A regulatory framework based on probabilistic hazard, exposure, and risk assessment
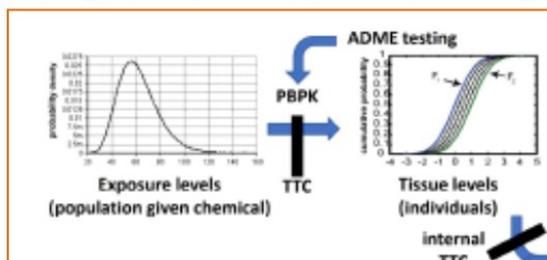
The principles of probabilistic risk assessment, including how and when NAMs are meant to be used. The approach are founded on four bricks/steps.

1. The initial step is to see if there is a probability of external exposure – if there is no exposure in the anticipated use of the chemical, there is no significant risk. The result will be included in the ADME testing (WP4) and if the concentration is so low that it's unlikely it will result in an internal toxic concentration on relevant organs, we can conclude that for this application and chemical there is no significant risk.
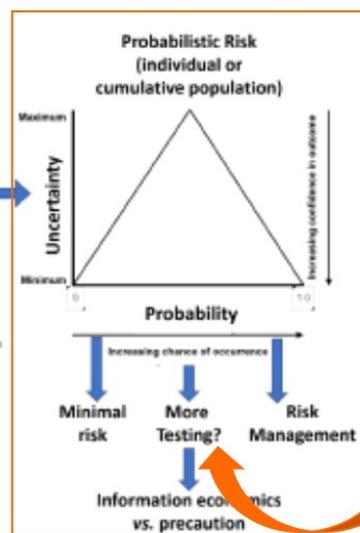
2. If there is a risk, next step is to look at the probability of hazard. The method is to look at existing data on a given substance, I.e., physiological data and animal guideline studies, information on similar substances enabling read across, structuring alerts enabling QSARs assessments and then mechanistic alerts from in vitro testing (2D or 3D).
   Read-across is meant to be automated read-across (RASAR = read-across-based structure activity relationships). Data are integrated together with exposure response data to conclude probability of hazard.

3. Next step is to conclude on probability of risk. If the conclusion is low probability and low uncertainty you can conclude there is a minimal risk for that specific chemical in that specific application. If the conclusion is high probability and low uncertainty you can conclude there is high risk requiring risk management.

4. If you are in the middle meaning some probability combined with high uncertainty you need more testing using relevant NAMs. Here the ONTOX developed in vitro/in silico test batteries are relevant to use.

Case studies and lessons learned on probabilistic risk assessment.

Probabilistic risk assessments can integrate multiple sources of knowledge ranging from NAMS to historical data: for example, a more efficient risk assessment for skin sensitization can combine LLNA results, *in vitro* tests, and human observations. (Reference: https://www.sciencedirect.com/science/article/pii/S0273230022000460) In addition, by avoiding the use of point estimates that have to be further divided by uncertainty factors to account for both variability and uncertainty, variability can be dealt with explicitly, which can have important policy implications, for example, in decision making about Superfund sites.(https://www.tandfonline.com/doi/abs/10.1080/10807039609383660) Finally, avoiding a binary cut-off for hazard, as is common for non-cancer endpoints such as a reference dose (RfD), allows for better calibration of population-level endpoints such as mild neurocognitive deficits after chronic exposure to solvents.https://ehjournal.biomedcentral.com/articles/10.1186/s12940-022-00918-z

Additional information.

There is a large body of literature that focus more narrowly on Superfund sites or other high impact risk assessment exploring the consequences of shifting from point estimates w/ uncertainty to mean estimate w/ probabilities, but this tends to be in policy/environmental econ literature.

Just a few examples here:

https://www.tandfonline.com/doi/abs/10.1080/10807039609383660

Going beyond the single number: Using probabilistic risk assessment to improve risk management

Recent efforts aimed at improving risk characterization emphasize the importance of uncertainty analyses and endorse probabilistic techniques as useful tools for performing them. One feature of ex...

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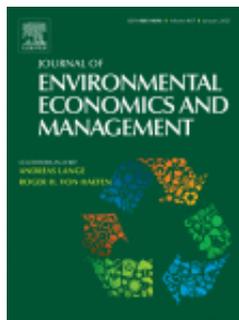
Conservative versus Mean Risk Assessments: Implications for Superfund Policies

This paper explores how a shift to more central estimates of risk would affect EPA decisions to remediate hazardous waste sites in the Superfund progr...

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