A Conceptual Model that Enables Quantitative Integration of Data into an AOP

Molecular initiating event → Intermediate Events → Adverse Outcome

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Histology and Histopathology Atlas of the Zebrafish V2.01
Risk assessors (regulatory or otherwise) need to:

- use many different kinds of data to make decisions
- weigh data in terms of relevance and reliability
- assess and document confidence in data and assumptions
- acknowledge uncertainties surrounding the assessment

A problematic element in regulatory toxicology and risk assessment is understanding the amount of uncertainty associated with a decision or a process.

→ To be useful in risk assessment, an AOP should demonstrably increase confidence in a decision
AOPs can increase certainty by:

- Providing biological plausibility for a decision
  - Qualitative assessment
  - Hypothesis testing
  - Providing transparent communication

- Providing a framework that allows valuing or quantifying the data input
  - Strengths of relationships within an AOP can be used to weigh data
  - WoE assessment is improved vs. a “naïve” approach where all evidence is considered with equal weight

- Allowing computational modeling of pathway elements with probabilistic outcomes
AOPs and regulatory use:

**AOP Continuum**

**Correlative/qualitative**
- mechanistic understanding of MIE/KE (Quantitative or not)
- simple statistical correlations with some biological plausibility between MIE/KEs and AOs

**Qualitative**
- some mechanistic understanding of linkages between MIE/KE and AO
- some evidence for causal linkages

**Semi-quantitative**
- some quantitative understanding
- dose-response information, toxicokinetics, metabolism

**Quantitative**
- Predictive causally-linked quantitative models
- Dose relationships
- Some understanding of intersecting pathways

**Predictive system**
- Quantitative understanding of relationships of intersecting pathways
- increased certainty of likelihood of a particular AO vs some other outcome

**USE**

**Integrated testing strategy design**

**Hazard characterization**

**Risk Assessments**

**Predictive toxicology**

**Examples**

- Narcosis due to respiratory failure
- Mitochondrial Fatty Acid Beta-Oxidation Inhibition Leading to Steatosis
  - Cancer caused by exposure to 1,4-dioxane
  - Skin Sensitization Initiated by Covalent Binding to Proteins
  - Aromatase inhibition leading to reproductive dysfunction (in fish)
Context of application for AOPs
A Qualitative AOP

- composed of a MIE, KE_A, KE_B, and an AO
- assign a semi-quantitative value of weak, adequate or strong evidence to KERs

→ **Linkage Strength**: measure of confidence between events

* → **Inference Strength** is the ability of an event to infer the likelihood of an AO
A Quantitative AOP

- **Location Value:**
  - KEs closer to the AO are likely to provide more predictive information
  - less chance of interference by connecting pathway
  - *→ Location Value* is equal to the position in the pathway (MIE = 1)

- **Linkage Strength:** between each event
  - weak, adequate or strong => values of one, two, or three

- **Inference Strength:**
  - quantitative or statistical prediction that KE leads to AO
  - i.e. the probability that an event (MIE or KE) will correctly infer the AO
Objective Decision Formula

\[ KE_{Score} = \frac{\text{Position}_{KE}}{\text{AOPLength}} \times \left( \text{Inferability}_{KE} + \sum_{i=\text{Position}_{KE}}^{\text{AOPLength}} \text{Linkages}_i \right) \]

- for quantifying the value or weight of an event within an AOP
- a **score for each KE** can be calculated based on
  - **Location**
  - **Linkage Strength**
  - **Inference Strength**

→ Weighting score for each KE

- **identify which KE will provide the most valuable information with respect to the probability of the AO occurring**
Calculation of KE weights is based on position of event within the AOP and empirical data according to the ODF:

\[
KE_{Score} = \frac{Position_{KE}}{AOPLength} \times \left( \text{Inferability}_{KE} + \sum_{i=Position_{KE}}^{AOPLength} \text{Linkages}_i \right)
\]
Mitochondrial Fatty Acid Beta-Oxidation Inhibition Leading to Steatosis as an example AOP structure

- Consider all possible circumstances:
  - **Linkage strength** varied from 1, 2, 3, 4, 5
  - **Inference strength** varied from 0%, 0.1%, 0.4%, 0.7%, 0.85%, 0.95%

  → 30 possible combinations for each event
  → over 24 million possible scenarios based on this structure
An analysis of the distribution of scores shows:

- that KE 3 is most often the most informative
- early KEs reach high scores in situations of low accuracy and linkage weights of downstream events
- scores of KEs closer to the AO are similar indicating that there may be several choices of KE’s to query at that end of the pathway
In summary

**Derivation of a KE weight allows:**

- reduced uncertainty by weighting input in a weight-of-evidence assessment
- choice the most appropriate/valuable tests to use for assessment
- increase efficiency of chemical assessment and reduced animal use

More advanced techniques are available that may provide a more accurate and better incorporation of the data; however, the *simplicity of our ODF means that it can be easily calculated for any given AOP that is currently available.*
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