Drivers for the Application and Acceptance of *In Silico* Safety Assessment Based on Chemical Exposure

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Conflict of Interest Statement

- No conflicts of interest to declare
In Silico Safety Assessment—What and Why

• Ensuring the safety of the consumer and environment to chemical exposure... without being able to obtain further “traditional” data

• Applying computational (in silico) models to assist in the safety assessment
  − Using existing information
  − Predicting new information from chemical structure alone

• Desire for better, more relevant and rapid safety assessment
Assessing Safety Needs Knowledge of Exposure: Types of Models and Information Needs

Exposure
- Amount
- Frequency
- Route

ADME
- Absorption
- Distribution
- Clearance

PBPK
- Organ
- Tissue
- Cellular

Products and Use
- Physico-Chemical
- Pharmacokinetic
Exposure and Use

• A variety of models and databases are available
  − Product use and individual exposure estimates
  − See: Madden et al (2019); Pawar et al (2019)

• Safety decisions can be made using Threshold of Toxicological Concern (TTC) if exposure known
  − Currently based on oral NOEL values → internal exposure

With thanks to Dr. Corie Ellison (P&G)
“Rules of thumb” often used, e.g., for uptake, membrane permeability, etc.  
- Usually related to cut-offs based on molecular properties  
- e.g., Lipinski Rule of Five  

Quantitative Structure-Activity Relationships (QSARs) are a statistical model between an ADME property and physico-chemical properties and/or structural descriptors of a series of molecules  
- Predictions directly from chemical structure  
- Many applications for ADME and physico-chemical properties  
- Software available  
Physiologically-Based Kinetic (PBK / **PBPK** / PBBK/ PBTK) models

Predicting Concentration at Organ and Tissue Level


With thanks to Dr. Annie Lumen (FDA)
Key Drivers for *In Silico* Based Models of Exposure

- Regulation
- Animal Free
- New Opportunities
- Better Science
- Public Image
Key Driver 1: Safety

• Ultimate driver is to ensure (reasonable) exposure to all products is safe
• Acceptable and appropriate margins of safety
• Businesses have an ethical and commercial responsibility for safety
• Relevant to humans and environmental species
• Desire to assess safety on the basis of realistic exposure estimates
Key Driver 2: Regulation

- Compliance is required
  - Although most legislation is focused on hazard
- Regulation through legislation
  - Food safety
    - General Food Law Regulation (EC) No 178/2002
  - Cosmetics
    - Cosmetics Regulation (EC) No 1223/2009
  - Moves to implement 3Rs
    - EU Directive 2010/63/EU on the protection of animals used for scientific purposes
Key Driver 2: Regulation

- There is a desire to move chemical regulation to be more inclusive of exposure-based decisions
- EU REACH: Exposure-Based Adaptation
  - exposure is absent or not significant (Annex XI, VIII) or unlikely (Annex IX)
  - strictly controlled conditions apply for the whole life cycle (Annex XI)
  - substances incorporated into an article so that the substance is not released during the whole life cycle and that the likelihood of exposure of man or the environment is negligible (Annex XI)
- Increased acknowledgement of techniques such as the Threshold of Toxicological Concern (TTC)
Key Driver 3: Animal-Free Testing

- Traditional means of obtaining data may not be possible or viable
  - Hazard identification by traditional animal testing may be inappropriate
- Time
  - Rapid decisions on safety may be required
  - Emergency decisions e.g., food contamination
- Legislation
  - Cosmetics

**Exposure**: Evidence?

**Hazard Identification**: In Silico Screening, Genotoxicity, TD50 or NOAEL Prediction

**Hazard Characterisation**

**Risk Characterisation**

**Decision**

Adapted from Schilter et al (2014)
Key Driver 3: Animal-Free Testing

- *In silico* methods for hazard identification e.g., for cosmetics
- Use of structure-based knowledge

- Including: ToxTree, Derek Nexus and others

- Ames +ve

- Structural Alert: Aromatic Amine

- Compilations of Alerts

- *In Silico* Toxicity Software

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety
Key Driver 3: Animal-Free Testing

- Use of QSARs
  - Many approaches from simple to complex

  - Including: VEGA, ChemTunes (hybrid), and others

  ![Graphs of Toxicity vs. Property and Property 1 vs. Property 2 with SVM, Neural Networks, etc.]

- Including: VEGA, ChemTunes (hybrid), and others
Key Driver 3: Animal-Free Testing

• Use of grouping and read-across

• Including: OECD QSAR Toolbox and others
Key Driver 3: Animal-Free Testing

- Tiered decision tree approach for extrapolating oral TTC to dermal exposure
- Applies *in silico* models for e.g., calculation of skin permeability
- Described in Williams et al (2016)
Key Driver 3: Animal-Free Testing

- Practicality
  - Assessment of large number of compounds or products
  - REACH found many chemicals with insufficient data
- Better use of resources e.g., big data

Taken from ECHA (2017)
Key Driver 3: Animal-Free Testing

- Many *in silico* tools to assist with the application of Thresholds for Toxicological Concern (TTC)
  - Cohort of Concern e.g., ChemoTyper
  - DNA reactivity e.g., ToxTree, VEGA, OECD QSAR Toolbox
  - TTC Workflow e.g., COSMOS NG
- Move towards internal TTC
Key Driver 3: Animal-Free Testing

- *In silico* implementation of Cramer classification: COSMOS NG

With permission from:
Key Driver 3: Animal-Free Testing

• TTC Workflow: COSMOS NG
Key Driver 4: Better Science

• Better use of existing information and models
  - The National Health and Nutrition Examination Survey (NHANES)
  - US EPA Chemical and Products Database (CPDat)
  - US EPA ExpoCast

• Increased availability of data resources to support exposure-based decisions
  - Dissemination
  - Education

• Making better use of models e.g., integration of *in vitro* data
Key Driver 4: Better Science

• Need to determine internal exposures
  – To support all parts of the risk management process
• More relevant to realistic exposures to humans
• Increase relevance and accuracy
  – Children, elderly, pregnant
Key Driver 4: Better Science

• Supporting read-across through better application and understanding of toxicokinetics
  − Often has been overlooked
  − See Laroche et al (2018)
• Better *in silico* techniques
  − From fundamental science to personalised safety
• Better, more sophisticated, more complex modelling approaches
  − Allowing for mechanistic and multilevel models of compound distribution
• Opportunities to use new methodologies
  − Better, more accessible, platforms for e.g., PBPK
Key Driver 4: Better Science

• Move from single substance/single exposure to cumulative exposure
  − Creme RIFM™ model for aggregate systemic and dermal exposure assessment for fragrance compounds

• Product use and exposure modelling
  − Improved models for PK prediction
  − Integration ADME → PBPK → Mechanistic Model

• As part of an Integrated Approach to Testing and Assessment (IATA)
Key Driver 5: New Opportunities

• Cooperation in a global marketplace
  − Consistency/reproducibility
  − Integration of international standards

• Increasing acceptance of exposure-based decision making

• New ways of performing safety assessment
  − Next Generation Risk Assessment (for cosmetics see Dent et al, 2018)
Key Driver 5: New Opportunities

A strategy for tiered safety assessment


With thanks to Dr. Corie Ellison (P&G)
Key Driver 5: New Opportunities

- Opportunities for new safety assessment paradigms
- Mode of Action ontology (Desprez et al. (2019))

New challenges:
- Botanicals, food contact materials, nanoparticles, microplastics, etc.
- New exposure scenarios
Key Driver 5: New Opportunities

- Better ways of understanding and dealing with uncertainty
  - Dempster-Shafer Theory
- Following the innovations
  - Artificial Intelligence
  - Machine Learning
  - Virtual humans and medicine
Key Driver 6: Improving Public Image

• Pubically available models to demonstrate how compounds are distributed and cleared *in vivo*
• Models for exposure could help explain how we perform safety science of everyday products
• Allow for openness and transparency
Key Driver 6: Improving Public Image

• Demonstrate values shown by industry and regulators
  − The consumer and environment at the heart of all decisions
  − Using better, animal-free, science

• Use as educational tools
  − From schools to PhDs
  − Students can learn about exposure to substances
  − Increase understanding of toxicological principles, safety science, etc.
Conclusions

- Many *in silico* models used for exposure assessment
- Many applications of *in silico* models
- There is a desire to improve models to support safety assessment
- Acceptance may be achieved through demonstration of good use e.g., as part of tiered frameworks
Freely Available Web Resources

- Chemotyper: https://chemotyper.org
- COSMOS NG: http://www.ng.cosmosdb.eu/
- Creme RIFM™: https://www.cremeglobal.com/products/creme-rifm/
- OECD QSAR Toolbox: https://qsartoolbox.org/
- ToxTree: http://toxtree.sourceforge.net/
- US EPA Rapid Chemical Exposure and Dose Research
  https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research
- US EPA Chemical and Products Database (CPDat)
  https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat
- VEGA: https://www.vegahub.eu/portfolio-item/vega-qsar/
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