Modeling mechanistic processes from source to outcome to support evidence integration and inform risk assessment

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Introduction

- Evidence integration in current IRIS assessments considers the contributions of human health, animal, and mechanistic data streams according to PECO criteria in a hierarchical and parallel approach. (*Fig. 1*)

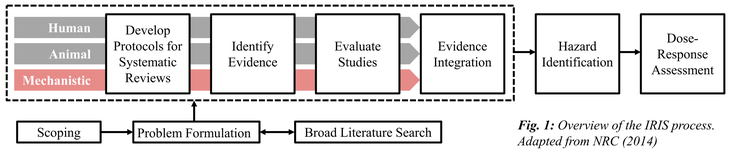

Fig. 1: *Overview of the IRIS process. Adapted from NRC (2014)*

- The NAS has emphasized the use of mechanistic process models of pathogenesis to evaluate relationships among biomarkers (exposure/effect/susceptibility) as well as modernizing risk predictions using exposure science and computational models.
- We propose mechanistic data should serve as a scaffold for the use of process models when integrating evidence across human health and ecological endpoints. *(Fig. 2)*

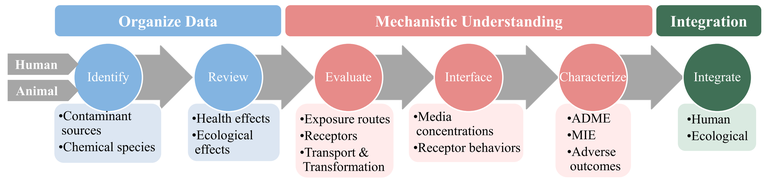

Fig. 2: *Mechanistic workflow for evidence integration*

Case Study Example

- We demonstrate how the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks create a source to outcome continuum using a case study of the perchlorate anion (ClO_4^-).

Teeguarden et al. (2016), Ankley et al. (2010)

Quantitative AEP (A)

- Constructed a six compartment fate-and-transport network for the hypothetical site. *(Fig. 3)*
- Considered inputs to site from surface water, atmospheric deposition, and groundwater contamination.
- Literature values were used to restrict parameter ranges.
- A Monte Carlo approach (n=10,000) was used to estimate variability in the exposure network based on variability in literature data.

Exposure Scenarios (B)

- Behavioral assumptions:
  - Groundwater from well
  - Media (Surface water)
  - Grass (95%) Surface water (5%)
- Contamination input scenarios:
  - **Mild**: Inputs from literature, similar to published concentrations
  - **Moderate**: 10x Mild scenario inputs
  - **High**: 100x Mild scenario groundwater inputs

Analyses (C D E)

- Estimated external exposure and source apportionment using Network Environ Analysis

Fath and Patten (1999)

- Linked **AEP network** to multispecies **AOP network** using previously published PBPK models
- Estimate hazard index (HI) using EQ. 1

$$HI = \sum_{i=1}^{n} \frac{E_i}{AL_i}$$

EQ 1: *i is each exposure source, E is the exposure level, and AL is the acceptable limit of exposure. AL was the lowest reported LOAEL for each species*

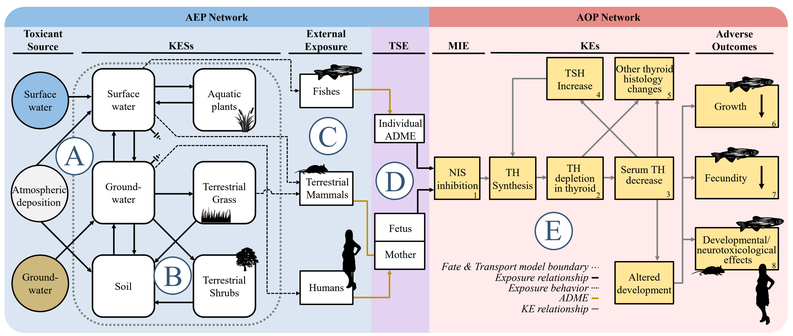

Fig. 3*: Joint AEP-AOP construct for the ClO_4^- case study. Detailed description of AOP network in Hines et al. (2018).*

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Quantitative Case Study

(B) Exposure Estimation

	Mild			Moderate			High		
	1%	Med	99%	1%	Med	99%	1%	Med	99%
	<0.1	0.1	0.3	0.4	1.0	2.7	4.0	10.3	25.4
	0.1	0.5	1.4	1.2	5.4	14.1	2.1	9.8	28.6
	3.1	15.8	34.2	89.5	159.4	395.7	369.5	2990.1	8072.4

Tab. 1*: Lower confidence interval (1%), median (Med), and upper confidence interval (99%) external toxicant doses predicted for human, fish, and small mammals in each scenario.*

Table units are μg/kg/d.

(C) Source Apportionment

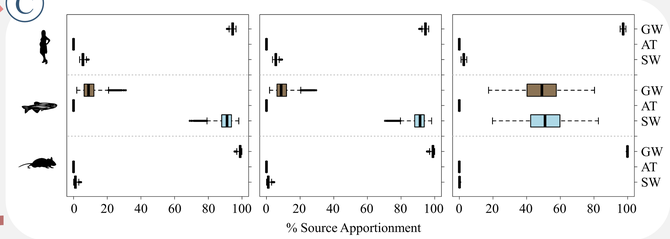

Fig. 4: *Species-specific source apportionment*

- Groundwater (GW)
- Atmosphere (AT)
- Surface water (SW)

(D) MIE Activation

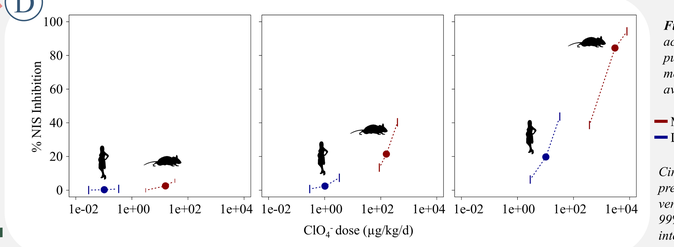

Fig. 5: *MIE activation. No published PBPK model was available for fish.*

- Merrill et al. (2003)
- Lumen et al. (2013)

Circles show median prediction and vertical points show 99% confidence interval.

(E) Evaluation of Risk

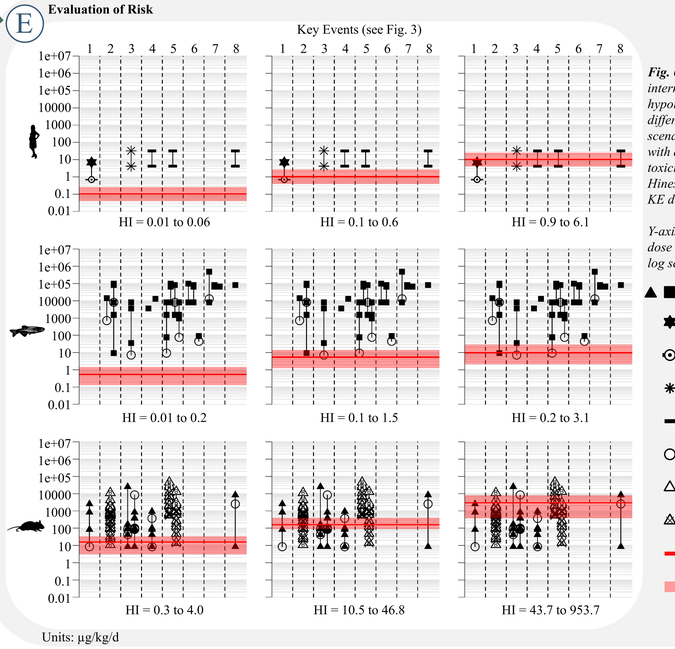

Fig. 6: *Predicted internal doses at the hypothetical site under different contamination scenarios compared with dose-response toxicity data. See KE Hines et al. (2018) for KE details.*

Y-axis shows toxicant dose in μg/kg/d on a log scale

- LOEL/LOAEL
- Point of departure
- Reference dose
- Model prediction
- Model extrapolation
- NOEL/NOAEL
- BMD
- BMDL
- Median internal dose
- Internal dose range prediction

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Discussion

- The source to outcome case study demonstrates how a workflow for using a mechanistic scaffold can facilitate evidence integration. (Fig. 7)

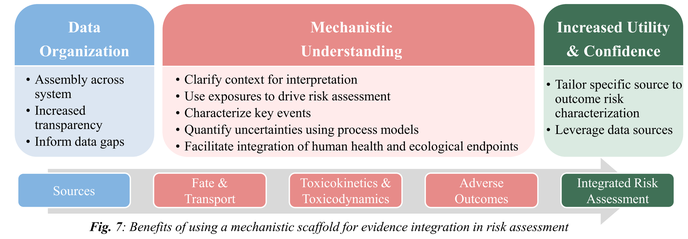

Fig. 7*: Benefits of using a mechanistic scaffold for evidence integration in risk assessment*

- The AEP and AOP frameworks facilitate exposure driven risk assessments in support of assessments required by the new TSCA
- Mechanistic approaches to data integration can act as an organizing framework to inform ontologies or evidence maps, leverage data sources, and facilitate quantitative characterization of key events in pathogenesis.
- Explicit elucidation of key events and parameters supports transparency in risk assessments.
- Risk assessments based on exposure use cases and toxicity pathways involved in pathogenesis allow for more targeted assessment and increased confidence.

Conclusions

A mechanistic scaffold informs problem formulation, aids evaluation of study quality criteria, and facilitates evidence integration to support source-to-outcome risk assessments that are:

1) Exposure driven to target specific use-cases
2) Quantitative for key events in relevant AOPs
3) Capable of characterizing human health and ecological endpoints

Literature Cited & Abbreviations

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Abbreviations: ADME, Absorption, Distribution, Metabolism and Elimination; AEP, Aggregate Exposure Pathway; AOP, Adverse Outcome Pathway; BMD, Benchmark Dose; BMDL, Benchmark Dose confidence interval; HI, Hazard Index; IRIS, Integrated Risk Information System; KE, Key Event; KES, Key Exposure State; LO[A]EL, Lowest Observed [Adverse] Effect Level; NAS; National Academy of Sciences; NIS, Sodium Iodide Symporter; NO[A]EL, No Observed [Adverse] Effect Level; PBPK, Physiologically Based Pharmacokinetic; PECO, Population, Exposure, Comparators, Outcomes; TH, Thyroid Hormone; TSE Target Site Exposure; TSCA, Toxic Substances Control Act