QSAR and Read-Across Approaches using *in silico* Tools in Food Ingredient/Contaminant Safety Assessments at the U.S. Food & Drug Administration

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Outline

- Introduction
- Safety paradigm
- How we use (Q)SAR at OFAS
- (Q)SAR tools available to OFAS
- Case study
- CERES
- Q&A

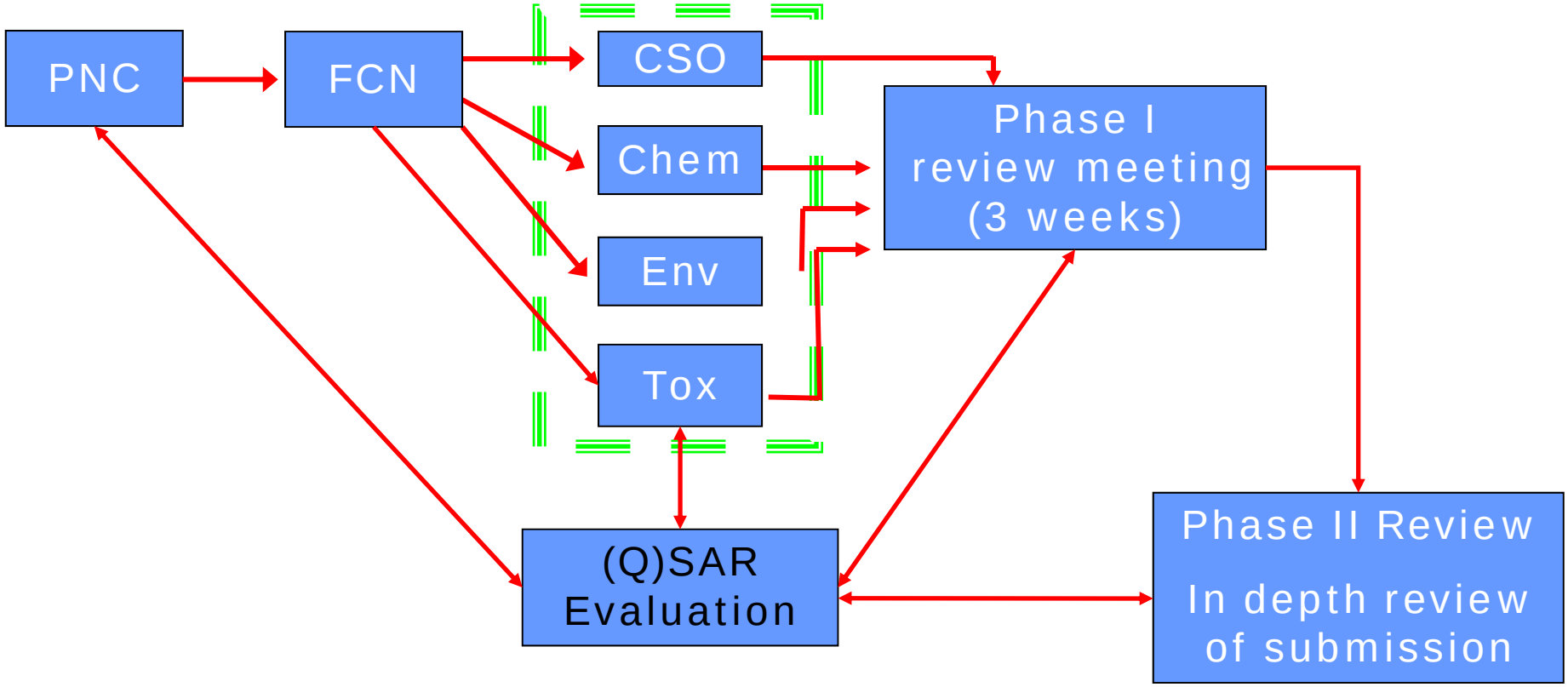
Office Of Food Additive Safety (OFAS)

- OFAS is a program office within CFSAN
  - Ensure the safety of food additives and packaging in U.S.
    - Evaluate safety information in industry submissions for various categories of food ingredients
      - Direct food additives (*e.g.,* high intensity sweeteners)
      - Biotech foods (*e.g.,* herbicide-ready soybeans)
      - Generally Recognized as Safe (GRAS – phosphoric acid)
      - Food contact substances (*e.g.,* plastic bottles, sanitizers)

Safety Paradigm

- Reasonable certainty of no harm
- No risk benefit analysis
- Delaney Clause
  - The anti-cancer (“Delaney”) clause of the Federal Food, Drug and Cosmetic Act states that “No additive shall be deemed safe if it is found to induce cancer when ingested by man or animal.”

(Q)SAR within the FCN Review Process



(Q)SAR Analysis in OFAS

- Hazard identification tool
  - Evaluate FDA's recommended endpoints
    - Identify data gaps in PNC toxicity data
    - Provide specific toxicity testing recommendations
- Decision support tool
  - Multiple (Q)SAR and database tools used
  - Fill gaps in toxicity data
  - Weight of evidence approach
- Risk Assessment
  - Identify structural analogs with bioassay data or TD50 values
  - Extrapolate a unit cancer risk (UCR) from the bioassay data or TD50 values
  - Use the UCR and exposure estimate to predict the lifetime cancer risk for the compound

Toxicity Databases

- Commercial
  - Leadscope
    - FDA CFSAN
    - FDA CDER
    - Public databases (NTP, DSSTox, RTECS)
  - Vitic
    - FDA CFSAN
    - FDA CDER
    - Public data
    - Industry data
- Public
  - ChemID Plus
  - ToxNet
  - DSSTox
  - CPDB

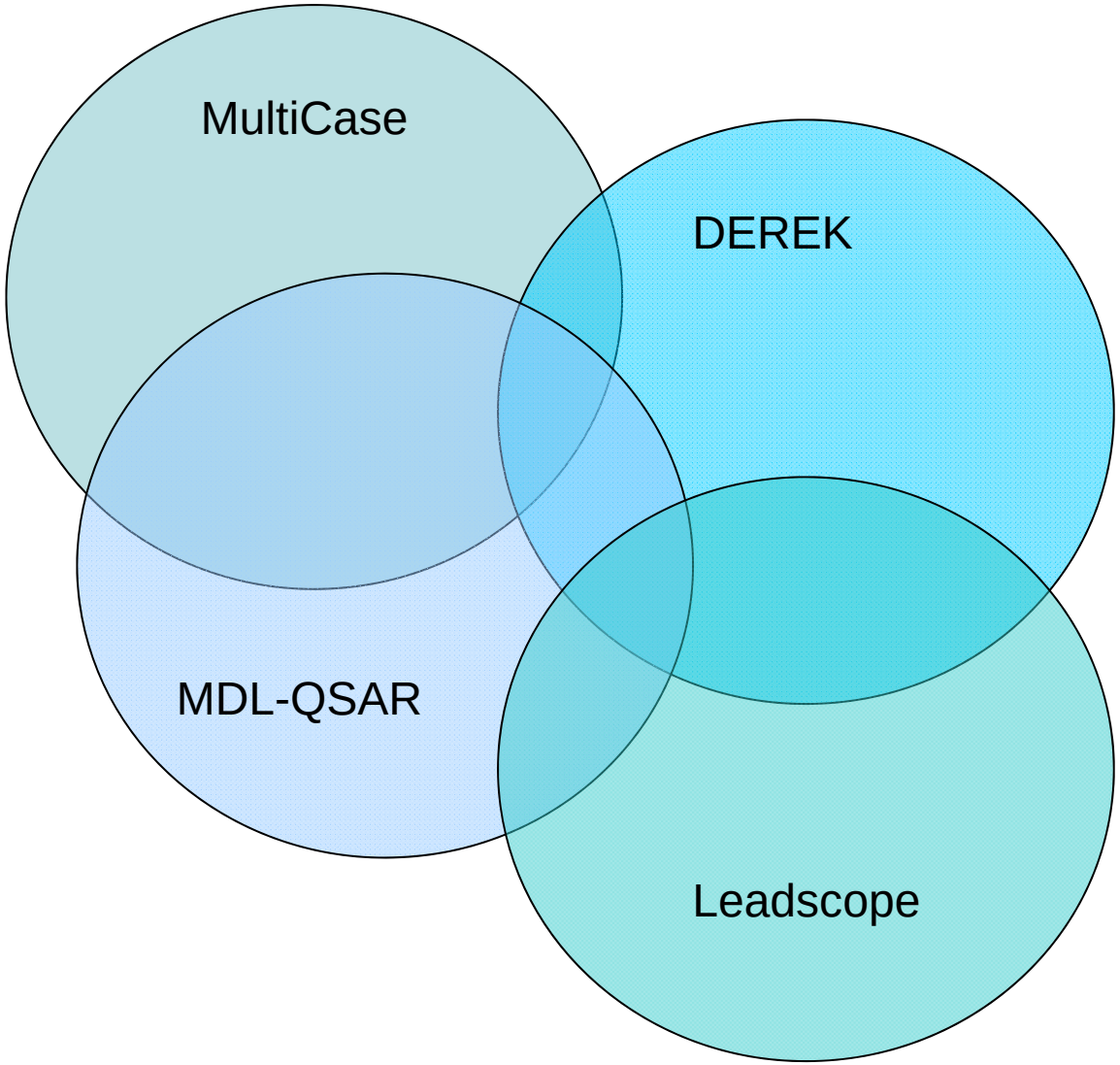
(Q)SAR Software

- Software currently used
  - ToxTree (EC-Joint Research Centre)
  - OncoLogic (EPA)
  - Derek for Windows (Lhasa, LTD)
  - MC4PC (MultiCase)
  - MDL QSAR
  - Leadscope Model Applier (Leadscope, Inc.)
- New software under evaluation
  - Advanced Chemistry Development Labs Suite (ACD)
  - BioEpisteme (Prous Institute)
  - SciQSAR (Scimatics)
  - ADMET Predictor, GastroPlus MedChem (Simulations Plus)

Why Multiple Software Packages?

- Software packages evaluate chemicals from a different perspective
  - MC4PC evaluates 2-10 atom fragments
  - Leadscope evaluates “fingerprints,” molecular properties
  - MDL QSAR evaluate whole molecule properties (electro-topographical descriptors, alogP values etc)
  - DEREK evaluates for alerting features
- Increases chemical space/domain of applicability
  - One model fails; others may be applicable
- Consensus predictions

Domain of Applicability (Chemical Space)



Handling multiple QSAR predictions

- Types of predictions
  - Consensus prediction
    - Call overall result positive or negative only if all or majority of the software programs give a positive or negative prediction
  - Modified Consensus

Handling multiple QSAR predictions

Software	Consensus predictions		
DEREK for Windows	Alert	No alert	Alert
Leadscope	+	-	Eqv
MC4PC	+	-	-
MDL-QSAR	+	-	NA
Oncologic	No Alert	No alert	NA
Overall prediction	+	-	No call

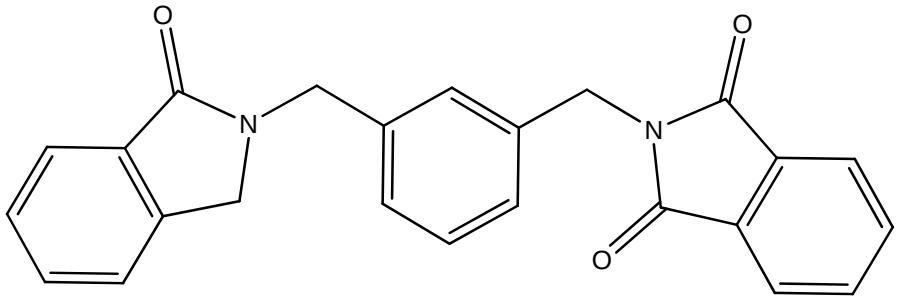
Software	Modified Consensus Predictions		
DEREK for Windows	Alert	No alert	Alert
Leadscope	+	-	Eqv
MC4PC	+	-	-
MDL-QSAR	+	-	NA
Oncologic	No Alert	No alert	NA
Overall prediction	+	-	+

Handling multiple QSAR predictions

- Framework dependent
  - Drug screening at the development stage
  - Regulatory safety evaluation
- Conservative approach
  - One positive may trigger additional levels of action
    - Structure analogs
    - Additional toxicity testing

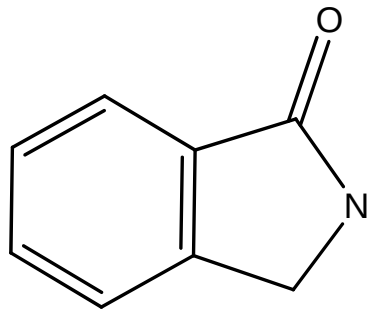
(Q)SAR Case Study

- Impurity in oxygen scavenger
- Low exposure
  - Impurity < 0.6 μg/p/d
  - Suspected potential developmental toxicity
  - No developmental data available

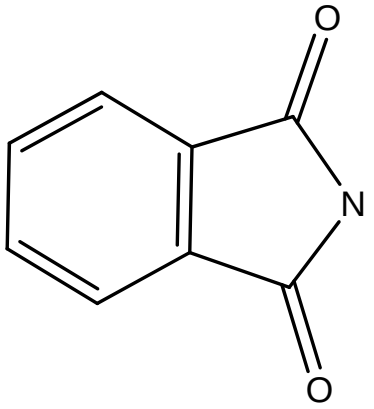


(Q)SAR Case Study

- Structure Analog
  - Structure similarity search
    - Leadscope Enterprise
    - ChemID- Plus
    - no analogs
  - Substructure search on
    - isoindol-1-one
    - phthalimide
    - to identify additional safety data



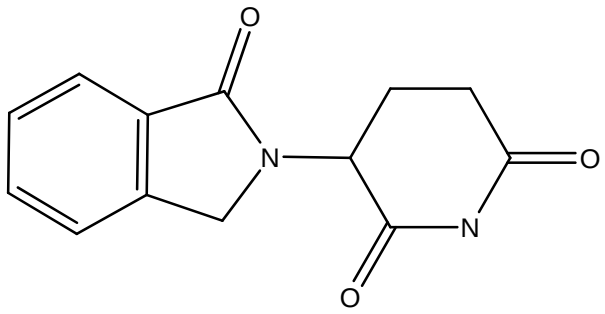
2,3-Dihydro-1H-isoindol-1-one



Phthalimide

(Q)SAR Case Study

- Substructure search identified numerous chemicals containing the phthalimide and isoindol-1-one substructure
- Literature contains mixed results on the teratogenicity of related query compounds from highly potent to inactive



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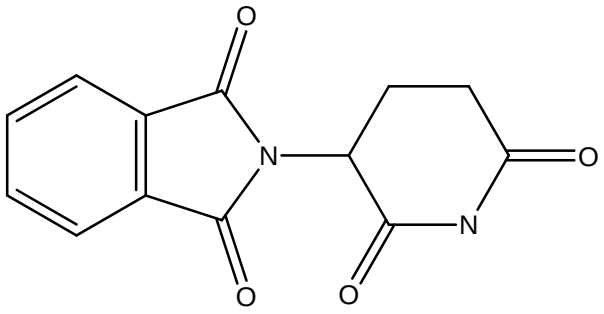


Thalidomide

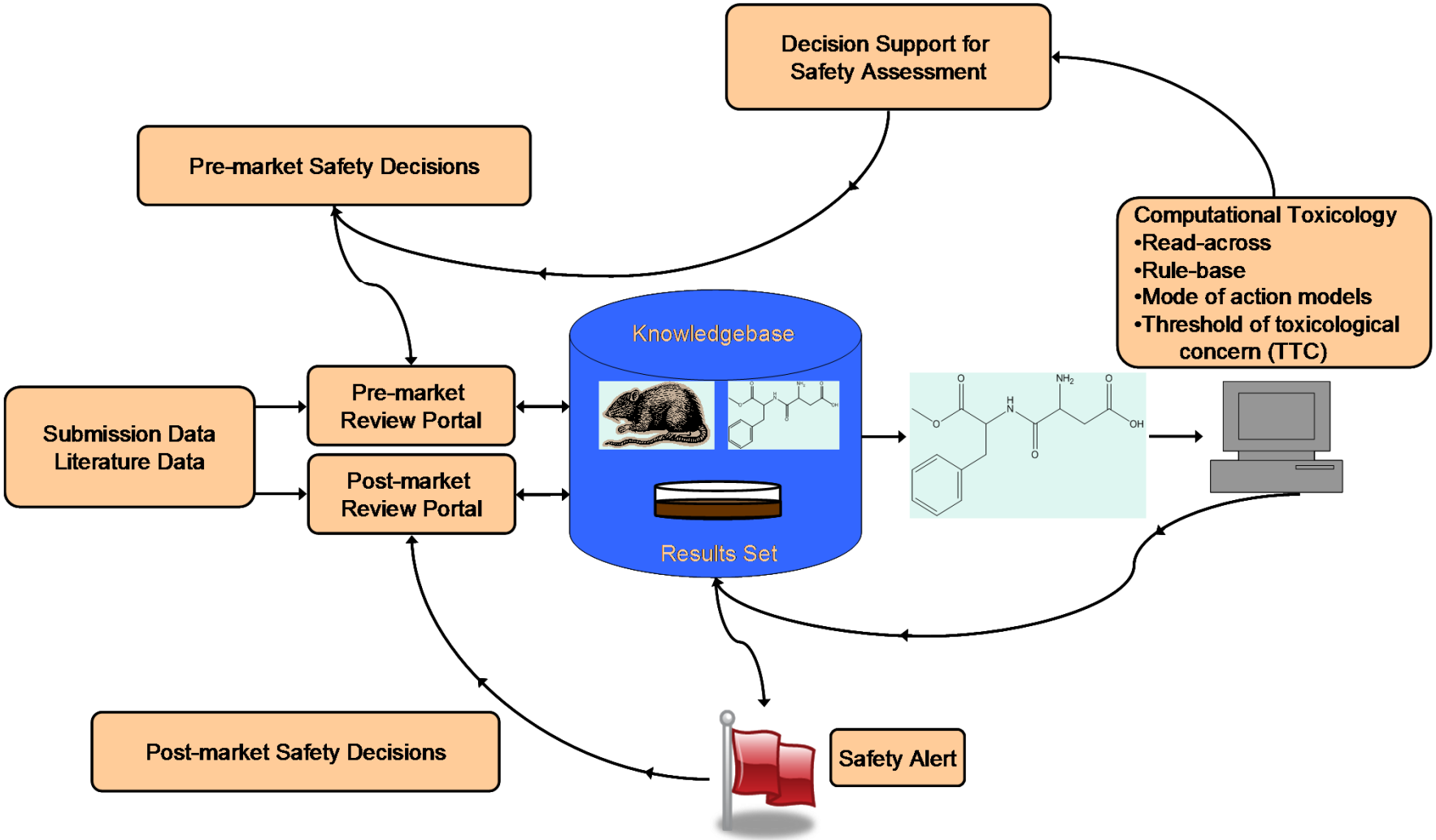
(Q)SAR Case Study

- (Q)SAR results inconclusive on safety of materials
- Recommendation:
  - Teratogenicity study with most sensitive species (Himalayan rabbit, 20 does/group, full scale macro- and microscopic examinations)
- Results
  - No treatment-related effects found in study

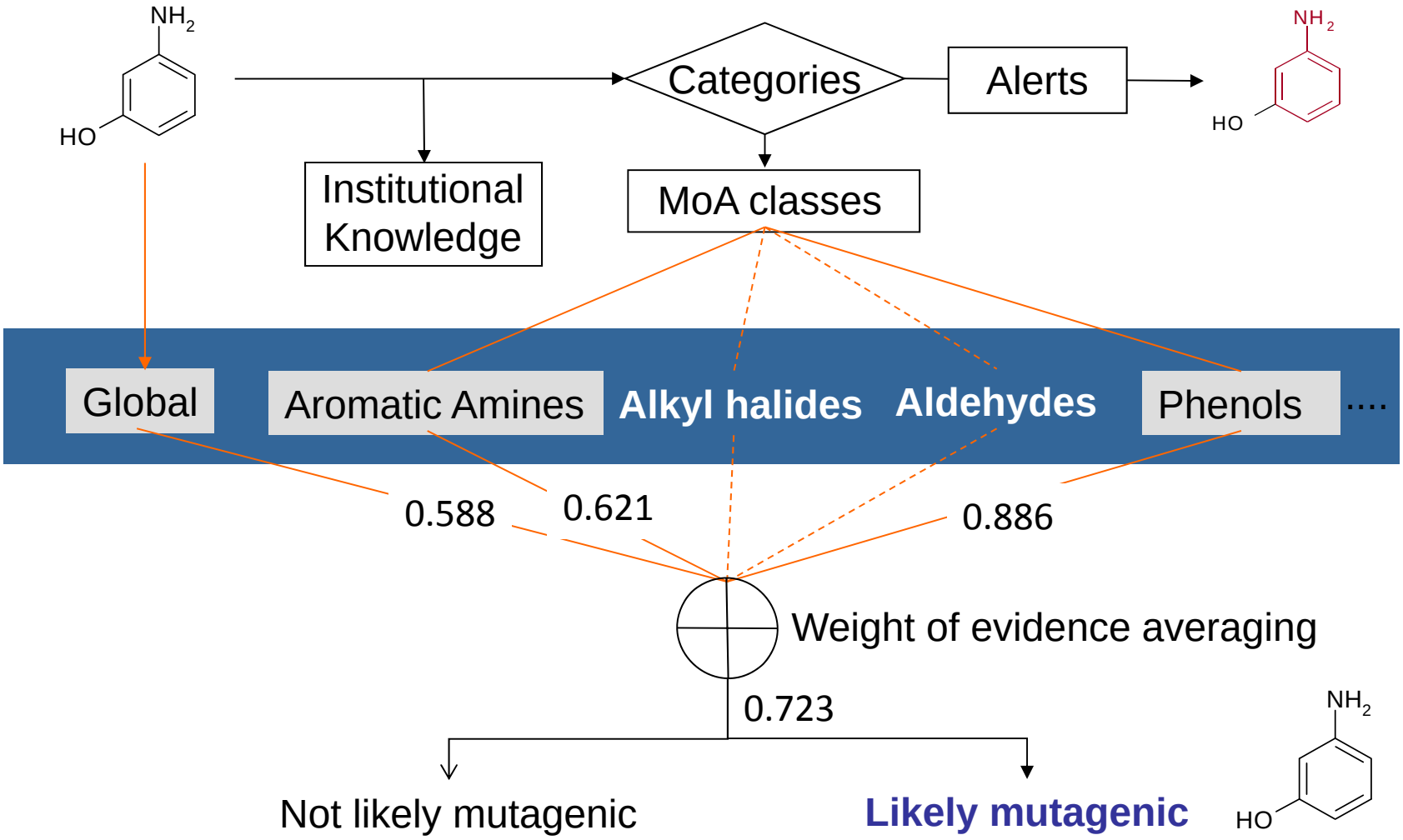
Future *in silico* Tools

- Decrease reliance on institutional knowledge
- Chemical Evaluation and Risk Estimation System (CERES)
  - Food additives knowledge base
    - Captures institutional knowledge
    - Chemical centric
    - Structured data/controlled vocabulary
  - Desktop access to:
    - Internal and external chemical and toxicity data
    - Structure analog searching and data retrieval
    - QSAR Models
    - Threshold of Toxicological Concern evaluations

CERES Workflow



Weight of evidence and mode of action models



Conclusion

- Hazard Identification tool
  - Evaluate FDA recommended endpoints
    - Identify data gaps in PNC toxicity data
    - Provide specific toxicity testing recommendations
- Decision support tool
  - Multiple (Q)SAR and database tools used
  - Fill gaps in toxicity data
  - Weight of evidence approach
- Not black box
  - Models are run and predictions evaluated by SAR Team

Conclusion

- Conservative approach, one positive may trigger additional levels of action
  - Structure analogs
  - Additional toxicity testing
- CERES
  - Improve Pre- and Post-Market Review
    - Consolidates information on chemical structure, physical properties and toxicity data to allow for more robust safety analysis
  - Relate new and existing data in new ways
    - Provide molecular level mechanistic insights that eventually help us understand ***human effects***
    - Metabolism knowledge will also be incorporated.

References

- Kirk B. Arvidson, Ronald Chanderbhan, Kristi Muldoon-Jacobs, Julie Mayer and Adejoke Ogungbesan “Regulatory use of computational toxicology tools and databases at the United States Food and Drug Administration's Office of Food Additive Safety” Expert Opinion on Drug Metabolism & Toxicology, 2010, 6(7), 793.
- Rene E. Sotomayer, Kirk Arvidson, Julie Mayer, Andrew McDougal, Chingju Sheu “Assessing the Safety of Food Contact Substances” *Food Safety Magazine*, **2007**.
- Bailey, et al. (2005) Reg. Toxicol Pharmacol 42: 225-235
- Cramer GM, Ford RA, Hall RL (1978) Estimation of toxic hazard – a decision tree approach. *Food Cosmet Toxicol* **16**: 255–76.
- Ashby J, Tennant RW (1991) Definitive relationships among chemical structure, carcinogenicity and mutagenicity for 301 chemicals tested by the US NTP. *Mut Res* **257**: 229–306.