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

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The Issue

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

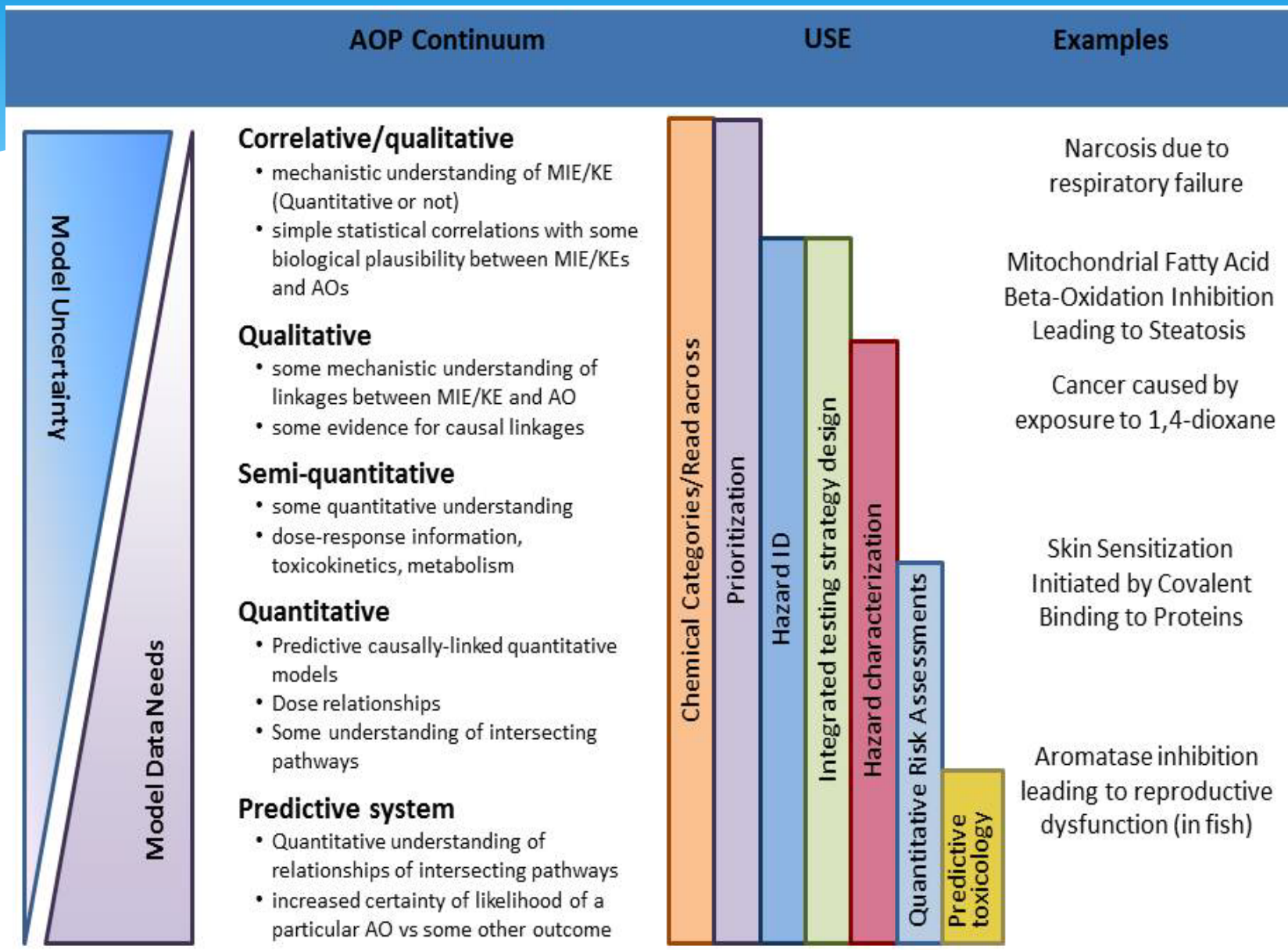
A problematic element in regulatory toxicology and risk assessment is understanding the amount of uncertainty associated with a decision or a process.

→ To be useful in risk assessment, an AOP should demonstrably increase confidence in a decision

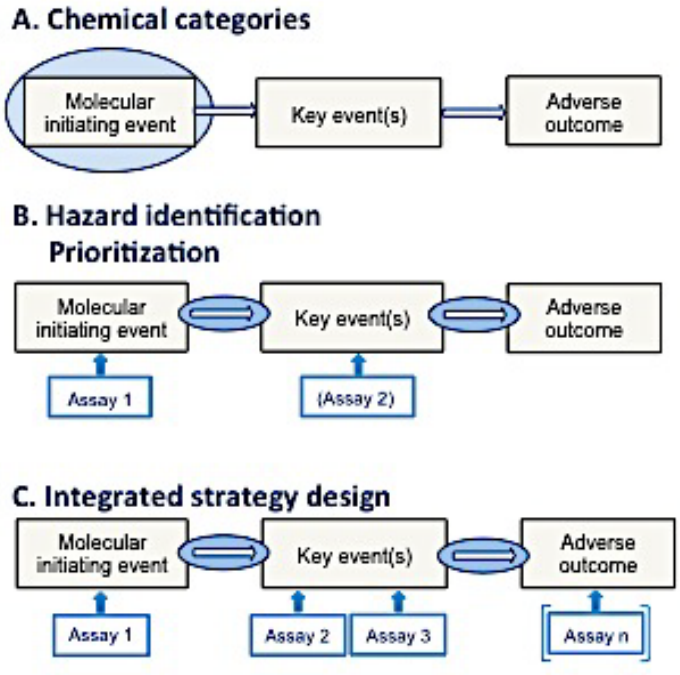
AOPs can increase certainty by:

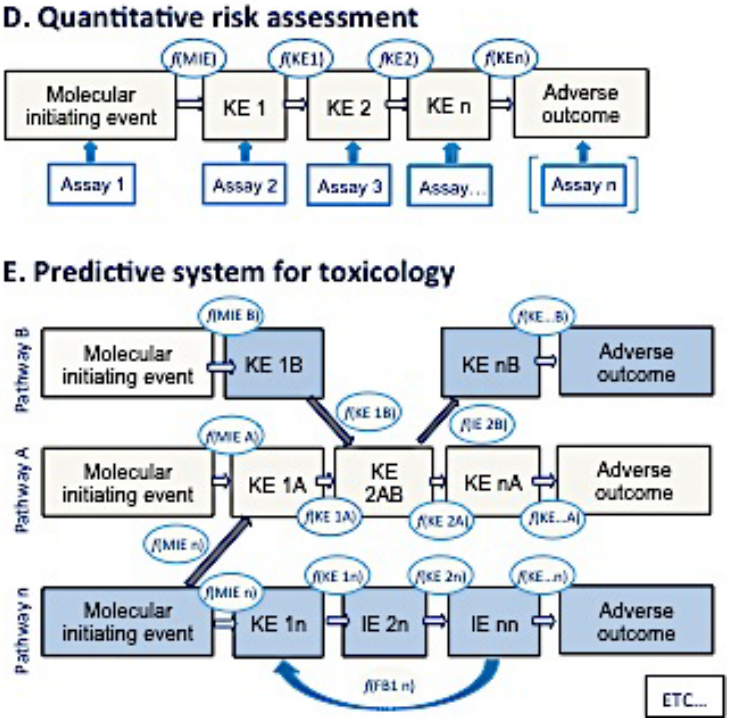
- Providing biological plausibility for a decision
  - Qualitative assessment
  - Hypothesis testing
  - Providing transparent communication
- Providing a framework that allows valuing or quantifying the data input
  - strengths of relationships within an AOP can be used to weigh data
  - WoE assessment 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:



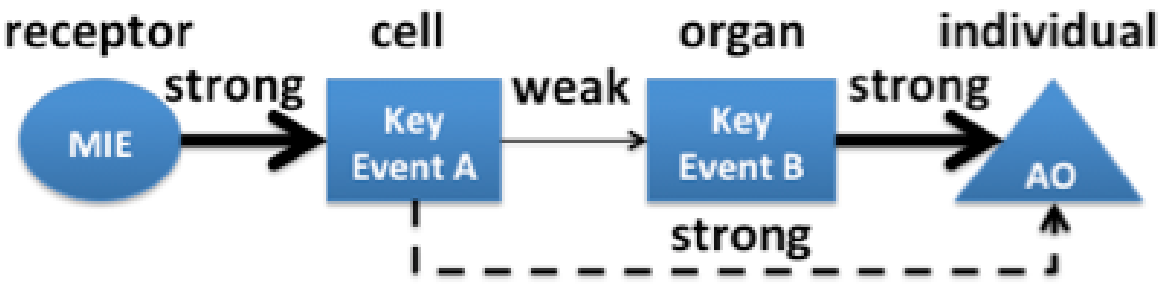
Context of application for AOPs





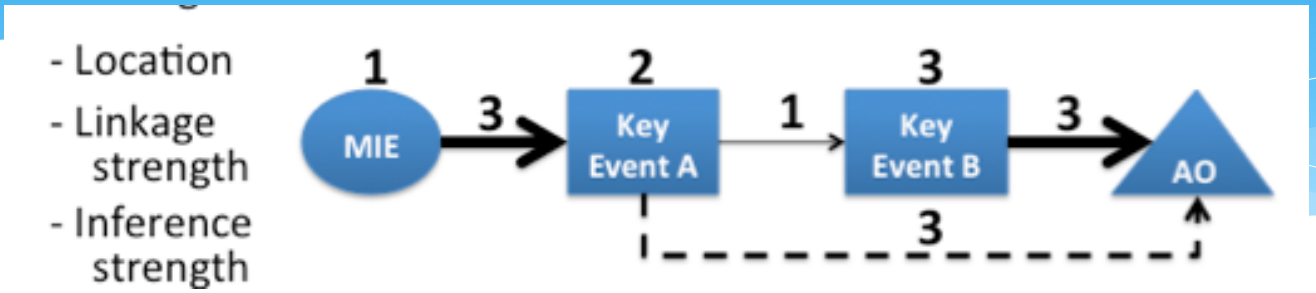
A Qualitative AOP

- Location
- Linkage strength
- Inference strength



- 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

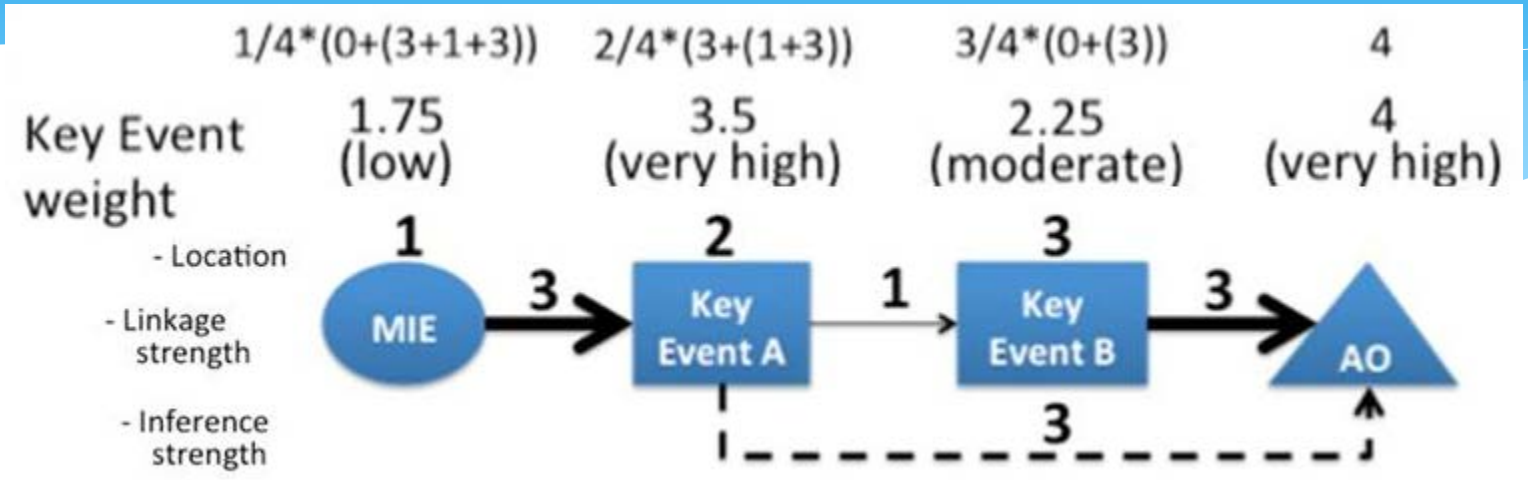
$$KE_{Score} = \frac{Position_{KE}}{AOPLength} * \left(Inferability_{KE} + \sum_{i=Position_{KE}}^{AOPLength} Linkages_i \right)$$

- 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***

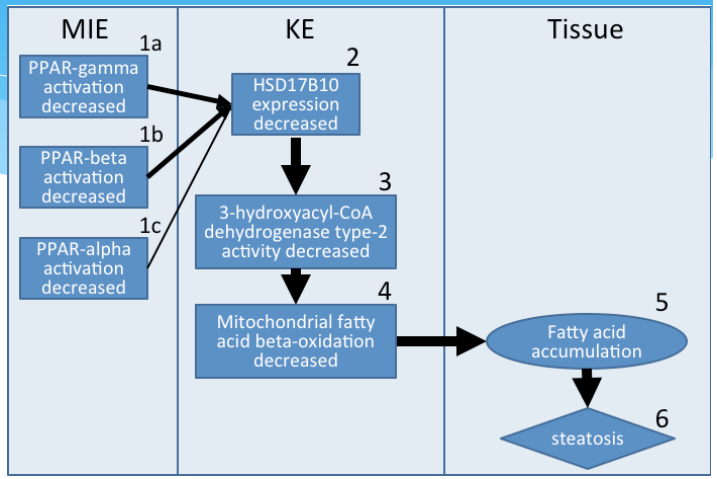
Application of the ODF



- ***Calculation of KE weights is based on position of event within the AOP and empirical data according to the ODF:***

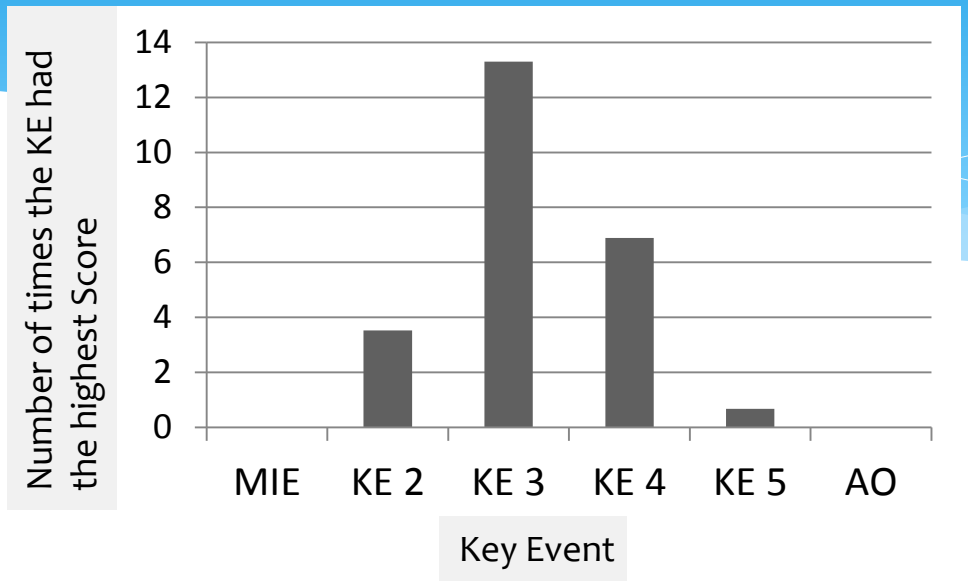
$$KE_{Score} = \frac{Position_{KE}}{AOPLength} * \left(Inferability_{KE} + \sum_{i=Position_{KE}}^{AOPLength} Linkages_i \right)$$

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

ODF Analysis; a hypothetical case



- 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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