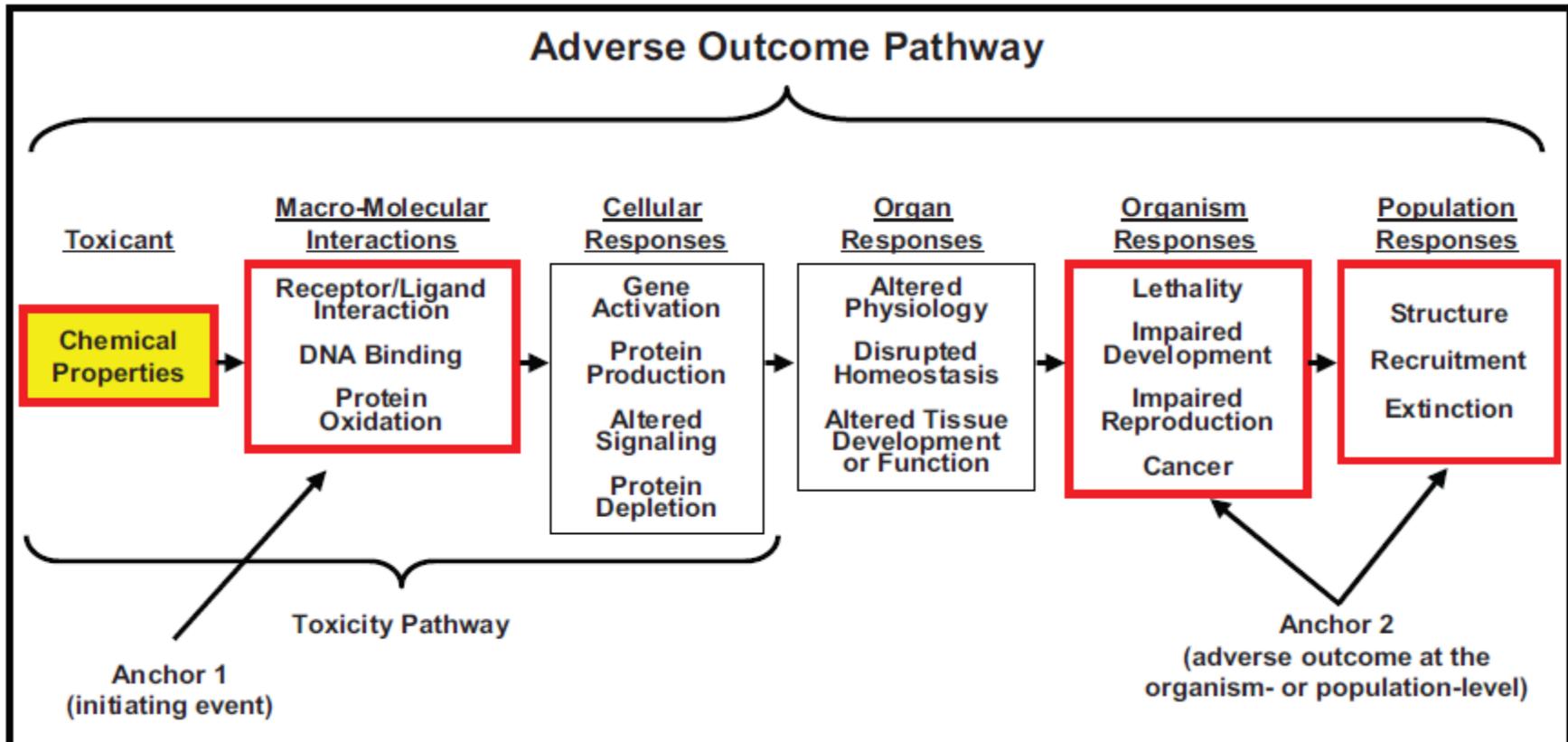
In Vivo Exposures/In Vitro Assays



Key role of circulating factors

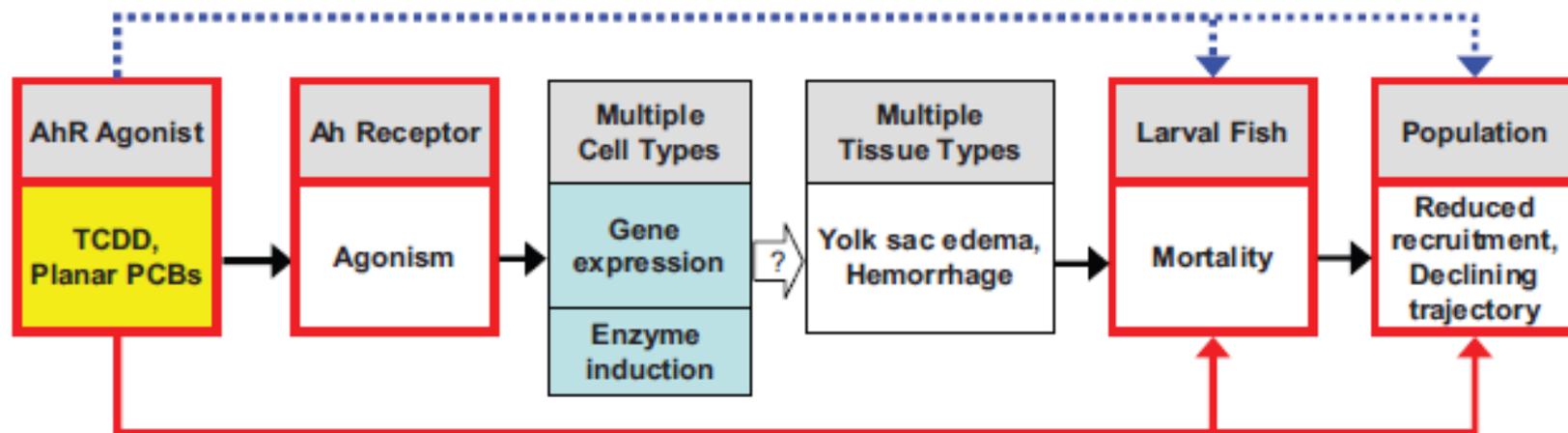
Channell et al., Tox Sci 127: 179, 2012

IL-8: Interleukin-8; sLOX: soluble lectin-like receptor for oxidized low density lipoprotein



Ankley, et al., Env Tox Chem 29: 730, 2010

C AOP: Aryl Hydrocarbon Receptor (AhR)



KEY

- Established mechanistic linkage with quantitative or semi-quantitative data
- Plausible linkage with limited data
- Empirical linkage based on quantitative exposure-response data
- Predictive model linkages based on chemical structure/property and quantitative exposure-response data
- ⊃? Hypothetical linkage
- Potential biomarker associated with exposure/response information

Ankley, et al., Env Tox Chem 29: 730, 2010

“The AOP framework also illustrates how effects caused by mixtures of chemicals that act via the same molecular initiating event...or affect pathways that converge at common intermediate steps ...can be aggregated for risk characterization.”

“AOPs do not, however, address the question of what dose of chemical will cause sufficient perturbation to drive the pathway to the adverse outcome.”

Ankley, et al., Env Tox Chem 29: 730, 2010



Review

Conceptual model for assessing criteria air pollutants in a multipollutant context: A modified adverse outcome pathway approach



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ABSTRACT

Air pollution consists of a complex mixture of particulate and gaseous components. Individual criteria and other hazardous air pollutants have been linked to adverse respiratory and cardiovascular health outcomes. However, assessing risk of air pollutant mixtures is difficult since components are present in different combinations and concentrations in ambient air. Recent mechanistic studies have limited utility because of the inability to link measured changes to adverse outcomes that are relevant to risk assessment. New approaches are needed to address this challenge. The purpose of this manuscript is to describe a conceptual model, based on the adverse outcome pathway approach, which connects initiating events at the cellular and molecular level to population-wide impacts. This may facilitate hazard assessment of air pollution mixtures. In the case reports presented here, airway hyper-responsiveness and endothelial dysfunction are measurable endpoints that serve to integrate the effects of individual criteria air pollutants found in inhaled mixtures. This approach incorporates information from experimental and observational studies into a sequential series of higher order effects.

The proposed model has the potential to facilitate multipollutant risk assessment by providing a framework that can be used to converge the effects of air pollutants in light of common underlying mechanisms. This approach may provide a ready-to-use tool to facilitate evaluation of health effects resulting from exposure to air pollution mixtures.

Background

- Air pollution is a complex mixture of particulate and gaseous components.
- Conventional epidemiologic and toxicological approaches cannot evaluate all of the possible unique multipollutant mixtures.
- A large number of toxicological studies have been conducted for the purpose of elucidating underlying changes in genes, biomarkers, proteins, etc. in response to air pollutants.
- The utility of toxicological findings is limited because of the inability to link such changes to an adverse outcome that is relevant to risk assessment.
- This type of mechanistic data may be most informative for risk assessment when translated into measurable changes including organ responses, clinical consequences, and impacts to the population at large.

Goals

- Develop a conceptual model for air pollution mixtures that links initiating events at the cellular and molecular level to population-wide impacts
- Identify measurable endpoints which serve to integrate the effects of individual criteria air pollutants found in inhaled mixtures
 - **Airway hyperresponsiveness - a key feature of asthma (Case Report 1)**
 - **Endothelial dysfunction - a risk factor for cardiovascular (CV) disease (Case Report 2)**
 - **Physiological changes at the organ level which can be measured in the clinic/laboratory**
- Incorporate information from experimental and observational studies into a sequence of steps occurring over multiple levels of biological organization

Case Report 1:

Irritant gases, airway responsiveness, and respiratory morbidity

Irritant gases = O₃, NO₂, and SO₂

Airway responsiveness reflects the sensitivity of airway smooth muscle to natural or pharmacological stimuli.

Epidemiologic Studies

- **Short-term exposures and associations with:**
 - Respiratory symptoms
 - Asthma medication use
 - Respiratory-related emergency department (ED) visits
 - Hospital admissions (HA) including those for asthma
- **Long-term exposures and associations with:**
 - Respiratory symptoms
 - Bronchitis
 - Asthma
 - New onset asthma
- **Potential co-pollutant confounding for both short- and long-term studies but more evidence for independent effects in short-term studies**

Case Report 1

Controlled Human Exposure Studies

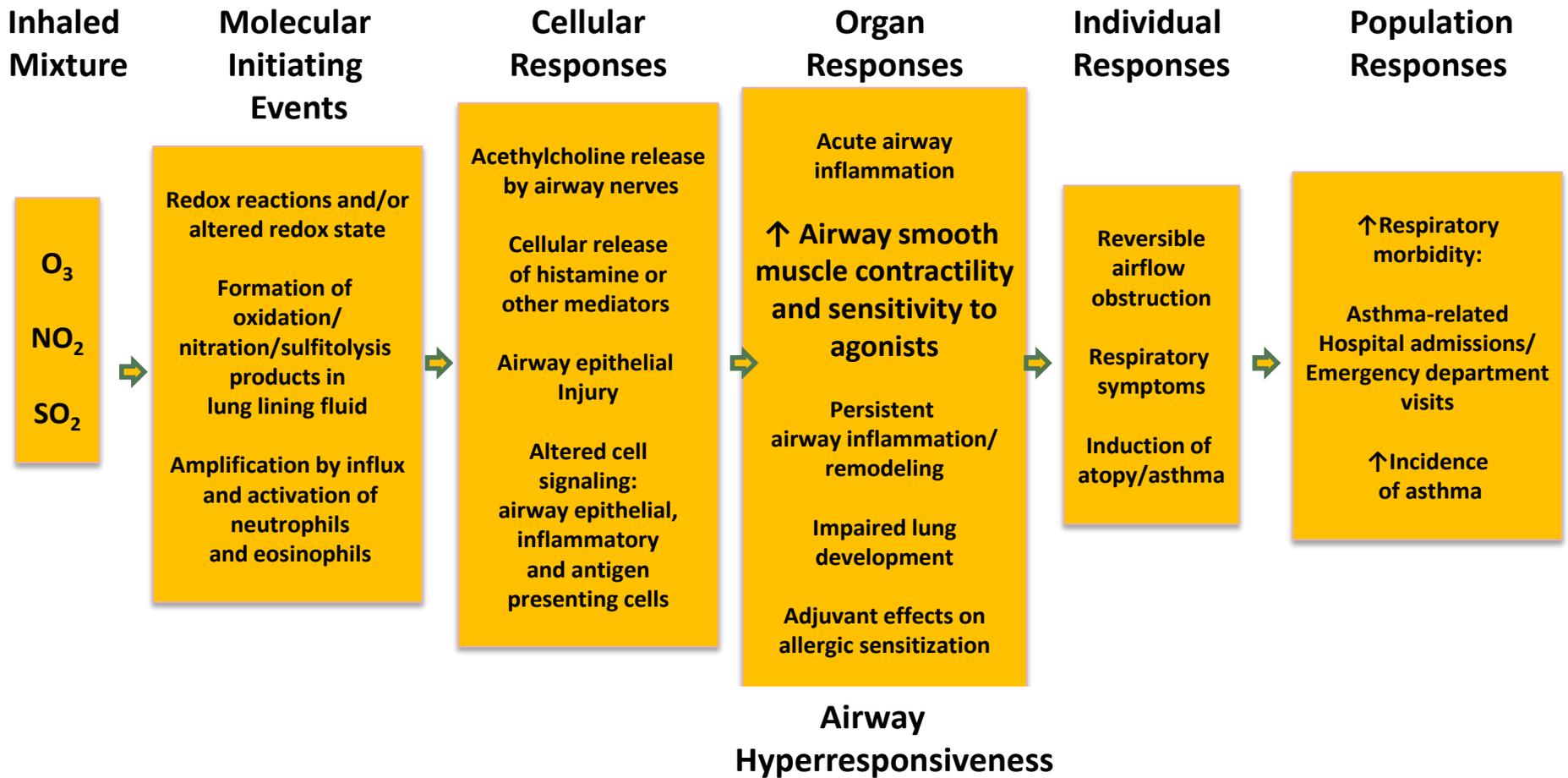
- **Formation of secondary oxidation products in the lung lining fluid**
- **↑ immune responses in healthy individuals**
 - Neutrophil influx in airways
 - Th2 polarization (repeated exposures)
 - Altered cell surface molecules on monocytes that are characteristic of innate immunity and antigen presentation
- **↑ immune responses in allergic asthmatics**
 - Eosinophils, ECP in lung lining fluid
 - Pro-allergic cytokines
 - Activation of the TLR4 pathway
- **Physiologic changes in airway smooth muscle (healthy and asthmatics)**
 - ↑ airway resistance due to acetylcholine release by airway nerves and to inflammatory mediators
- **↑ Inherent reactivity of airway smooth muscle (healthy and asthmatics)**
 - Airway hyperresponsiveness following a direct or allergen challenge

Th2: T helper cell 2 ; ECP: eosinophil cationic protein; TLR4: Toll receptor 4

Case Report 1

Toxicological Studies

- **Formation of secondary oxidation products in the lung lining fluid**
- **↑ immune responses**
 - Allergic sensitization in naïve animals
 - Activation of the TLR4 pathway
 - Dendritic cell maturation
 - Polarization to Th2 and Th17 phenotype
 - Enhanced allergic responses in allergen-sensitized animals
- **Physiologic changes in airway smooth muscle**
 - ↑airway resistance due to neural reflexes involving vagus nerve
- **↑Inherent reactivity of airway smooth muscle**
 - Hyperreactivity of vagal nerves due to inflammatory mediators
 - Stimulation of local axon reflexes with release of tachykinins
 - Mast cell degranulation
 - Airway remodeling
 - Disruption of the epithelial-mesenchymal unit during lung development



- This simplified AOP illustrates a sequential series of higher order effects linking exposure to NO_2 , O_3 , and SO_2 to an adverse outcome with relevance to risk assessment.
- Airway hyperresponsiveness is a measurable endpoint which can serve to integrate the upstream effects of O_3 , NO_2 and/or SO_2 in the respiratory tract.

HA: hospital admissions; ED: emergency department

Case Report 2

PM and O₃, endothelial dysfunction, and CV disease

Endothelial dysfunction is defined as impaired blood vessel response to specific vasodilators. It can occur in conduit arteries and microvascular resistance vessels.

Epidemiologic Studies

- **Short-term exposures to PM and associations with:**
 - CV morbidity/mortality
 - Myocardial infarction (MI)
 - Endothelial dysfunction
- **Long-term exposures to PM and associations with:**
 - CV morbidity/mortality
 - Atherosclerosis
 - Endothelial dysfunction
- **Short-term exposures to O₃ and associations with:**
 - Clinical CV events related to coronary artery disease, MI, atherosclerosis

Case Report 2

Controlled Human Exposure Studies

- **PM:** Endothelial dysfunction in healthy subjects and subjects with CV disease
- **O₃:** No endothelial dysfunction in healthy subjects

Toxicological Studies

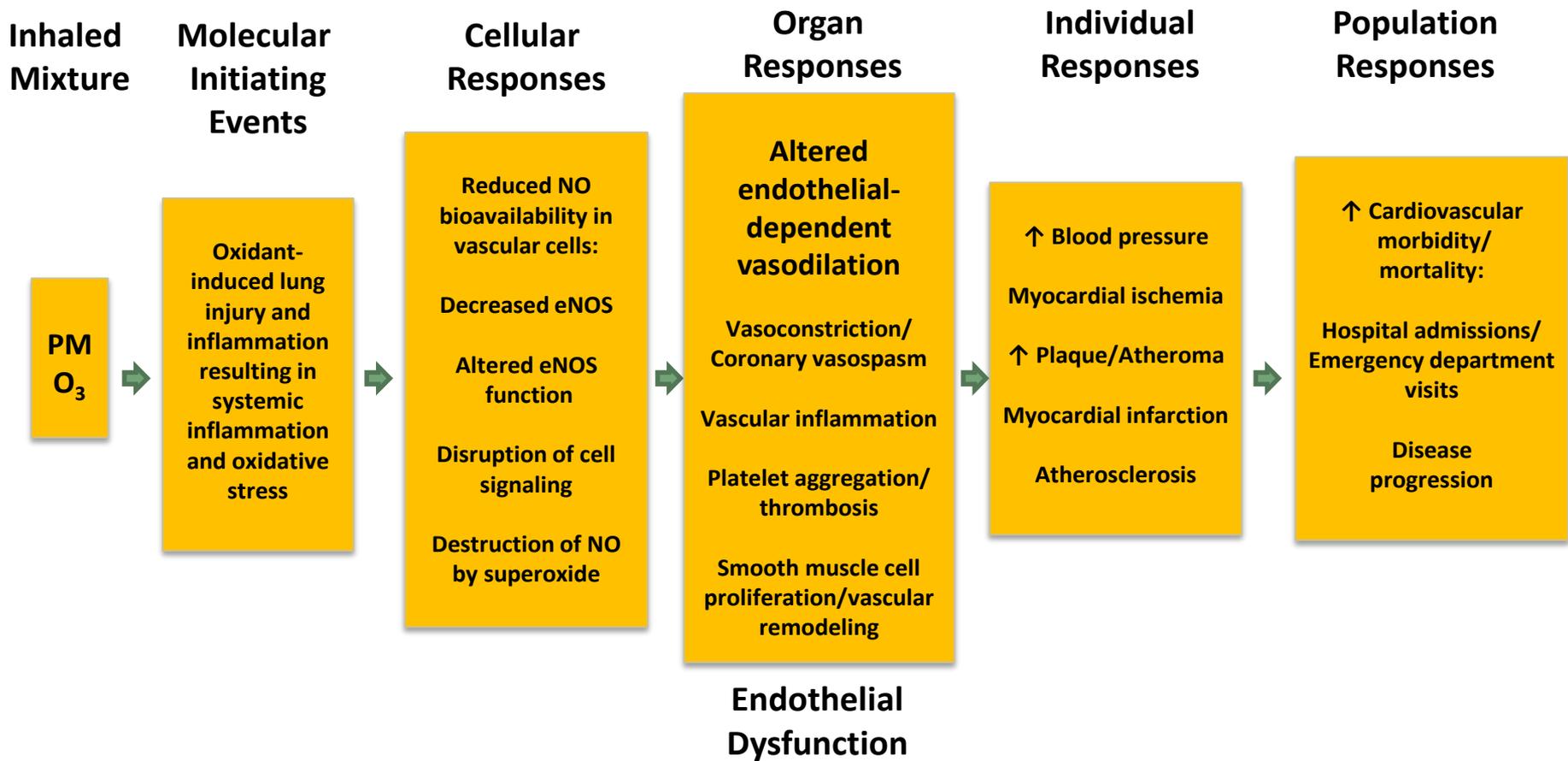
- **PM and O₃:** Endothelial dysfunction

How does PM or O₃ inhalation lead to systemic effects?

- Evidence suggests that pulmonary inflammation/oxidative stress mediates systemic inflammation/oxidative stress

What is the mechanism underlying endothelial dysfunction?

- It is likely due to decreased nitric oxide bioavailability which can occur via several mechanisms



- This simplified AOP illustrates a sequential series of higher order effects linking exposure to PM and O₃ to an adverse outcome with relevance to risk assessment.
- Cellular responses refer to responses in all vascular cell types.
- Endothelial-dependent vasodilation is a measurable indicator of endothelial dysfunction which can serve to integrate the upstream effects of PM and O₃ in the vasculature.

Relevancy

The proposed model has the potential to facilitate multipollutant risk assessment by:

- Providing a framework that can be used to converge the effects of air pollutants based on common underlying mechanisms
- Identifying data gaps
- Enabling prioritization of targeted research in the most efficient and cost-effective manner possible
- Allowing the incorporation of biomarker data that is predictive of clinically significant outcomes

Limitations

- Population effects may be mediated by alternative mechanisms than the ones identified
- Model does not account for adaptation and repair
- Model does not address dose-response considerations
- Toxicokinetic and toxicodynamics data have not been incorporated

“Dosimetry links exposure and response”

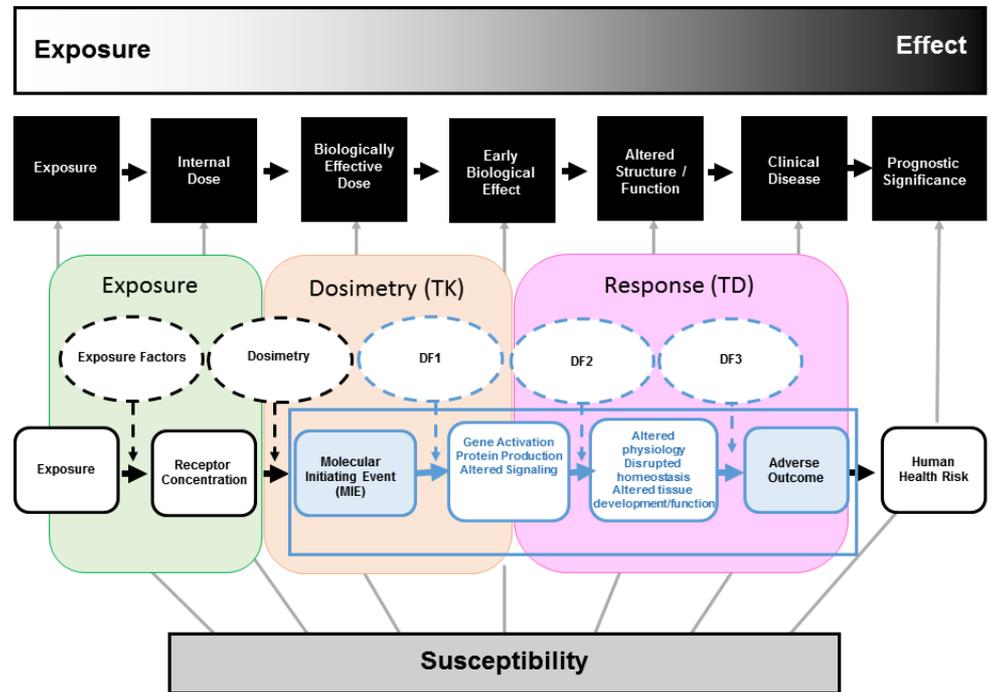
Annie Jarabek

What a Difference the Dose Makes

Webinar Series

April 28, 2016

- **Need to define different dose metrics in order to apply key events of adverse outcome pathways (AOP) and mode of action (MOA) in risk assessment**
 - Screening dosimetry insufficient for quantitative response analysis
 - Portal-of-entry descriptions
 - Broad context re: both endpoints and chemical classes
- **Support transparency, causal linkage and interoperability along continuum: exposure to dose-response analysis**



Source: US EPA Human Health Risk Assessment (HHRA) FY16-19 Strategic Research Action Plan

<https://www.epa.gov/research/strategic-research-action-plans-2016-2019>

Impact

- This approach facilitates the evaluation of health effects resulting from exposure to air pollution mixtures.
- Evidence from epidemiologic, controlled human exposure and toxicological studies of single criteria pollutants can be utilized to develop AOPs for mixtures of these pollutants.
- AOPs may be simplified, as illustrated here, or more detailed, including multiple effects occurring in multiple compartments at each level of biological organization.
- They may be used to indicate the certainty of mechanistic linkages between steps and to portray potential biomarkers of exposure or effect.
- AOPs may allow the incorporation of toxicodynamic, toxicokinetic data into a conceptual model.
- This may lead to the quantitation of exposure-response relationships for multipollutant mixtures.

Future Direction

The outputs from this project are helping to advance EPA's science assessments, moving us one step closer to explicit consideration of multipollutant evidence in reviews of the NAAQS.

