U.S. Environmental Protection Agency Activities on Combined Exposure to Multiple Chemicals: Latest Developments

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Disclaimers

The views expressed in this presentation are those of the author and do not reflect the views or policies of the U.S. EPA. While the author is a former EPA employee and still active in certain EPA research projects, he is presenting this work as an independent researcher. This talk has not been reviewed by the Agency and is based on publicly available information.

Topics

- Review of EPA's legislative responsibilities for assessing risk from combined exposure to multiple chemicals
- EPA's approaches to assessing risk from combined exposure
- EPA activities 2018 to the present
- New directions at the Agency

Legislative responsibilities

- Hazardous and Solid Wastes (RCRA and CERCLA)

- Pesticides (FIFRA and FFDCA)

- Water (SDWA and CWA)

- Air (CAA)

- Commercial products (not otherwise regulated) (TSCA)

- Environmental permitting programs (Title VI of the Civil Rights Act of 1964)

Science-policy issues for combined exposures

- U.S. and E.U. use similar approaches for assessing combined exposures to multiple chemicals
  - Whole mixture and component approaches
  - Tiered approaches to exposure and toxicity analysis
- Two science-policy issues
  - Component versus whole mixture approaches
  - Defining Cumulative Assessment Groups (CAGs)

Component versus whole mixture approaches

- Component-based approaches are favored over whole mixture approaches:

  - Challenge of assessing which mixtures are similar and which are unique
  - Avoiding additional testing
  - Ability to address temporal and spatial changes in mixtures
  - The potential for more chemical standards from high throughput standard setting

- Complex mixtures that cannot be easily regulated using component approaches can be regulated using "markers". Where markers are:

  - Certain measures that are markers of low risk (microbial contaminants - Escherichia coli and culturable enterococci)
  - Mixture components that dominate combined risk (disinfection by products - haloacetic acids and halomethanes)
  - Direct measures of total risk (radionuclides - total alpha and beta emissions)

Whole mixtures approaches are favored when the physical characteristics of a stressor influence toxicity

- This occurs with complex mixtures in air (wildfire smoke and diesel exhaust) where the size and surface characteristics of the particles influence toxicity of the chemicals.
- Combined effects from such mixtures are more difficult to predict using component-based approaches

Cumulative Assessment Groups

- Different EPA programs have different approaches for establishing CAGs
  - The Office of Pesticide Programs has defined assessment groups narrowly (USEPA, 2016)
  - The Office of Land and Emergency Management advocated screening approaches for hazardous waste sites based on all chemicals and refined CAGs based on common targets (organs or systems affected by chemicals) (USEPA, 1991)
- In the last five years, EPA ORD has sought to bring the concepts of the Aggregate Exposure Pathways (AEPs) and Adverse Outcome Pathways (AOPs) to address this question

Aggregate Exposure Pathways - Adverse Outcome Pathways Networks (AEP-AOP Networks) and CAGs

- AOPs provide a better basis for defining CAGs than the nature of apical effects.
  - Observation that two chemicals cause the same effect or effect a common organ or system are not sufficient to determine if a chemical will follow dose additivity model, response additivity models, or if they will interact (antagonism or synergy).
  - Information on chemicals' abilities to affect Molecular Initiating Event (MEIs) and Key Events (KEs) of an AOP network leading to a common apical endpoint can provide such information (Villeneuve et al. 2018, Nelms et al., 2018, Knapen et al. 2018, Price et al. 2020).
- AOPs networks are <u>not</u> sufficient to address kinetic interactions between chemicals. AEP-AOP networks are required to address kinetic interactions (Price et al. 2020).

Recent activity at EPA on combined exposures

- Both the EPA as a whole and EPA's Office of Research and Development have five-year strategic plans.

- The most recent EPA and EPA-ORD strategic plans (for years 2018 to 2022) provide a starting point for understanding the Agency's recent activities on combined exposures

- The initial draft of the 2022-2026 EPA strategic plan provide a basis for describing where the Agency is going in the future

Activities related to combined exposures: 2018 to the present

- The terms mixtures, cumulative, and aggregate exposures do not appear in the 2018 to 2022 Strategic Action plans for either the Agency as a whole or for the EPA Office of Research and Development.

- EPA programs focused on performing mandated actions (core mission) and responding to the needs of the States. This was not seen as requiring new initiatives on mixtures or combined exposures.

- The emerging issue of combined exposures to per- and polyfluoroalkyl substance (PFAS) was identified as an issue of concern by the States.

https://www.epa.gov/sites/default/files/2019-09/documents/fy-2018-2022-epa-strategic-plan.pdf
https://www.epa.gov/sites/default/files/2020-07/documents/ord_strategic_plan_2018-22_update_7-21-20_dh.pdf

ORD activities related to combined exposures: 2018 to the present

- Development of guidance documents for combined exposures moved slowly during this time
- Fewer research projects on exposure and hazard from combined exposure were initiated
- Significant work performed on the basic science that supports assessments of combined exposures
  - Development and refinement of AOPs
  - Developing the concepts of AOP-networks and AEP-AOP networks
  - High throughput toxicokinetic modeling
  - Development of an infrastructure for exposure-related information

High Throughput Toxicokinetics (httk) model

- The httk model (Pearce, et al., 2017) designed to provide *in vitro-in vivo* extrapolation modeling for New Approach Methodologies (NAMs)

- httk is also an important tool for the assessment combined risk:

  – Integrates doses that occur by multiple routes,

  – Determines relevant measures of internal doses for time-varying external doses,

  – Addresses interindividual variation in ADME from differences in metabolism and physiology,

  – Current version can model multiple chemicals in one individual (but does not model kinetic interactions)

- Can be run using chemical specific inputs (plasma binding and liver clearance) based on QSARs (Breen et al., 2021)

- Model and code is publicly available https://cran.r-project.org/web/packages/httk/index.html

- Extensive QA/QC of data and model capabilities have been performed

Other relevant research

- Non-targeted analysis techniques
  - Analytical methods that identify all chemicals present in a sample
  - Significant technical process over the last five years for identification of chemicals
  - Quantification of estimates remains a challenge
- Analysis of existing data on monitoring and composition
  - Collection, organization, annotation, and curation of data
  - Monitoring data for environmental media, composition of consumer products, and measurements of occupational exposures
  - Making the data and documentation publicly available
- Identifying combinations chemicals that frequently co-occur (Tornero-Velez et al., 2012)
  - Patterns of chemical co-exposure in the NHANES biomonitoring data (Kapraun et al., 2017, Reyes and Price, 2018a,b);
  - Patterns of chemical co-exposure from use of multiple consumer products (Stanfield et al., 2021, Tornero-Velez et al., 2020).

Characterizing exposure to multiple chemicals from the use of consumer products

- Systems of categories:
  - Categories of consumer products. Products that provide a common service and have similar exposure characteristics
  - Function of a chemical in a consumer product
- Models
  - Modeling interindividual variation in personal and residential characteristics relevant to exposure
  - Characterizing longitudinal human activity patterns using agent-based modeling
  - Models of combined chemical exposure to one or more chemicals from daily use of consumer products (SHEDS-HT and CHEM)
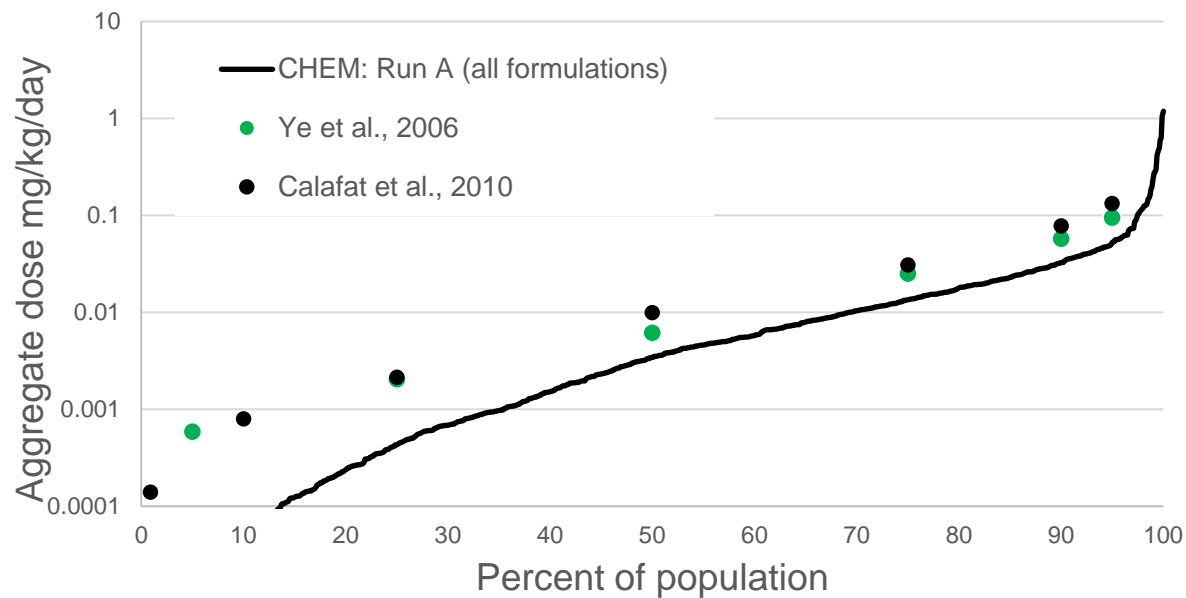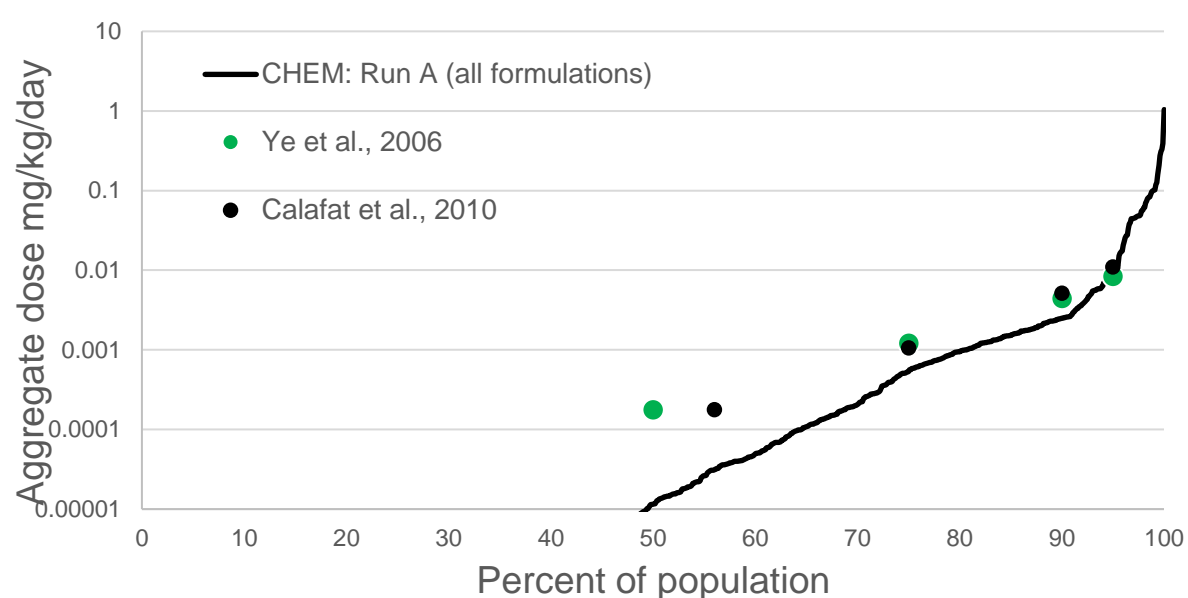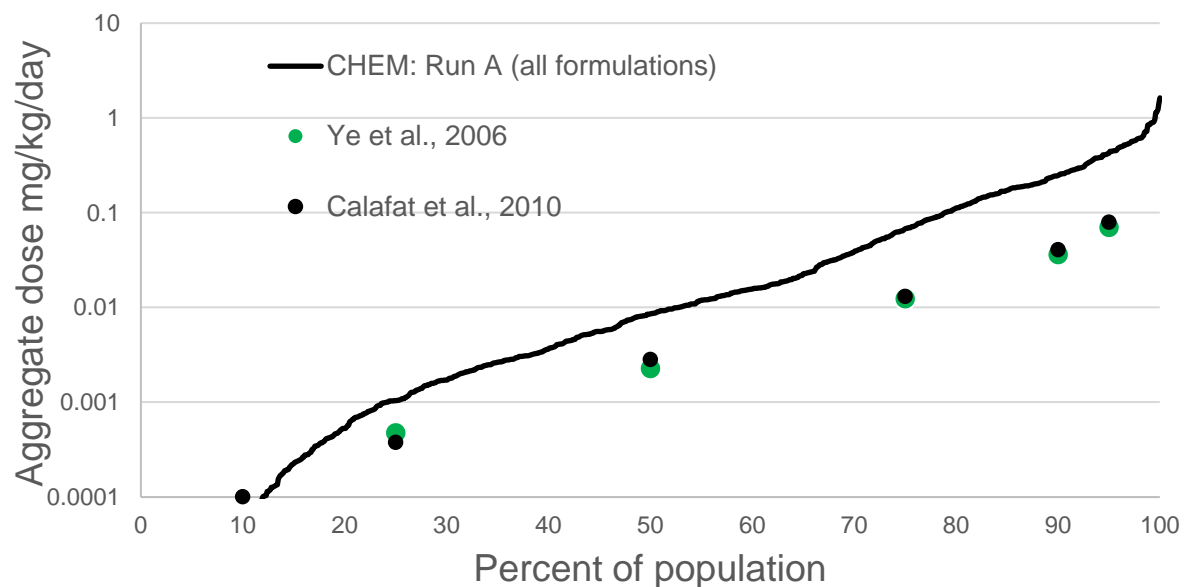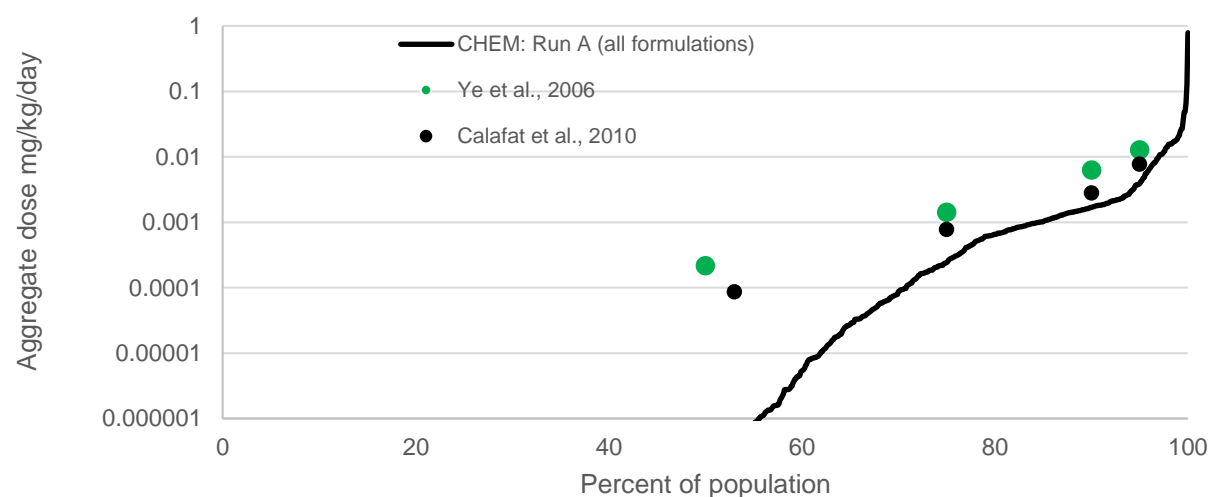
Quo Vadis? EPA

- Draft strategic action plan for EPA 2022-2027 (https://www.epa.gov/system/files/documents/2021-10/fy-2022-2026-epa-draft-strategic-plan.pdf)

- EPA Guidelines for Cumulative Risk Assessment Planning and Problem Formulation

- PFAS

- NAMs and mixtures

Draft Strategic Action Plan for EPA 2022-2026

EPA must make significant and urgent progress in fundamentally grounding its work in addressing disproportionality, which includes <u>understanding of and reacting to issues of cumulative impacts and cumulative risks</u>...

Communities that have multiple industrial and energy facilities and are saturated with legacy pollution want to see <u>EPA realign its enforcement in a way that provides action, accountability, and guidance for taking cumulative impacts and risks into account, even if they cannot be measured with precision.</u>

Many environmental justice advocates have raised concerns about the number of facilities permitted and re-permitted in their communities. <u>EPA cannot take enforcement action against these facilities unless they are in violation of the law and therefore faces constraints in addressing the concerns of cumulative impacts in these communities through enforcement alone</u>.

These assessments will inform the evaluation and selection of the levels of exposure for regulatory action that are protective of children and vulnerable populations, including the extent to which cumulative or <u>concurrent exposures to chemical and social stressors can modify exposure or hazard considerations.</u>

https://www.epa.gov/planandbudget/strategicplan

Quo Vadis? EPA

- New version of EPA Guidelines for Cumulative Risk Assessment Planning and Problem Formulation is under development and a public draft is expected in the near future.
  - Follow up to the 2003 report Framework for Cumulative Risk Assessment (https://www.epa.gov/risk/framework-cumulative-risk-assessment)
- PFAS mixtures
  - Research into the use of NAMs as a means of assessing the large numbers of individual PFAS compounds and mixtures of such compounds
- NAMs and mixtures
  - Mixtures have traditionally been a later phase in NAM development
  - These later phases of NAM development projects are now beginning to assess mixtures

Summary

- The various programs in the U.S. EPA use methodologies to assess risks from mixtures that are similar to those used in the European Union.
- For the last four years EPA has focused on building the infrastructure for advancing toxicity and exposure that supports NAM-based approaches for assessing risks from combined exposures to multiple chemicals.
- The new directions on mixtures reflect a goal of social justice in disadvantaged communities and will require the integration of physical and social stressors into the assessment of risks from combined chemical exposures

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Questions?