

NTP Evaluation Concept

Inflammation-based Atherosclerosis Associated with Environmental Exposures

Andrew Rooney, PhD

Office of Health Assessment and Translation
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
June 17 - 18, 2014



Outline

- Background and Rationale
 - Inflammation
 - Relevance to environmental health
 - Focus on a single inflammation-based health effect - atherosclerosis
- Key Issues
- Specific Aims
- Proposed Approach
 - OHAT literature-based evaluation
 - Adverse outcome pathway
- Significance
- Questions

NIEHS Strategic Plan

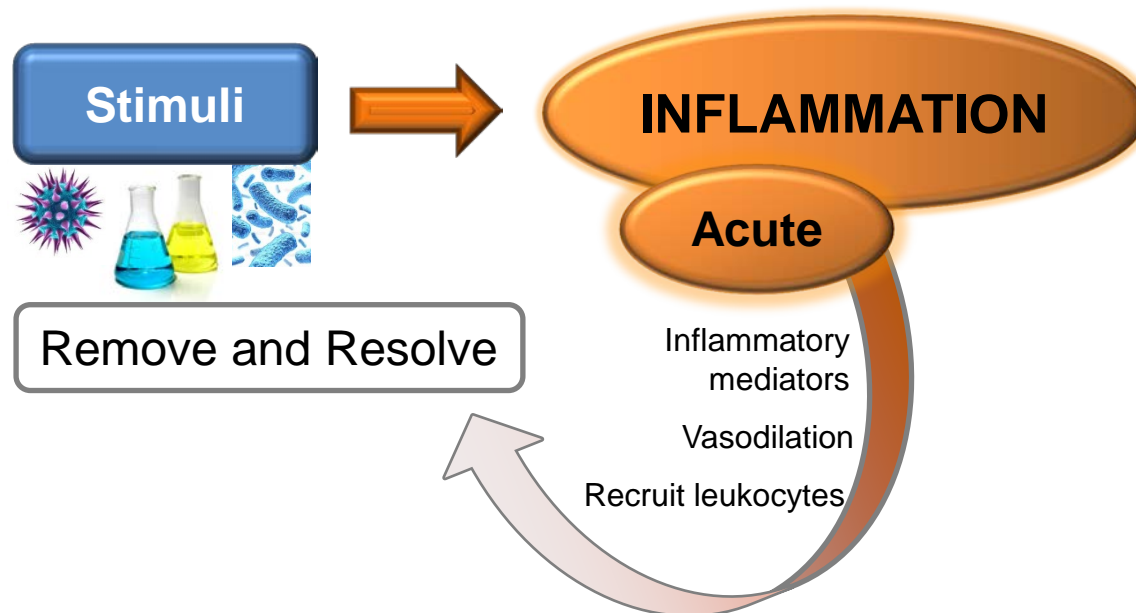
Goal 1: Inflammation as a Fundamental Mechanism

- Identify and understand fundamental shared mechanisms or common biological pathways, e.g., inflammation ... underlying a broad range of complex diseases, in order to enable the development of applicable prevention and intervention strategies
 - Understand key biological mechanisms in determining susceptibility to environmental stressors
 - Integrate high-throughput screening, cell systems, and model organisms, to identify fundamental mechanisms underlying responses to environmental toxicants
- Cross-Divisional Implementation Planning Committee on Inflammation
 - Need for review of the evidence that environmental exposure → inflammation → adverse health effects
 - Critical need for reliable biomarkers of inflammation



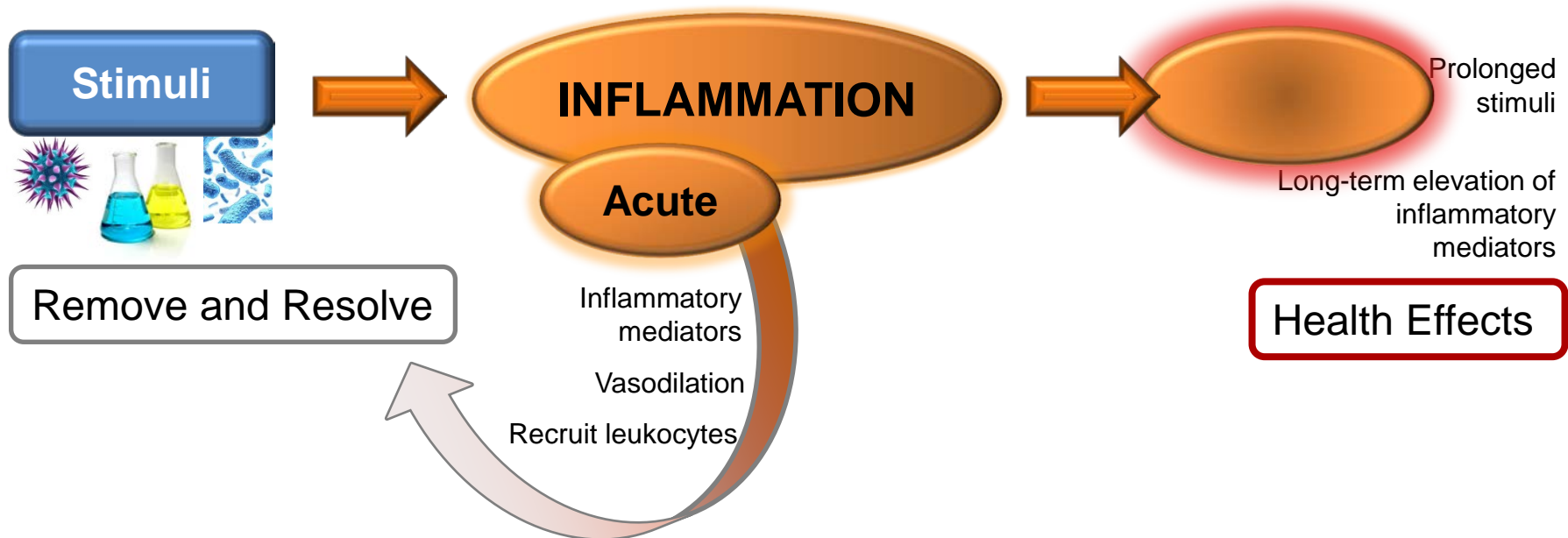
Background: Inflammation

- Localized protective reaction to stimuli (infection, physical or chemical injury) characterized by redness, swelling, fever
 - **Acute:** cellular response that is generally part of a healthy process



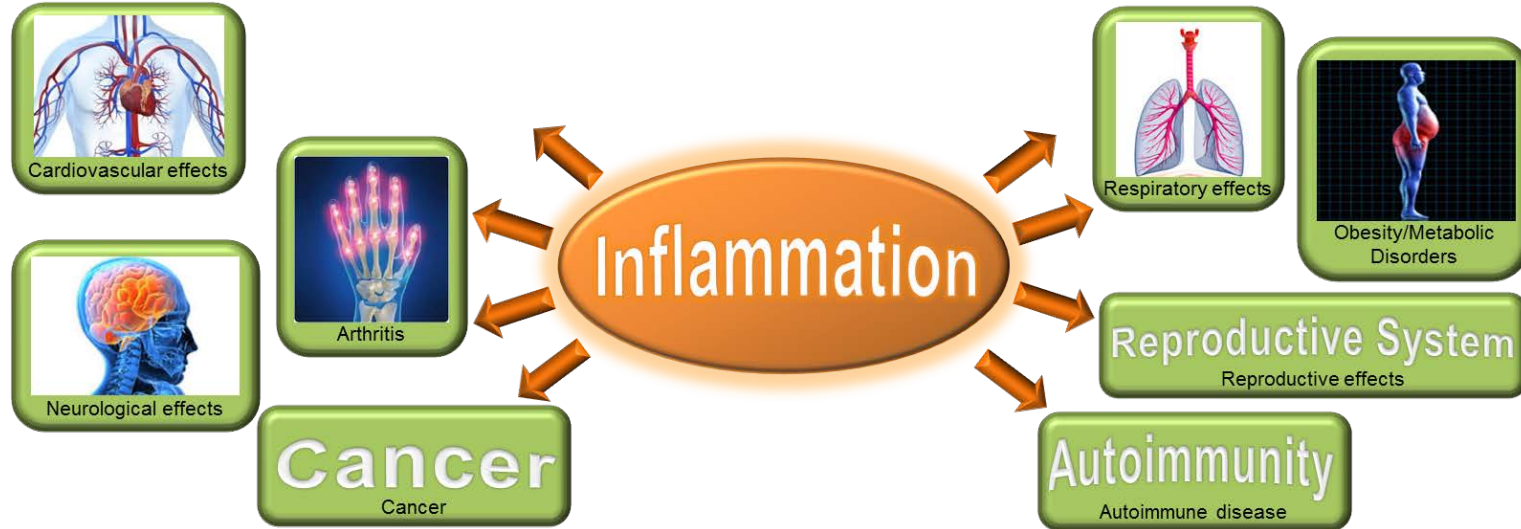
Background: Inflammation

- Localized protective reaction to stimuli (infection, physical or chemical injury) characterized by redness, swelling, fever
 - **Acute:** cellular response that is generally part of a healthy process
 - **Chronic:** may contribute to adverse health outcomes



Inflammation and Environmental Health

- Chronic inflammation contributes to multiple health effects

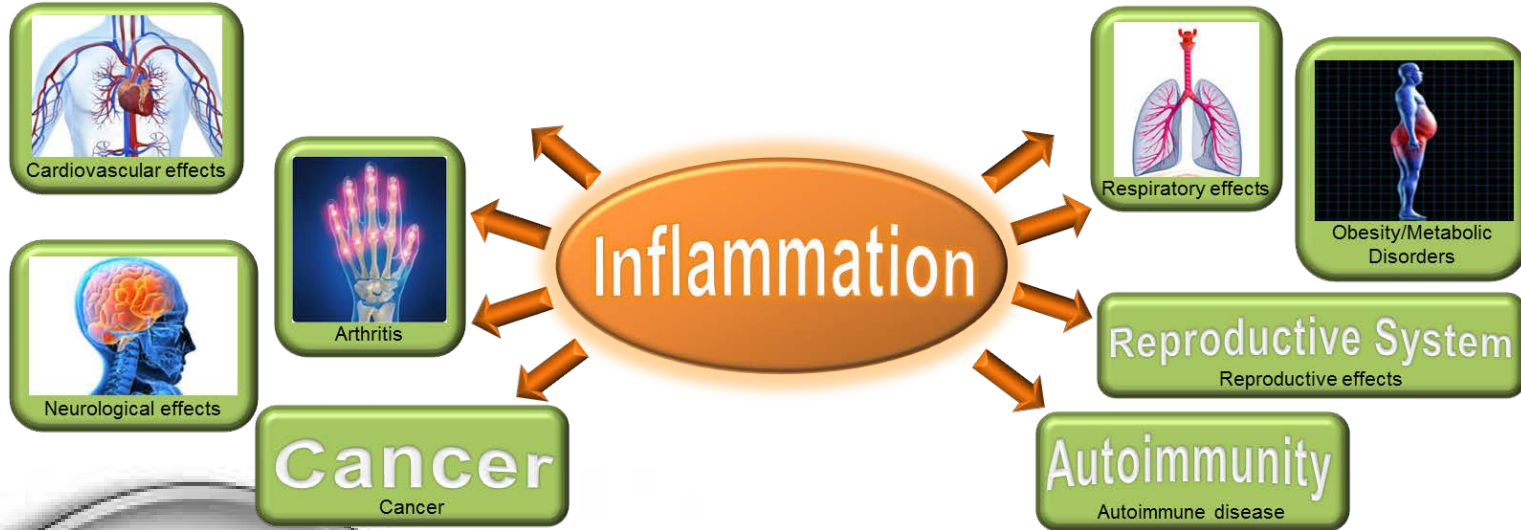


- Growing evidence of link to environmental exposures
- However, the extent to which environmental exposures ultimately lead to health effects through an inflammatory pathway remains unclear



Inflammation and Environmental Health

- Chronic inflammation contributes to multiple health effects



- Growing evidence of link to environmental exposures
- However, the extent to which environmental exposures ultimately lead to health effects through an inflammatory pathway remains unclear



Proposed Focus

- Restricting evaluation to a single health effect
 - Facilitate direct comparison of supporting or opposing evidence
 - Aid identification of specific indicators or markers of inflammation
 - Select health effect with manageable database

Scoping-level literature search using just MeSH terms

Health Effects Categories	Rough Number of References	Inflammation and Effect	Effect and Exposure
Inflammation	966,000+		197,000+
Cardiovascular	2,665,000+	165,000+	415,000+
Vascular diseases	1,314,000+	68,400+	212,000+
Atherosclerosis	21,300+	4,550+	3,450+

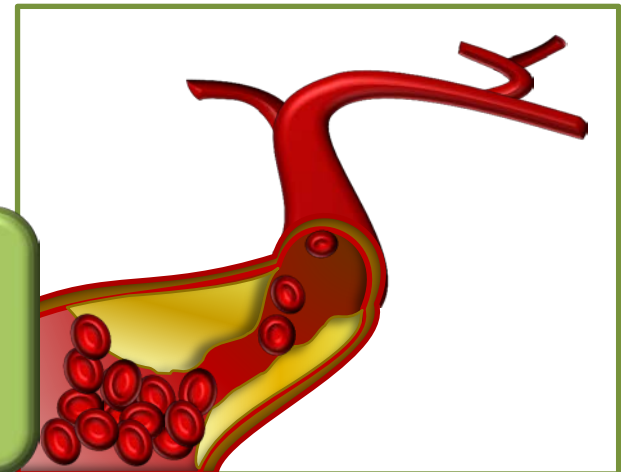
Searches may double, triple, or more from this scoping vs. more comprehensive text word searches

Proposed Focus

- Restricting evaluation to a single health effect
 - Facilitate direct comparison of supporting or opposing evidence
 - Aid identification of specific indicators or markers of inflammation
 - Select health effect with manageable database
- **Atherosclerosis**
 - Clear inflammatory mechanism
 - Associated with range of environmental agents
 - Significant public health impact
 - Underlying condition for ischemia, stroke, cardiovascular disease

Atherosclerosis

- plaques build up on artery walls
- leads to restricted blood flow



Key Issues

- 1) Selecting inflammatory markers associated with atherosclerosis
- 2) Addressing the extent to which conclusions can be integrated across environmental agents



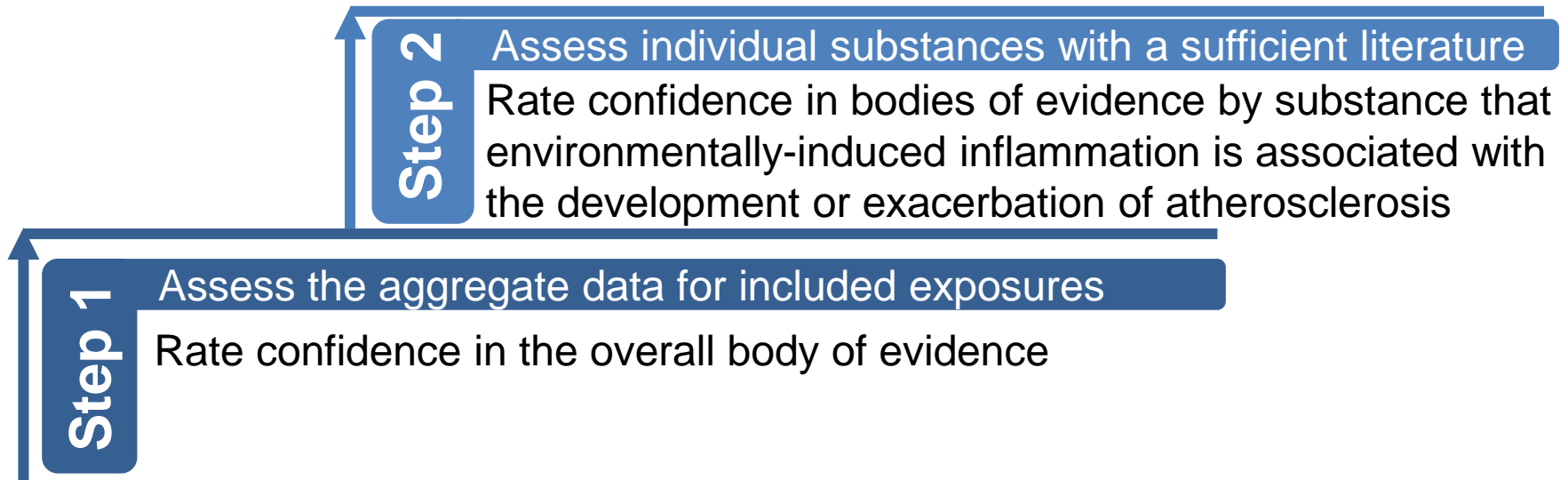
Specific Aims

- The overall objective is to evaluate the evidence that environmental substances contribute to inflammation that leads to atherosclerosis
 - To the extent possible, if data support the analyses, this would include:
 - Rating confidence in the body of evidence
 - Hazard identification and level-of-concern conclusions for specific substances
- An additional objective is to evaluate the evidence for specific biomarkers of environmentally-induced inflammation linked to atherosclerosis

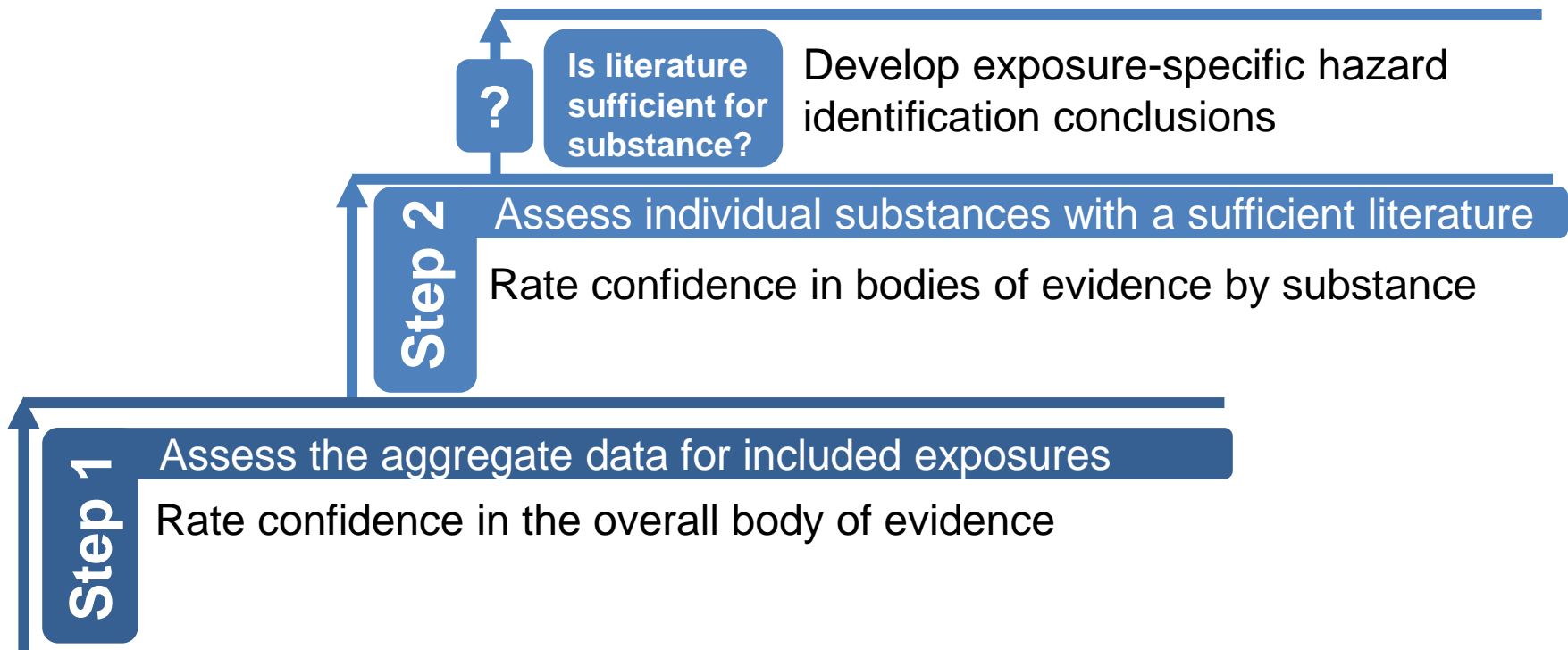
Proposed Approach: Complementary Methods for the Evaluation

- Literature-based evaluation
 - OHAT Approach to systematic review and evidence integration
 - Evaluate the evidence that environmental substances:
 - Are associated with inflammatory markers linked to atherosclerosis
 - Are associated with atherosclerosis
 - Contribute to inflammation that leads to atherosclerosis
 - Challenge to use systematic review methods to evaluate a pathway
- Adverse outcome pathway (AOP)
 - Develop an AOP for environmental influences on inflammation-based atherosclerosis
 - Examine the inflammatory pathway
 - Evaluate the evidence for specific biomarkers of environmentally-induced inflammation linked to atherosclerosis

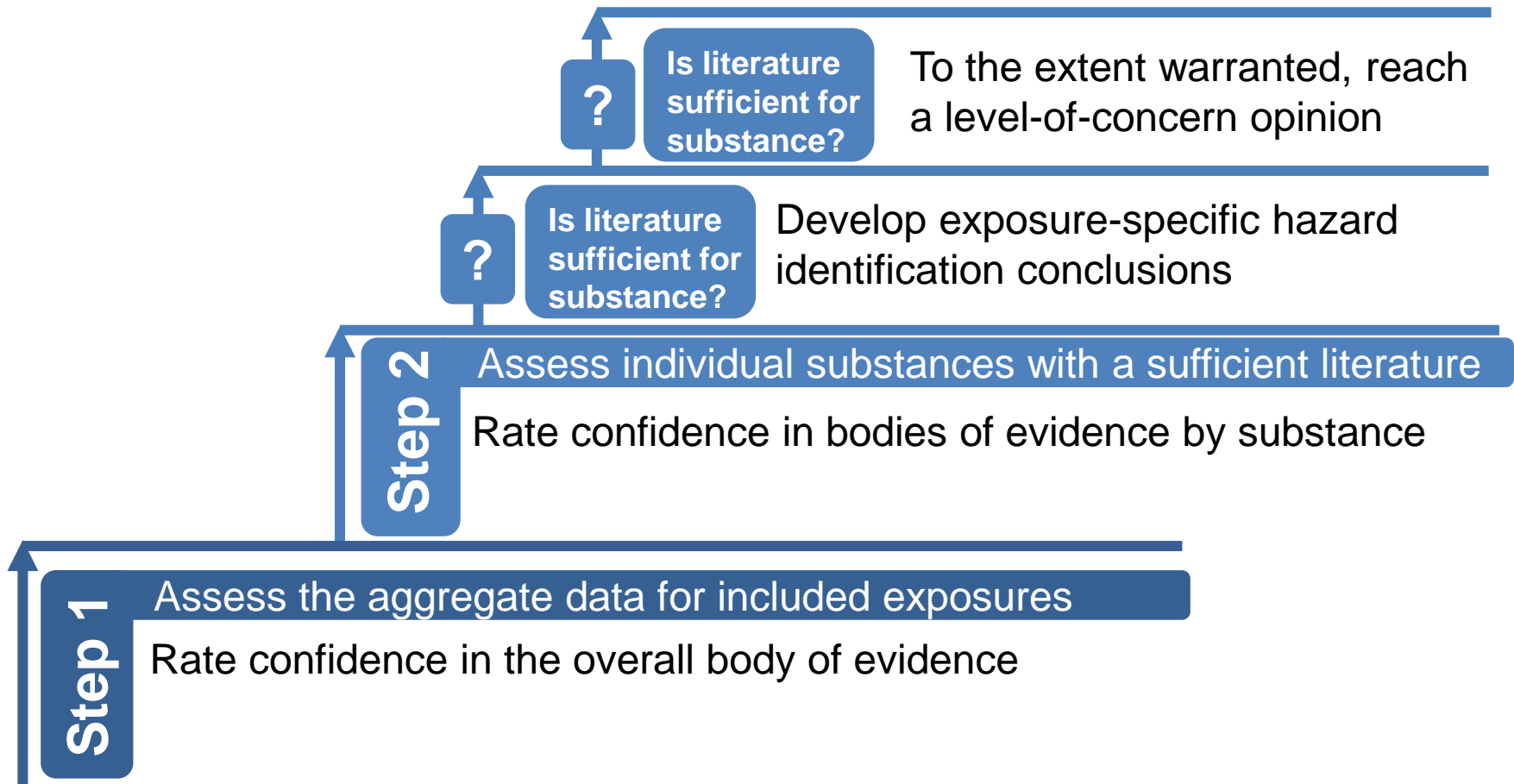
Proposed Approach: Literature-based Evaluation Conclusions Developed Stepwise



Proposed Approach: Literature-based Evaluation Conclusions Developed Stepwise



Proposed Approach: Literature-based Evaluation Conclusions Developed Stepwise



Key Questions for the Literature-based Evaluation

- Key Questions (KQ):

- What is our confidence in the body of evidence for the association between exposure to environmental substances and inflammation that may contribute to development or exacerbation of atherosclerosis?

- KQ #1: human studies

- KQ #2: animal studies

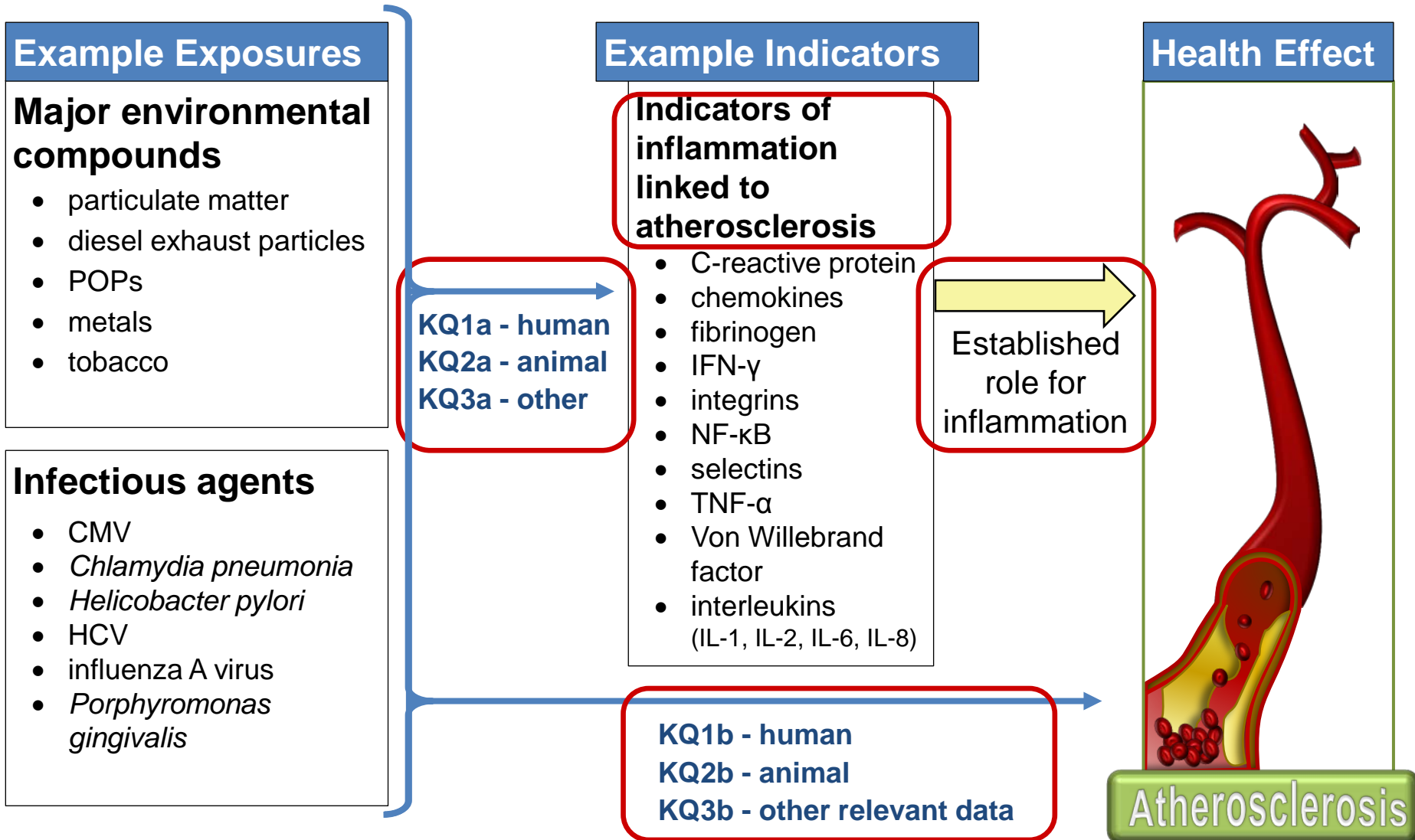


- KQ #3: other relevant data

How does the evidence from other relevant data (e.g., mechanistic or *in vitro* studies) support or refute the biological plausibility of the association between exposure to environmental substances and inflammation that may contribute to development or exacerbation of atherosclerosis?



Analytical Framework



Examine support for temporal sequence (i.e., exposure \rightarrow inflammation \rightarrow atherosclerosis)

Proposed Approach: Development of an AOP

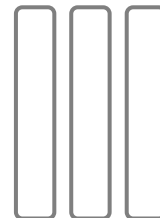
- Use a pathway approach to address a health effect question in which the pathway is central to the evaluation
- The AOP will describe and evaluate the
 - Pathway of events from exposure to atherosclerosis
 - Evidence for each relationship between sequential events
- Evaluate evidence for specific biomarkers or groups of biomarkers
 - Focus on early events
 - Are there good biomarkers?
Evaluate evidence that specific indicators of environmentally-induced inflammation are linked to atherosclerosis

Adverse Outcome Pathway

Molecular
initiating event



Intermediate events or
predictive relationships
spanning levels of
biological organization



Adverse outcome
relevant to
assessment

Simplified Illustration of Features of an AOP

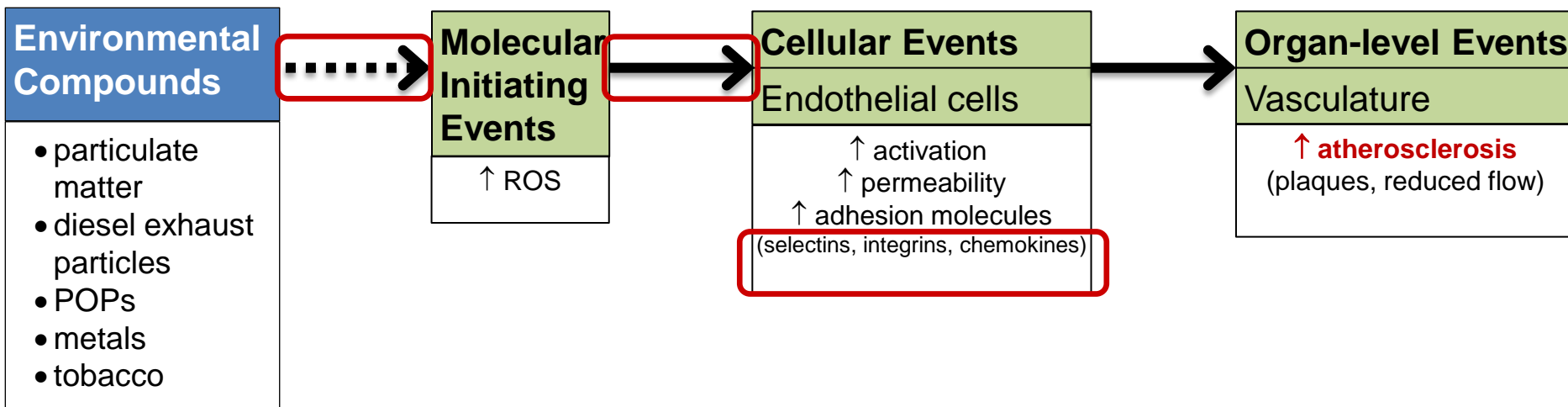
- Evaluation and clear documentation of the extent of the evidence linking sequential events

- Example descriptors of the extent of the evidence

.....➔ Plausible linkage with limited data

➔ Established linkage with quantitative data

- Biomarkers are likely to come from early events such as proteins released as part of cellular events



Proposed Approach: Mechanisms to Further Develop and Refine the Evaluation

- Continue problem formulation
 - Develop and refine list of indicators (potential biomarkers) of inflammation linked to atherosclerosis
 - Refine list of endpoints that indicate atherosclerosis
 - Text mining tools to agnostically query the literature
 - Consult technical advisors with expertise on inflammation on cardiovascular health effects
 - NIEHS Cross-divisional committee on inflammation
 - Evaluation design team
 - Additional direct from federal agencies with expertise on inflammation and cardiovascular effects (e.g., National Heart, Lung, and Blood Institute)
 - Post proposed search terms for public comment
 - Refined list of inflammatory indicators will form starting point for AOP

Significance

- Inform the selection of biomarkers in future studies of environmentally-induced inflammation
- Evaluate the utility of an AOP to as part of a dual approach for assessing a literature-based environmental health question
- Lessons learned in evaluating the role of environmentally-induced inflammation for atherosclerosis will inform the evaluation of inflammation on a wider range of health effects (e.g., cardiovascular effects in general)

Acknowledgements

- **Office of Health Assessment and Translation**

- Abee Boyles
- Kembra Howdeshell
- Andrew Rooney, Deputy Director
- Katie Pelch
- Kyla Taylor
- Kristina Thayer, Director
- Vickie Walker

- **Evaluation Design Team**

- Scott Auerbach (NIEHS/DNTP)
- Mike Devito (NIEHS/DNTP)
- June Dunnick (NIEHS/DNTP)
- Michel Fessler (NIEHS/DIR)
- Dori Germolec (NIEHS/DNTP)
- Jerry Heindel (NIEHS/DERT)
- Stephanie Holmgren (NIEHS/LISB)
- Michel Humble (NIEHS/DERT)
- Nicole Kleinstreuer (NIEHS contractor)
- Srikanth Nadadur (NIEHS/DERT)
- Fred Miller (NIEHS/DIR)
- Greg Travlos (NIEHS/DIR)
- Urmila Kodavanti (EPA/NHEERL)

- **Cross-divisional Implementation Planning Group on Inflammation**

Chair

- Janice Allen

Coordinators

- Caroline Dilworth
- Mike Humble
- Fred Miller
- Srikanth Nadadur
- Andrew Rooney

Charge

- To review and comment on the draft OHAT concept and determine whether the evaluation is an appropriate use of NTP resources.
- An evaluation concept is a brief document outlining the rationale, significance, approach, and expected outcome of a proposed evaluation.

Review Questions

- 1) Comment on the merit of the proposed evaluation relative to the mission and goals of the NTP. *The NTP's stated goals are to: Provide information on potentially hazardous substances to all stakeholders; Develop and validate improved testing methods; Strengthen the science base in toxicology; Coordinate toxicology testing programs across DHHS* (<http://ntp.niehs.nih.gov/go/test>).
- 2) Comment on the clarity and validity of the rationale for the proposed evaluation as articulated in the NTP evaluation concept document.
 - Has the scope of the problem been adequately defined?
 - Have the relevant scientific issues been identified and clearly articulated?
 - Are you aware of other scientific issues that need to be considered?
- 3) Comment on the proposed approach for further developing and refining the evaluation.
- 4) Rate the overall significance and public health impact of this evaluation as low, moderate, or high.
- 5) Provide any other comments you feel NTP staff should consider in developing this evaluation.