

Applying Adverse Outcome Pathways to evaluate the Health Impact of Environmental Chemicals

AUTUMN ITAPA 2024

November 25th – 28th, 2024

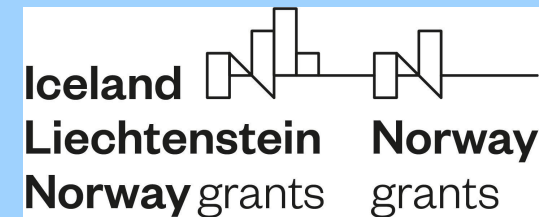
Crowne Plaza Bratislava

Presenter: Sivakumar Murugadoss PhD

Health Effects Laboratory

The Climate and Environmental Research Institute NILU

Norway



nilu

Overview

Environmental Chemicals and Health Effects

Challenges in Human Studies

Adverse Outcome Pathways (AOPs)

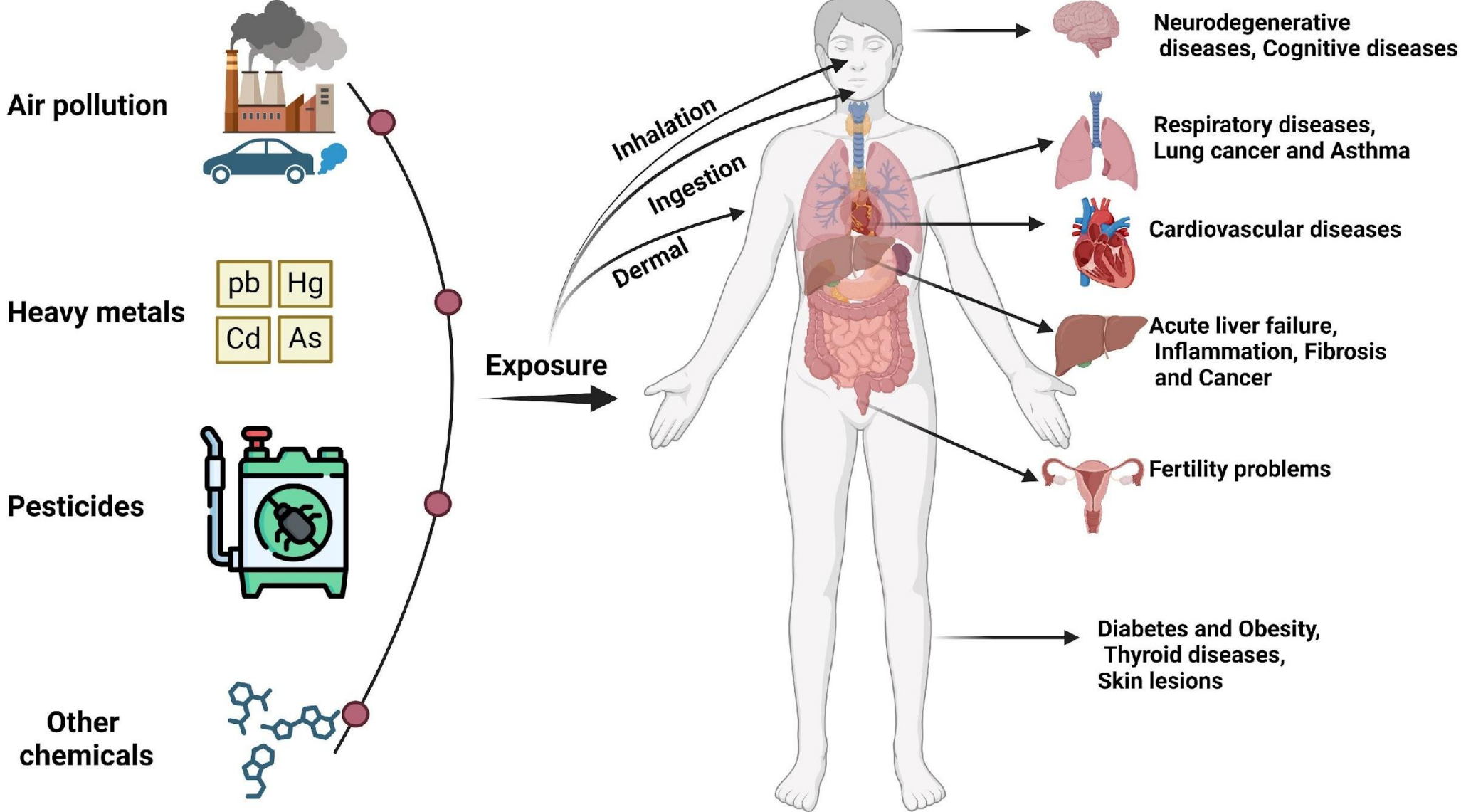
Integrated Approach

Case Studies

Challenges and Future Directions



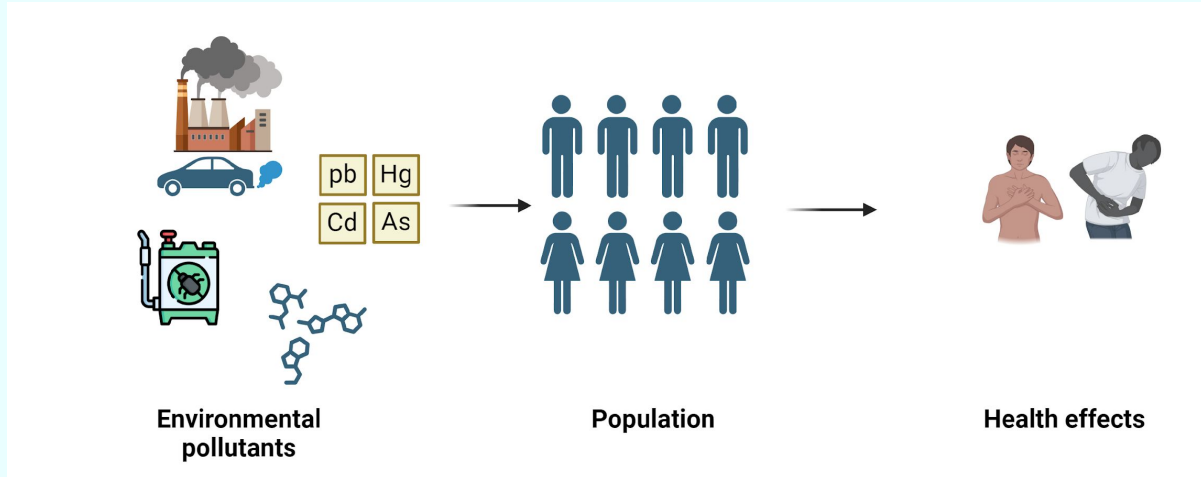
Environmental Chemicals and Health Effects



Modified from: Sharma, Amit Kumar, et al. "Mapping the impact of environmental pollutants on human health and environment: A systematic review and meta-analysis." *Journal of Geochemical Exploration* (2023): 107325.

Environmental Chemicals: Challenges in protection of Public Health

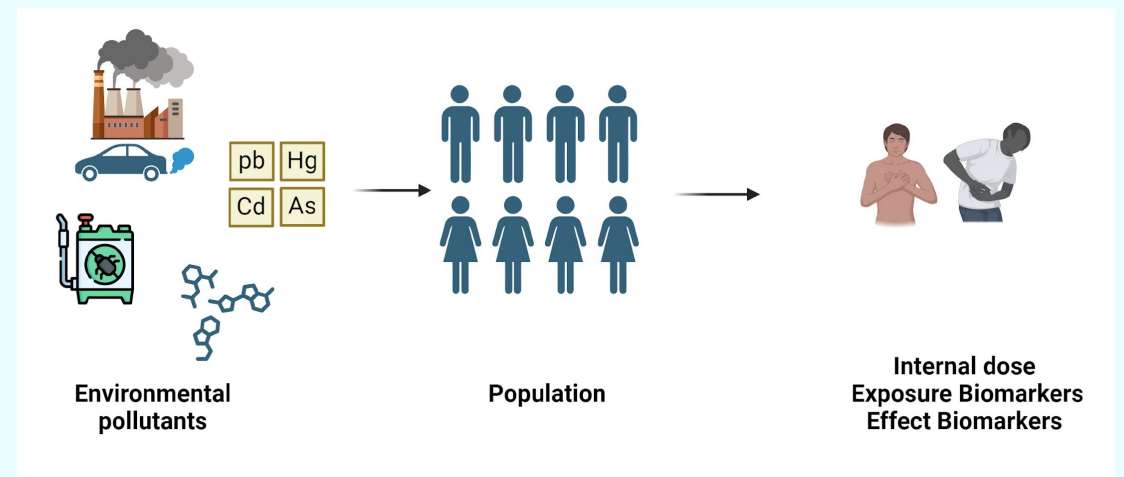
Epidemiological study



Limitations

- Low proof of causality

Human Biomonitoring

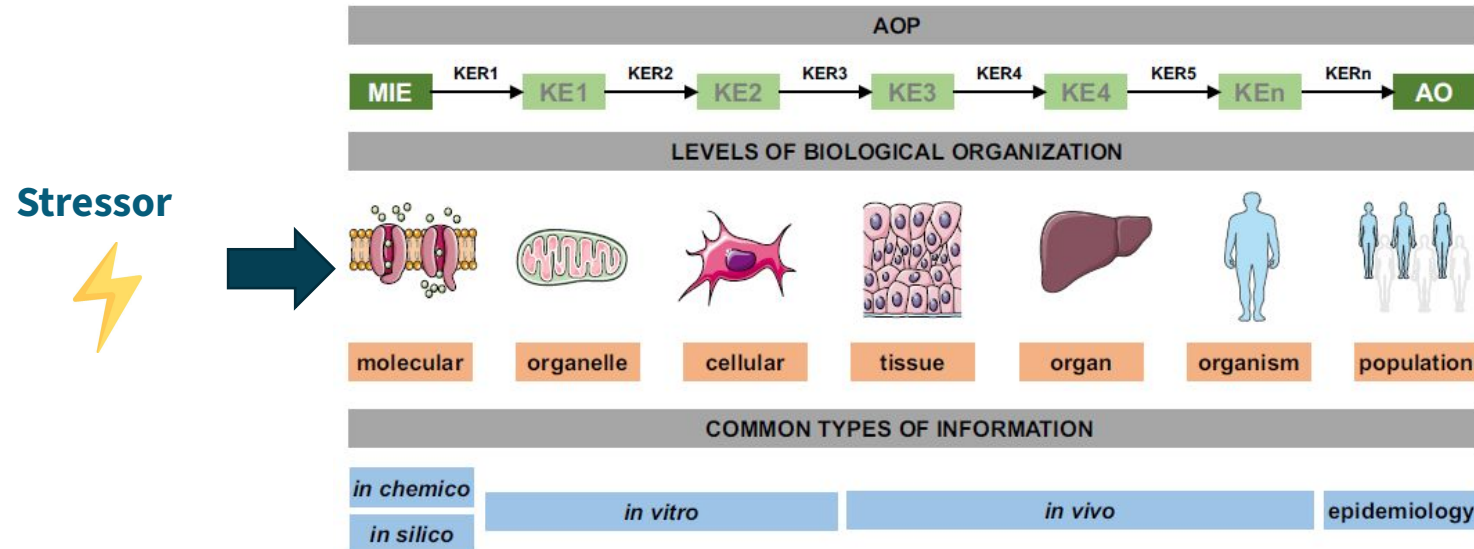


Limitations

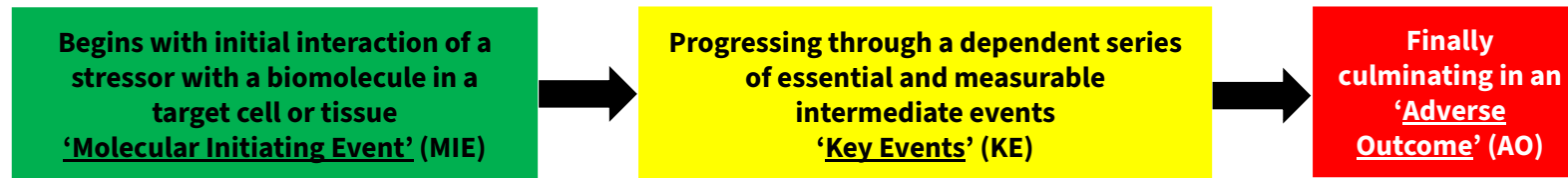
- Non-specific biomarkers
- Detection of changes at the later stage

Challenge in **protection of
Public Health**

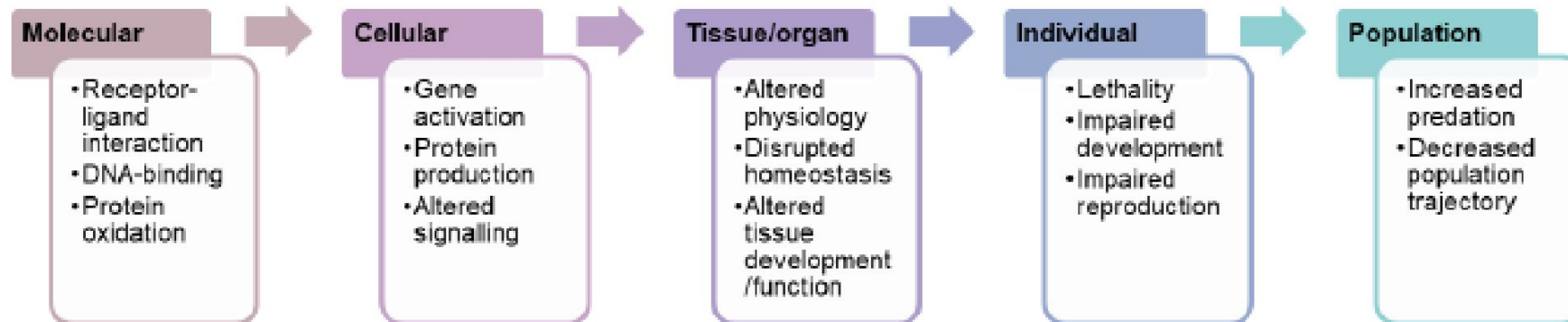
Introduction to AOPs



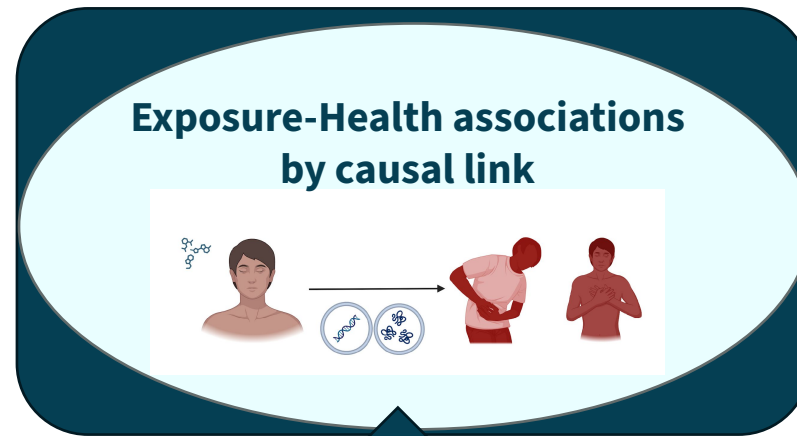
Stressor



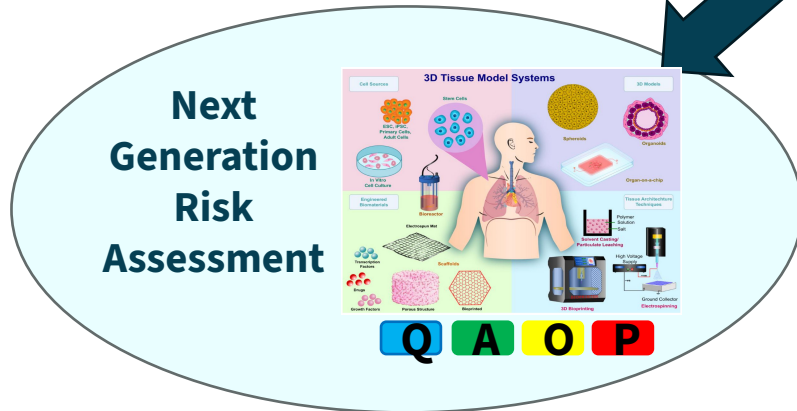
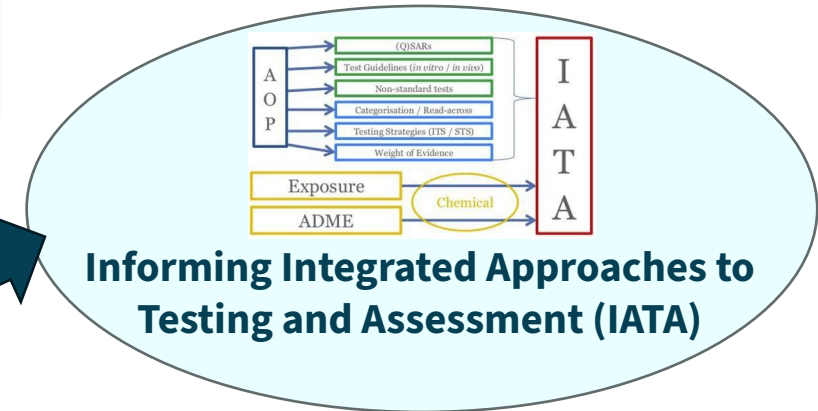
Linked together through **Key Event Relationships (KER)**



Application of AOPs

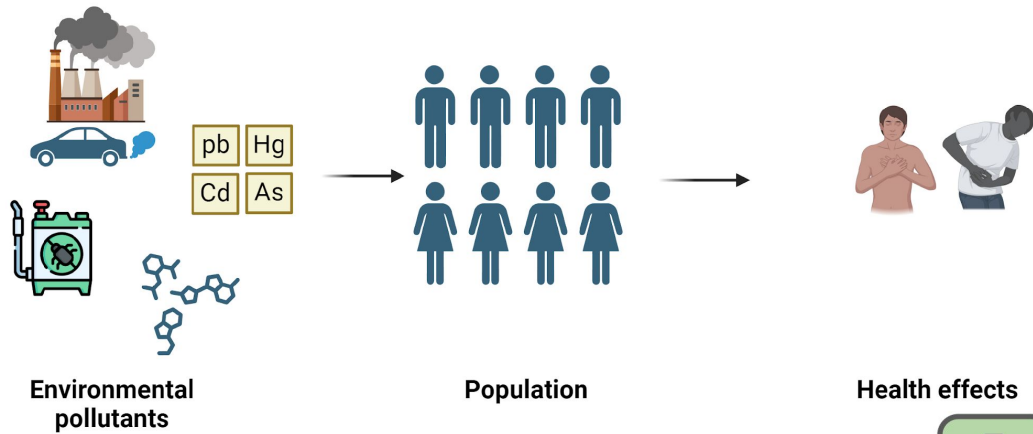


Today's focus

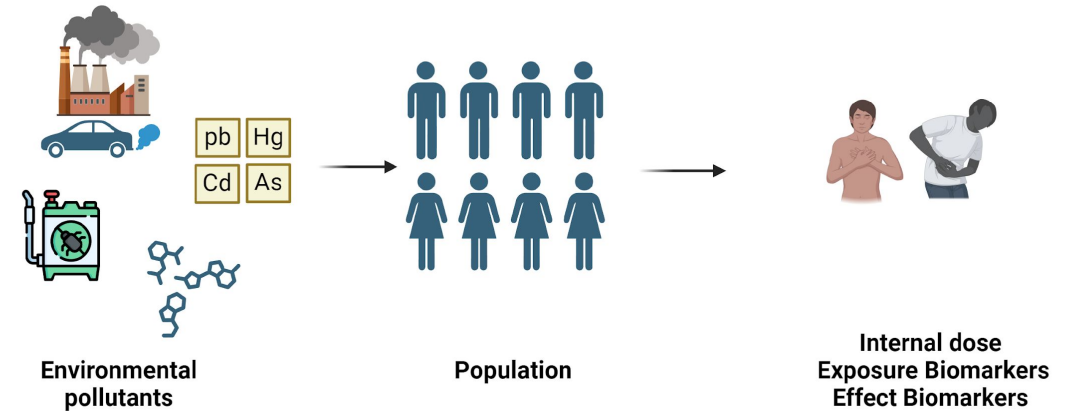


Protection of Public Health related to Environmental Chemicals: Integrated approach: AOP + Human studies

Epidemiological study



Human Biomonitoring



Impact

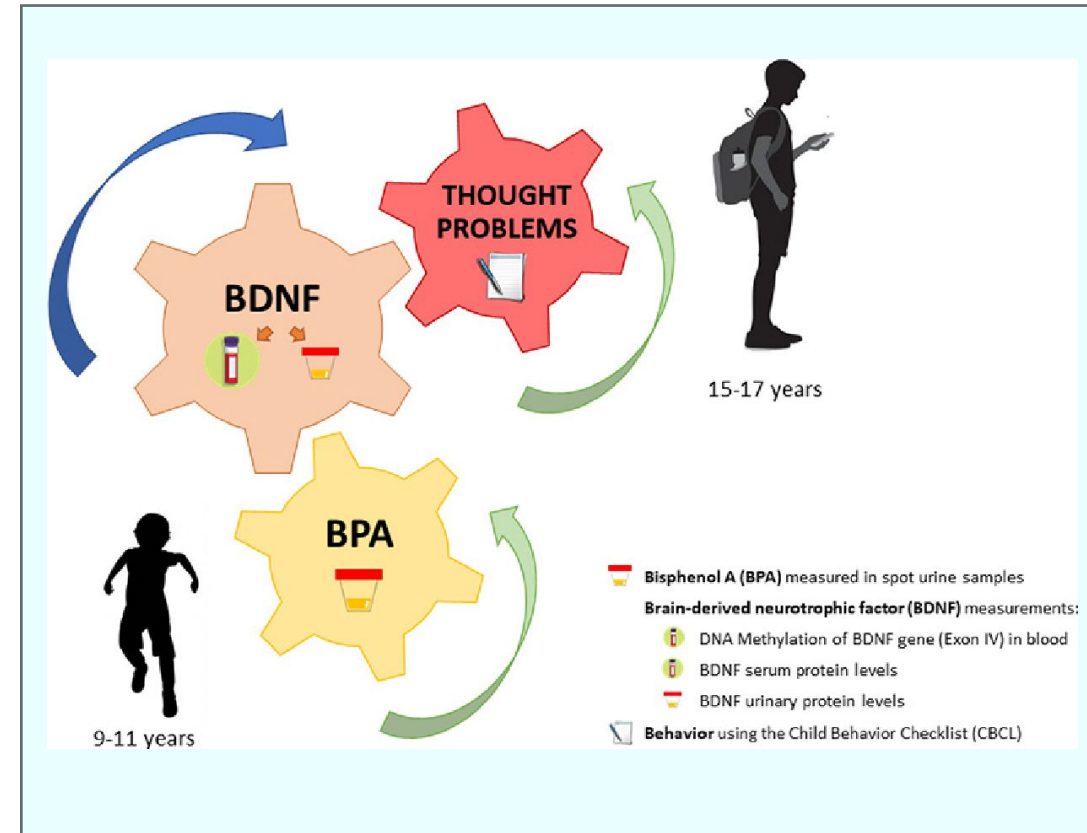
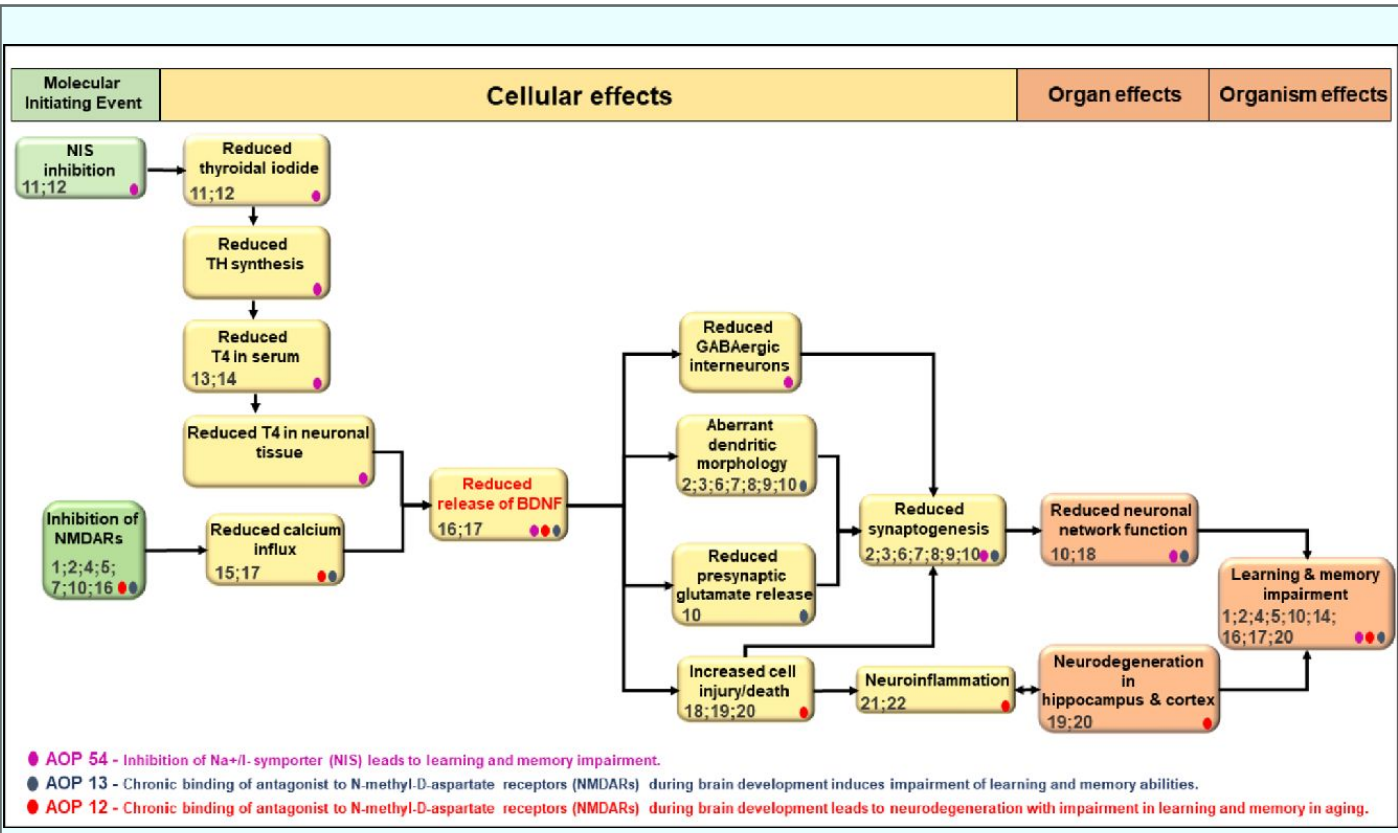
- Improved mechanistic understanding

Impact

- Early detection of molecular and cellular changes and threshold concentrations important for risk management

**Effective Public Health
Protection**

Case Study – Developmental Neurotoxicity

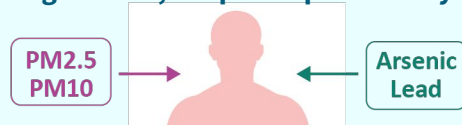


- In line with toxicological studies, **BPA exposure** was longitudinally **associated** with increased **BDNF DNA methylation**, supporting the biological plausibility of BPA-behavior relationships previously described in the epidemiological literature.
- Given its novelty and preliminary nature, this **effect biomarker** approach should be replicated in larger birth cohorts.
- **Epigenetic and gene expression changes related to BDNF – early detection of adverse effects**

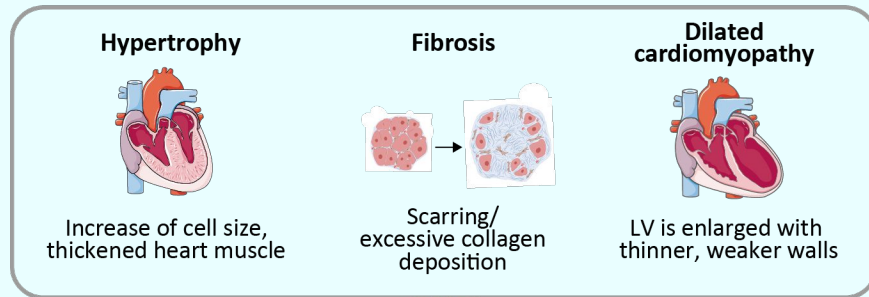
Case Study – Cardiotoxicity

Systematic review and meta-analysis of association between toxic environmental chemical exposure and early heart failure markers, focusing on left ventricular dysfunction (LVD)

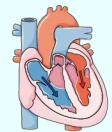
- 17 studies involving over 45,000 participants analyzed



Adaptive change in structure/
cardiac remodelling

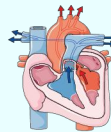


LV diastolic
function decrease



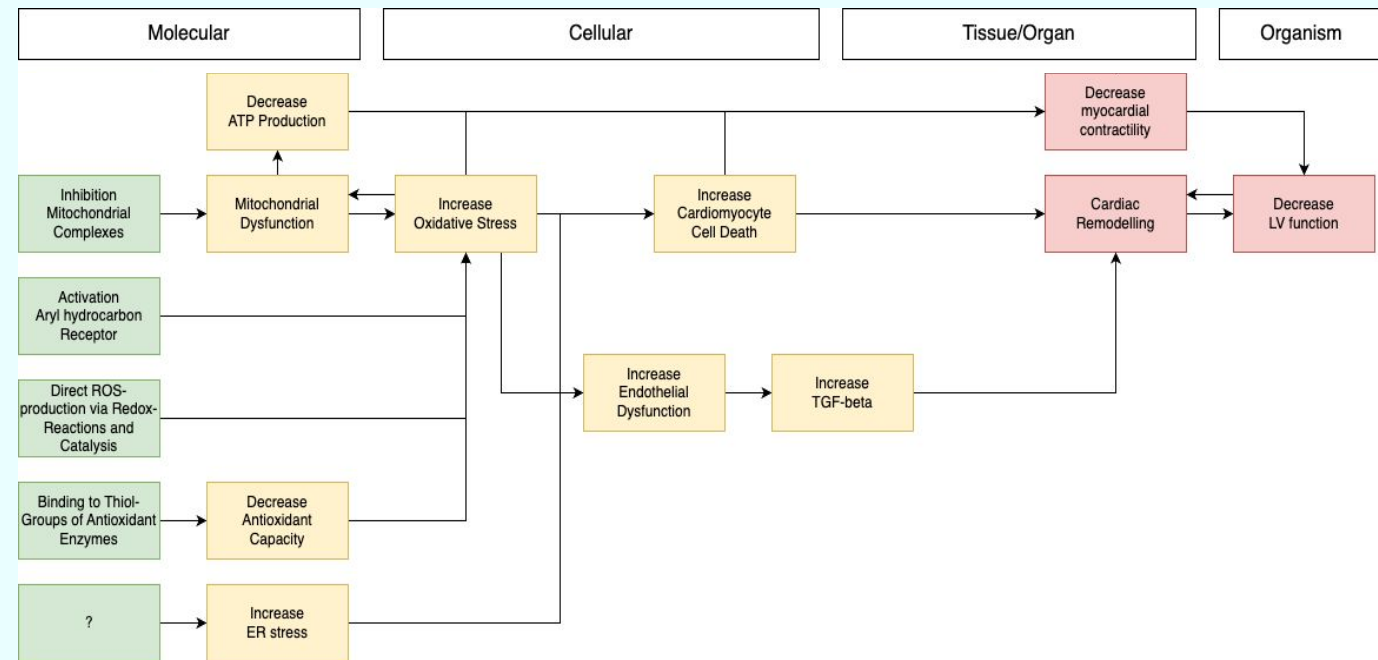
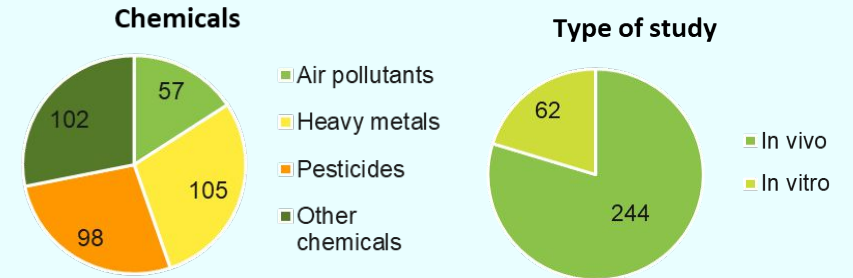
Inability to
fill properly

LV systolic
function decrease



Inability to contract properly
and pump enough blood

Cardiotoxicity induced by Environmental Chemicals *in vitro* and *in vivo*



Challenges and Future Directions

Take Home Messages

- **AOPs** provide proof of causality for **Exposure-Health effects** associations
- AOPs are promising tools for the **Identification of early Biomarkers of Effects** (BoEs) in human studies that are predictive, translatable, sensitive, specific, and robust for regulatory purposes
- Refined **Safe Exposure Limits** for environmental chemicals



Challenges and Future Directions

- Limited AOP **coverage**
- Health effects of chemical **mixtures**
- Health effects of **low dose, long term** exposure biomarkers of effects
- **qAOPs**

Health Effects Laboratory



Head of Section

- Elise Rundén Pran

Senior Scientist

- Maria Dusinska
- Ann-Karin Hardie Olsen
- Naouale El Yamani
- Eleonora Marta Longhin
- Tanima Sengupta

Scientist

- Alexandra Misci Hudecova
- Tatiana Honza
- Congying Zheng

Senior Engineer

- Solveig Brochmann
- Erin McFadden
- Xiaoxiong Ma

Thank you for
your attention