Leveraging probabilistic risk assessment methods to capture benefits of regulatory efforts to reduce environmental contamination

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Health risk from environmental chemical exposure is assessed differently for **cancer** versus **non-cancer** health effects

Non-cancer Health Effects:	**Cancer:**
There are “safe”* exposure levels that don’t increase risk of disease.	Any exposure increases risk of cancer.

*The assumption of a “safe level” is fundamentally flawed, as it does not sufficiently account for human variability and the many factors that make some people more susceptible than others.

Current non-cancer risk assessments fall short of protecting public health

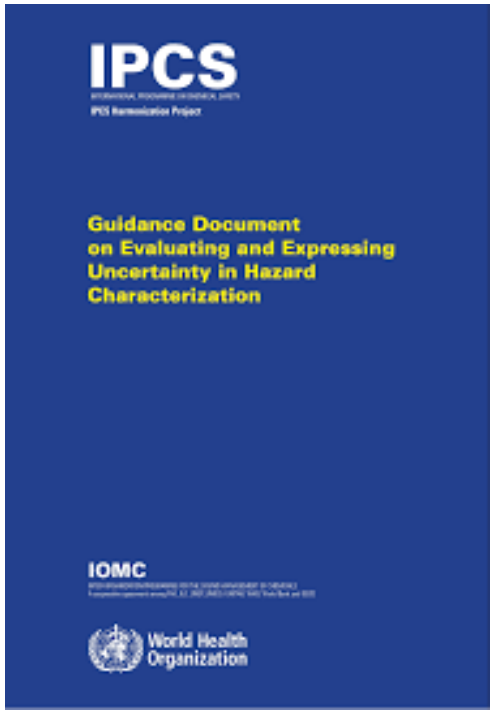
- No quantification of the **probability or severity** of risk or the proportion of population affected
  - Limits utility for economic or comparative analyses
- No distinction between **uncertainty** and **variability**
- No assessment of **uncertainty** in toxicity values
- No assessment of low dose linearity despite epidemiological studies showing a lack of threshold for non-cancer effects associated with multiple agents

We have **data** and **methods** to do this better!

Probabilistic risk approaches are **statistical methods** that incorporate uncertainty and variability into risk assessment

Probabilistic risk assessments address limitations with the RfD/RfC approach by

- Distinguishing between uncertainty and variability
- Defining the magnitude of non-cancer health effect
- Quantifying the proportion of the population expected to experience a non-cancer health effect
- Redefining RfDs/RfCs as risk-specific reference values



Probabilistic Methods for Non-cancer Risk Assessment

I. Distributional approach

Replace fixed uncertainty factors with distributions based on empirical data

II. Background clinical vulnerability

Clinical Use shared biomarkers between environmental exposure and disease or aging processes to model the additional risk of health outcomes due to environmental chemical exposure

I. Continuous risk functions

Leverage dose-response curves from human epidemiological studies and animal toxicity studies to model risk at environmentally relevant concentrations

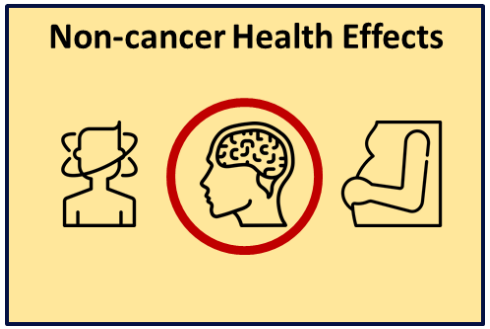
Perchloroethylene (PCE)

- Solvent commonly used in dry cleaning and metal degreasing and as a starting material in chemical manufacturing
- Volatile chemical that readily evaporates into air but is also mobile in soil and water
- Inhalation is the most common route of exposure though ingestion exposure can occur through contaminated water and soil as well
- PCE exposure negatively impacts neurocognitive function, liver, kidney, and reproductive function and is considered a probable carcinogen

PCE Case Study

- We used methods recommended by WHO, which are a significant improvement regarding the treatment of human variability compared to EPA's assumption of a safe level.

- We conducted a probabilistic analysis using a study critical to EPA's assessment - Echeverria et al., 1995, assessing PCE's effect on neurobehavioral function in dry-cleaning workers.



Case Study Goals

- Explore feasibility of different quantitative approaches to probabilistic non-cancer risk assessment that are recommended by the World Health Organization and National Academy of Sciences.
- Illustrate options with PCE RfC, neurotoxicity endpoint
- Compare risk estimates across approaches
- Estimate level of risk at various exposures
  - including the EPA RfC (0.04 mg/m^3, 0.0059 ppm)
- Compare non-cancer and cancer risk
- Identify main assumptions, uncertainties, data gaps
- Assess value-added of probabilistic approaches

Case Study Methods

- Selected one of the key studies supporting EPA's RfC for PCE to evaluate risk at and around the existing RfC (Echeverria et al., 1995)
- Assessed data availability to apply methods for probabilistic non-cancer assessment
- Conducted an approximate probabilistic analysis using the data from Echeverria et al., 1995
- Compared risk estimates across approaches and risk of cancer effects at the same dose
- Identified main assumptions, uncertainties, and data gaps
- Assessed value added of probabilistic approaches

Case Study Key Findings

- Probabilistic methods can be easily applied to more thoroughly analyze health risk at different exposure levels
- Approx. 1 in 1000 people are predicted to experience a 5% reduction in WMS-VR performance with chronic exposure to current USEPA RfC
- The risk for this neurological impairment at the current RfC is approximately 100 fold greater than the cancer risk at a comparable exposure level

Nielsen et al., 2023 PMID: 36635712

Take Home Message

EPA currently has **no method** to quantify health risks for non-cancer effects of toxic chemicals.

Probabilistic methods would let EPA quantify **how many people are at risk**, leading to better, more health-protective decision-making and incorporation of non-cancer health effects in cost benefit analyses.