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

Mark Cronin and Judith Madden

Liverpool John Moores University, Liverpool, UK

Email: m.t.cronin@ljmu.ac.uk

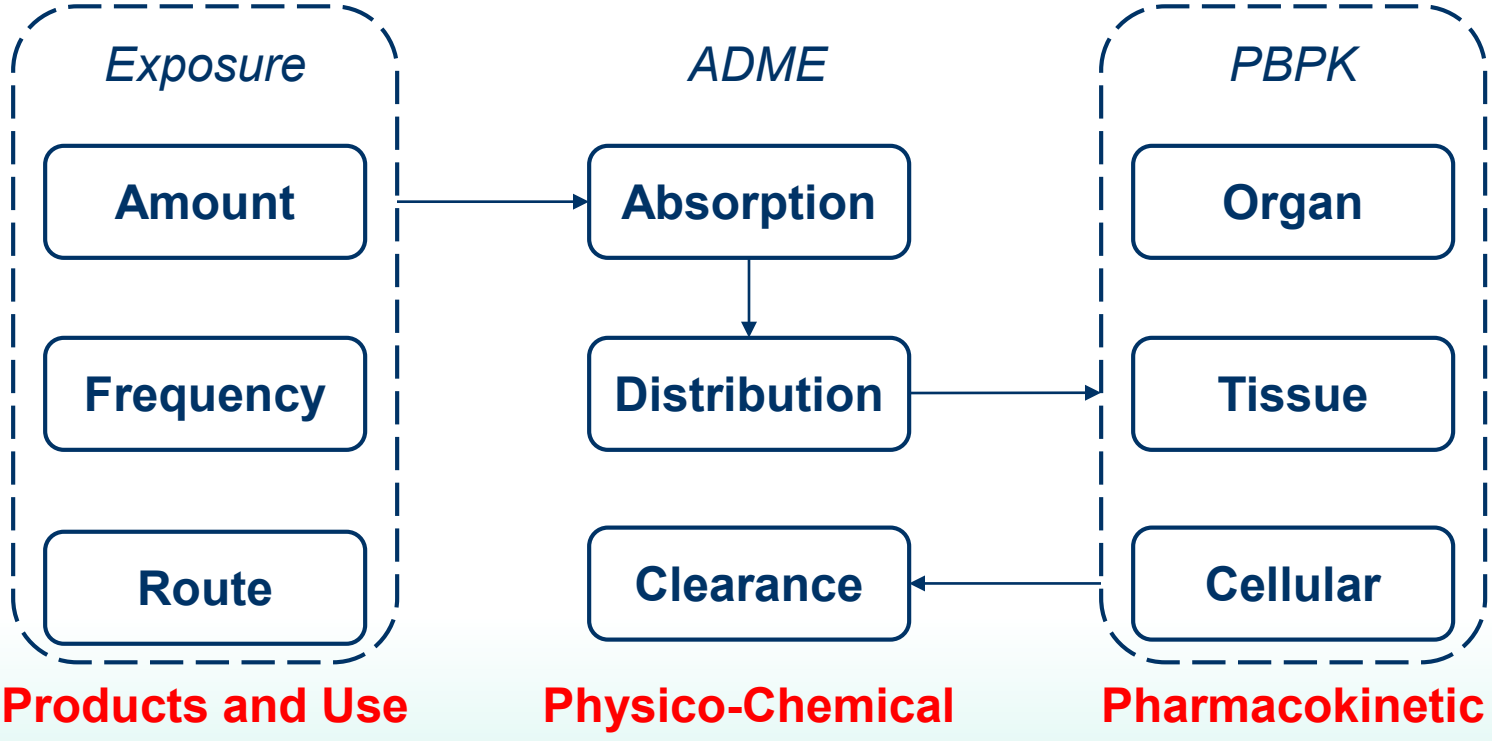
Conflict of Interest Statement

- No conflicts of interest to declare

In Silico Safety Assessment–What and Why

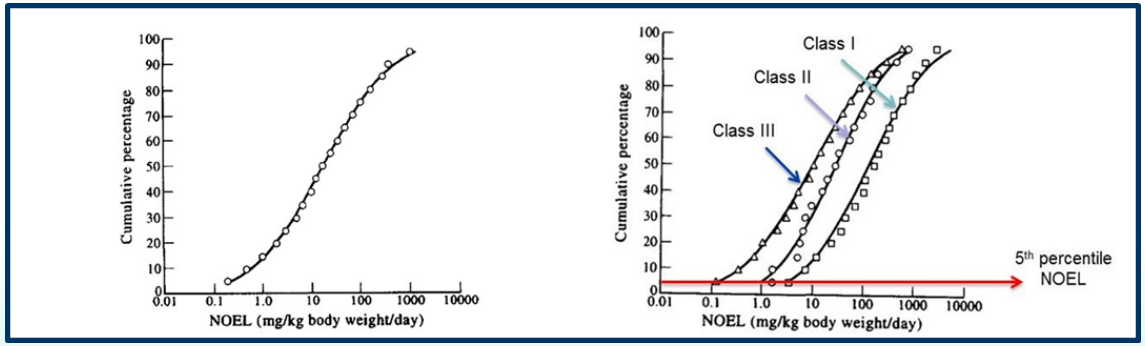
- Ensuring the safety of the consumer and environment to chemical exposure… without being able to obtain further “traditional” data
- Applying computational (*in silico*) models to assist in the safety assessment
  - Using existing information
  - Predicting new information from chemical structure alone
- Desire for better, more relevant and rapid safety assessment

Assessing Safety Needs Knowledge of Exposure: Types of Models and Information Needs



Exposure and Use

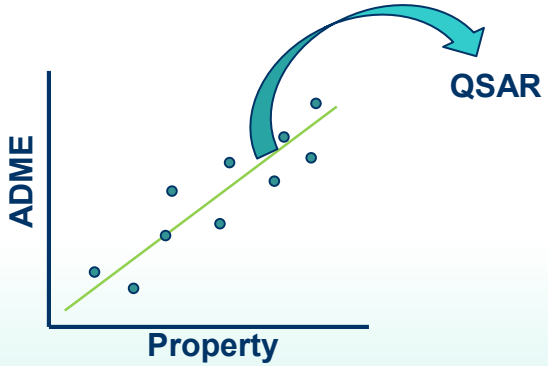
- A variety of models and databases are available
  - Product use and individual exposure estimates
  - See: Madden et al (2019); Pawar et al (2019)
- Safety decisions can be made using Threshold of Toxicological Concern (TTC) if exposure known
  - Currently based on oral NOEL values → internal exposure



With thanks to Dr. Corie Ellison (P&G)

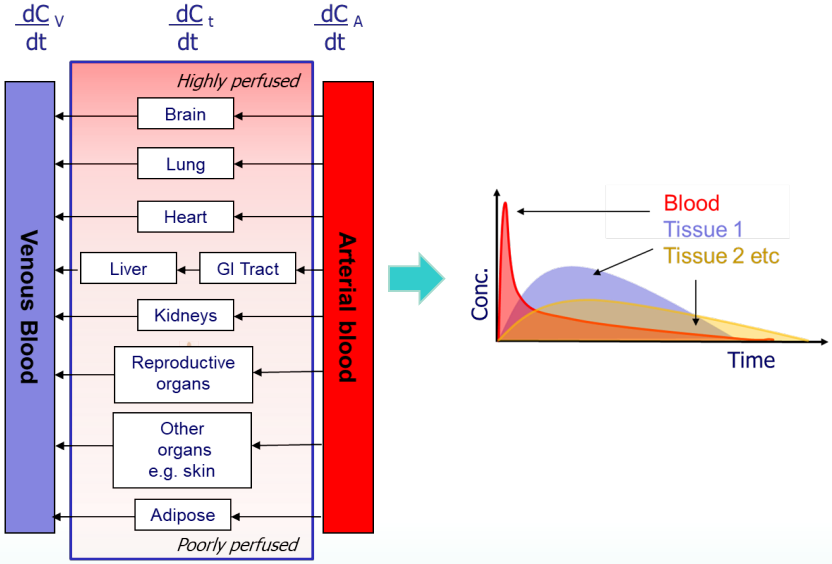
Predicting Absorption, Distribution, Metabolism, and Excretion (ADME) Properties

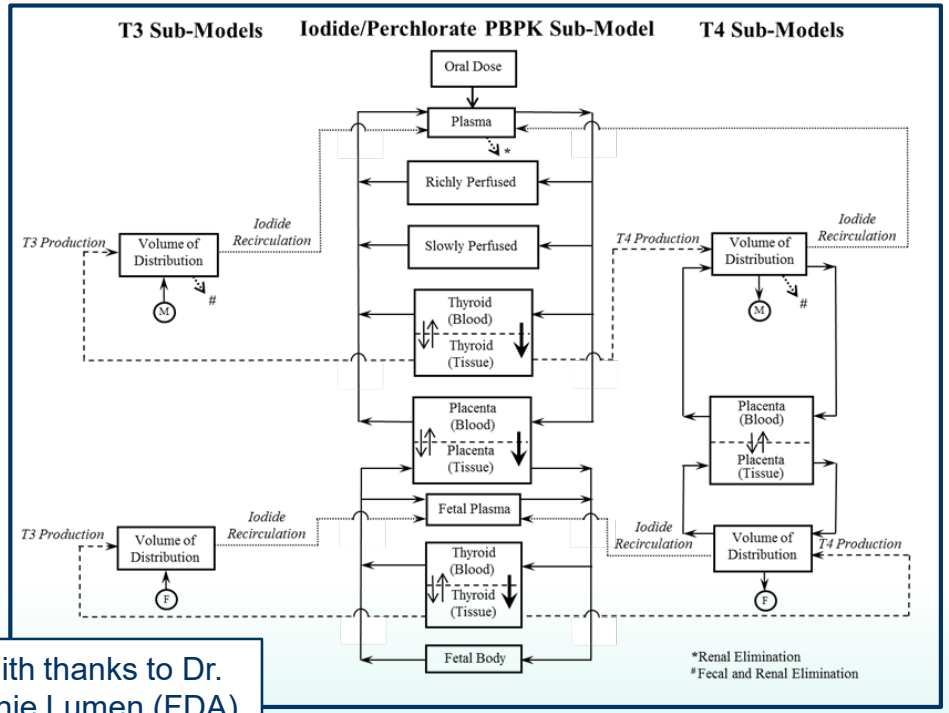
- "Rules of thumb" often used, e.g., for uptake, membrane permeability, etc.
  - Usually related to cut-offs based on molecular properties
  - e.g., Lipinski Rule of Five
- Quantitative Structure-Activity Relationships (QSARs) are a statistical model between an ADME property and physico-chemical properties and/or structural descriptors of a series of molecules
  - Predictions directly from chemical structure
  - Many applications for ADME and physico-chemical properties
  - Software available
  - Reviewed by Patel et al (2018)



Predicting Concentration at Organ and Tissue Level

- Physiologically-Based Kinetic (PBK / **PBPK** / PBBK/ PBTK) models

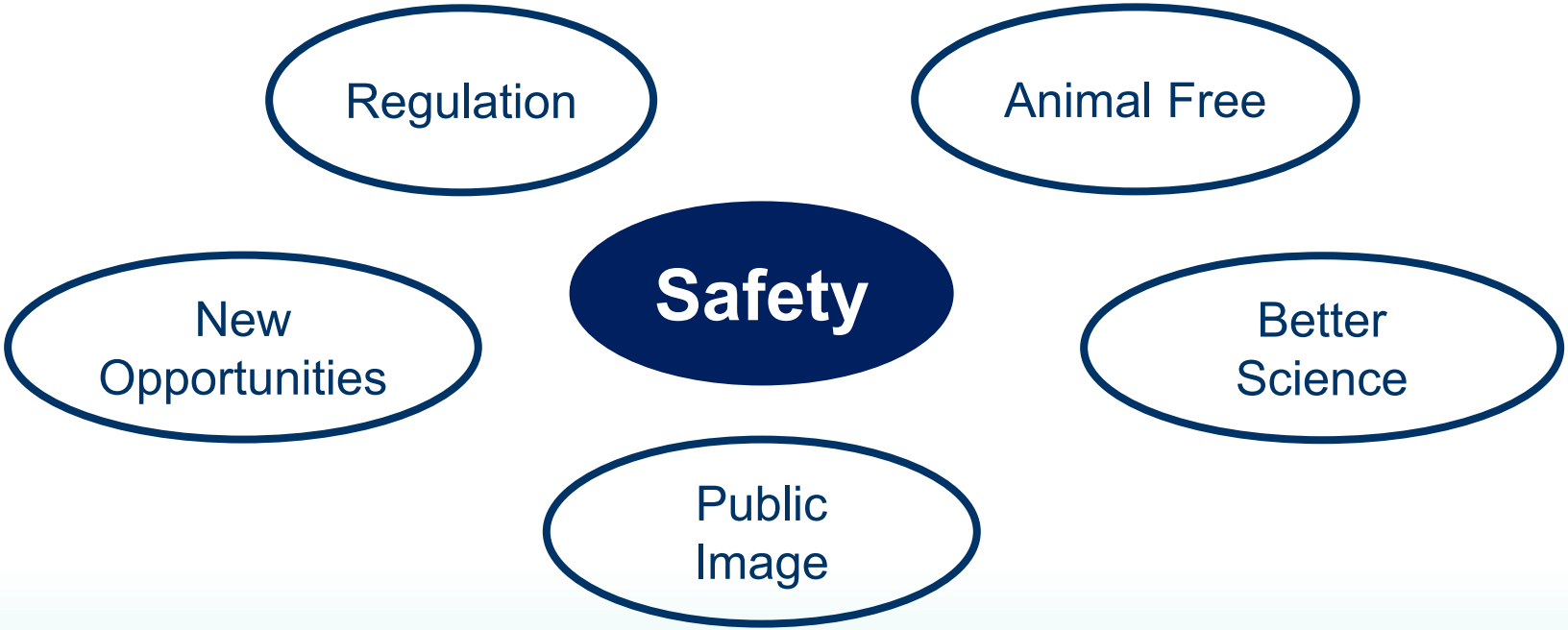




See: Paini et al (2017; 2019)

With thanks to Dr. Annie Lumen (FDA)

Key Drivers for *In Silico* Based Models of Exposure



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

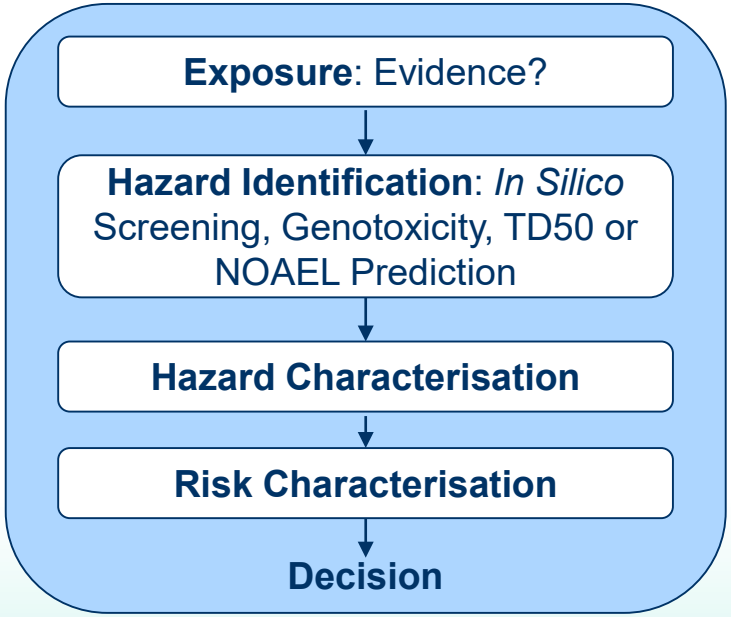
- Compliance is required
  - Although most legislation is focused on hazard
- Regulation through legislation
  - Food safety
    - General Food Law Regulation (EC) No 178/2002
  - Cosmetics
    - Cosmetics Regulation (EC) No 1223/2009
  - Moves to implement 3Rs
    - EU Directive 2010/63/EU on the protection 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

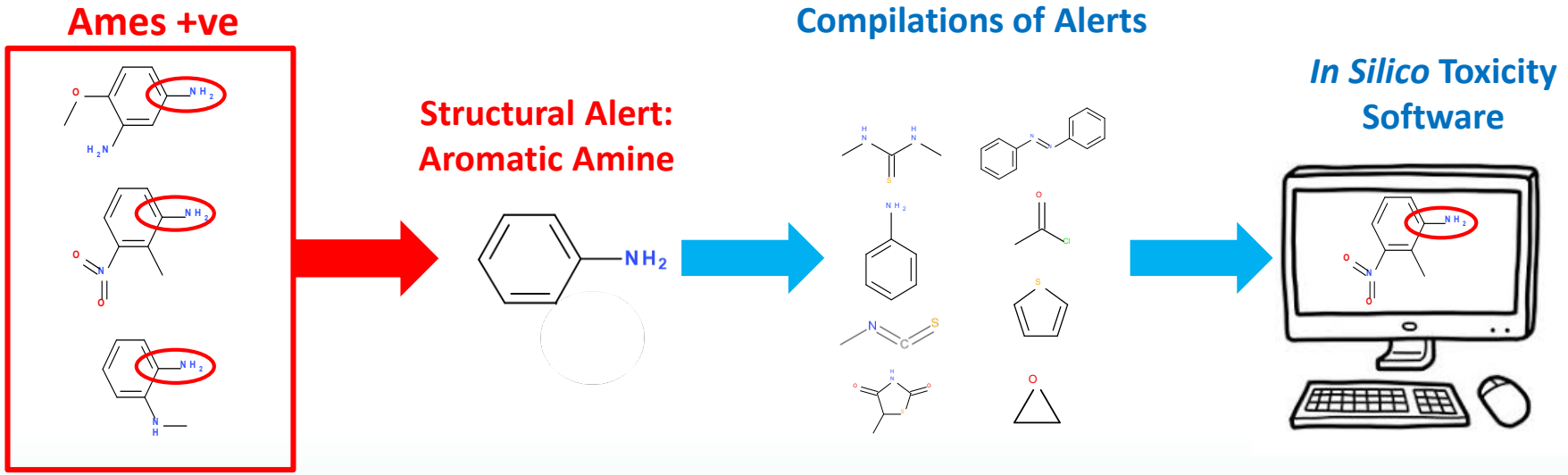


Decision Tree to Integrate Exposure of Toxicological Predictions

Adapted from Schilter et al (2014)

Key Driver 3: Animal-Free Testing

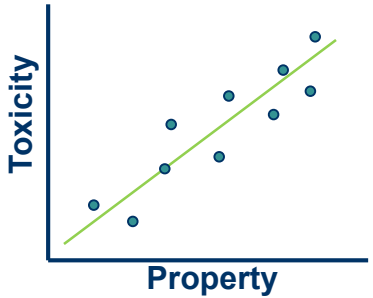
- *In silico* methods for hazard identification e.g., for cosmetics
- Use of structure-based knowledge



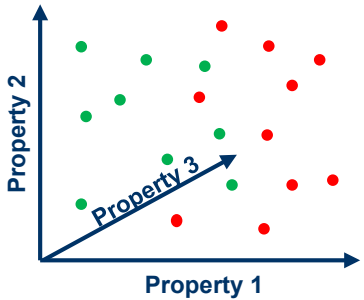
- Including: ToxTree, Derek Nexus *and others*

Key Driver 3: Animal-Free Testing

- Use of QSARs
  - Many approaches from simple to complex



Regression-based

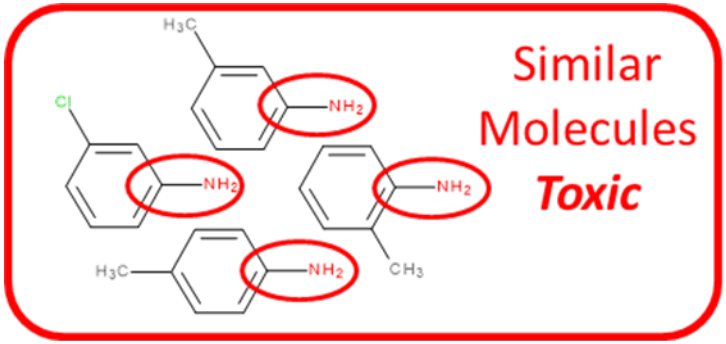


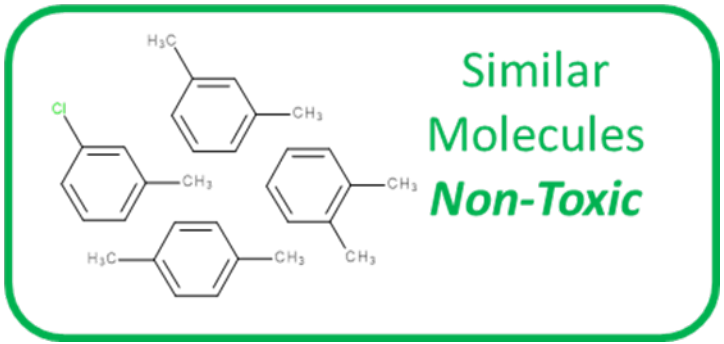
SVM, Neural Networks, etc.

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

Key Driver 3: Animal-Free Testing

- Use of grouping and read-across

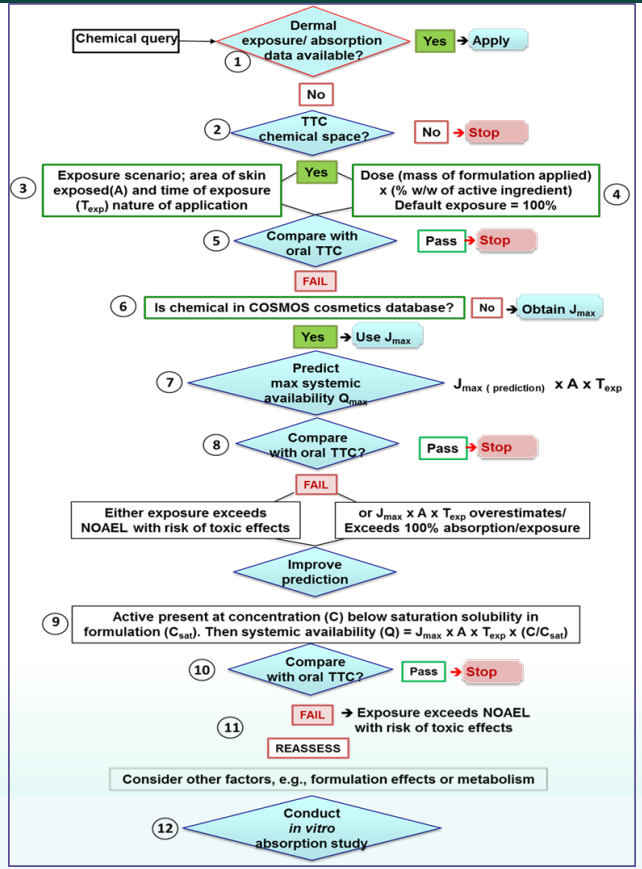




- Including: OECD QSAR Toolbox *and others*

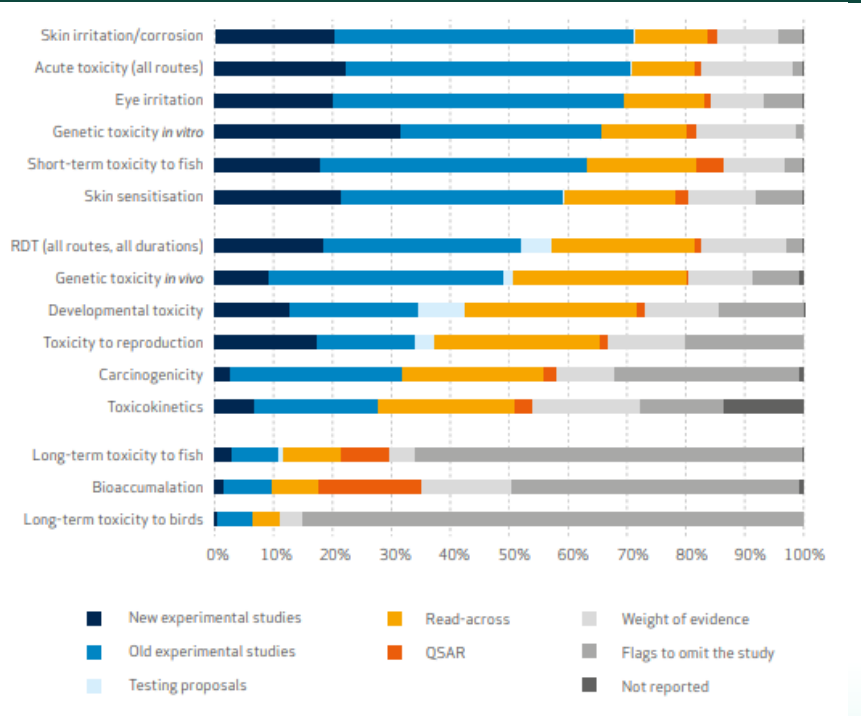
Key Driver 3: Animal-Free Testing

- 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



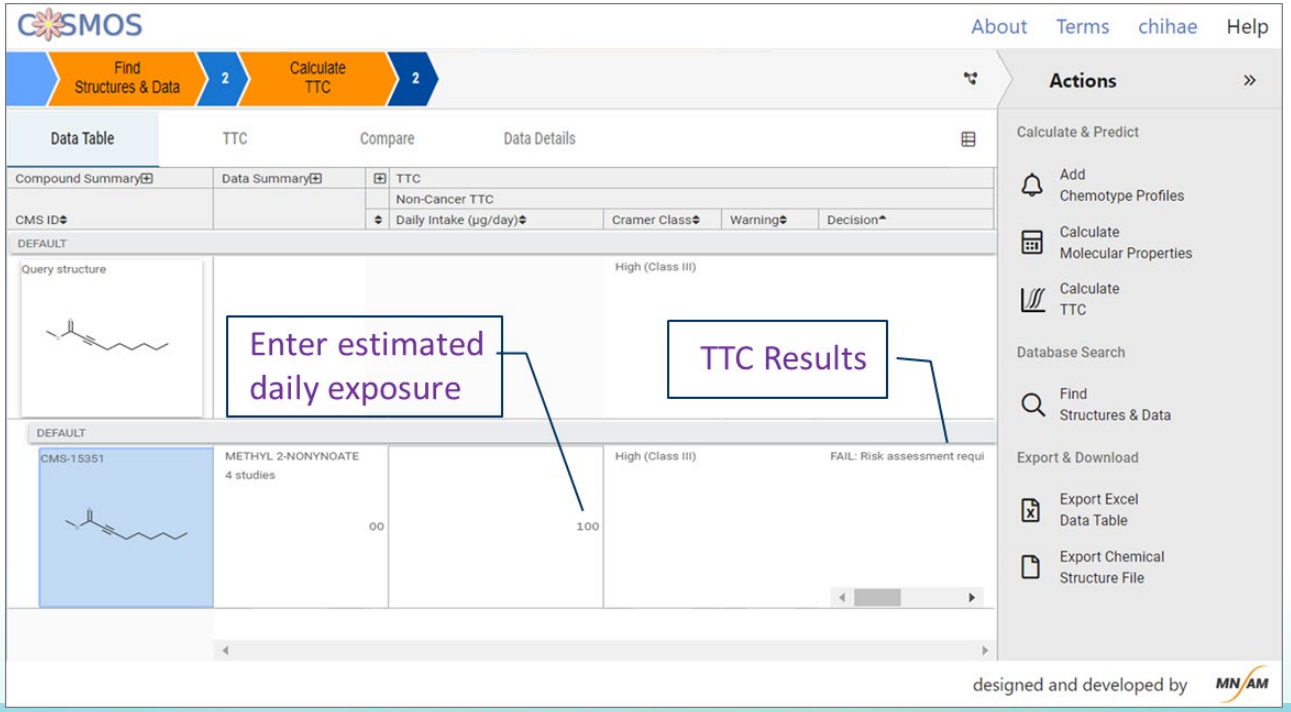
Taken from ECHA (2017)

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

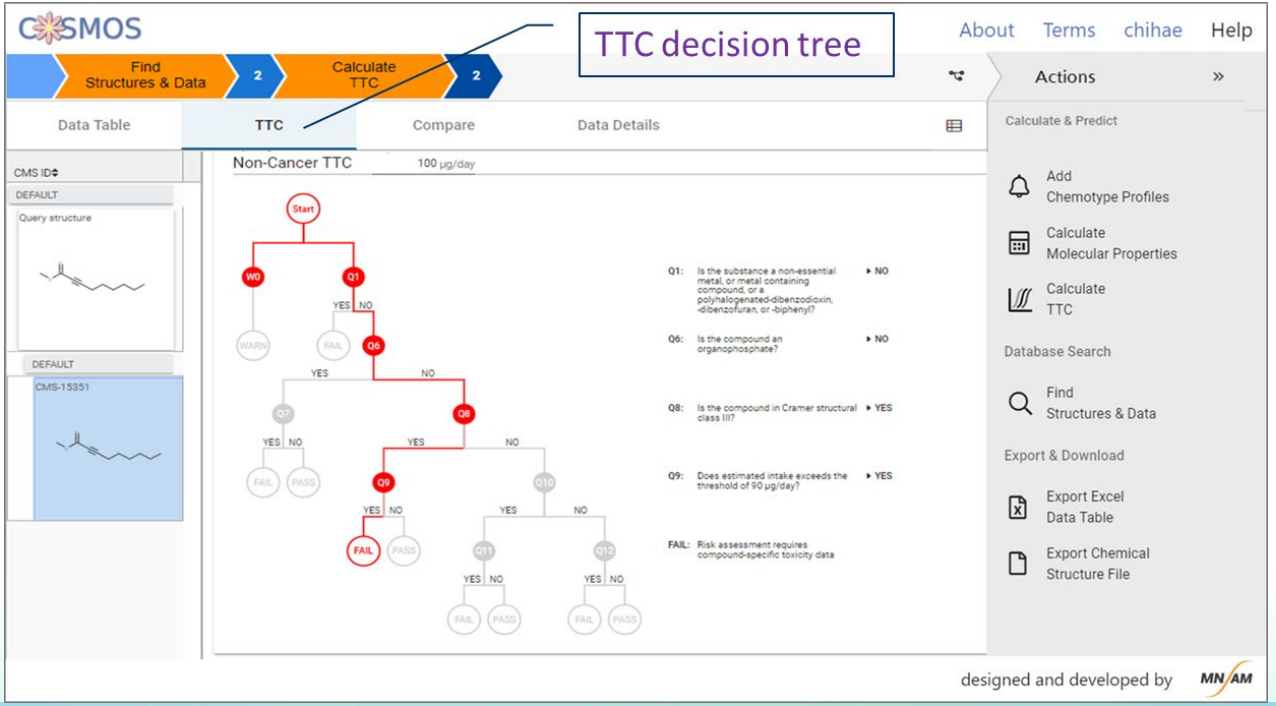


With permission from:

MN AM

Key Driver 3: Animal-Free Testing

- TTC Workflow: COSMOS NG



With permission from:

MN AM

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
  - Reviewed by Madden et al (2019); Pawar et al (2019); Przybylak et al (2018)
  - 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

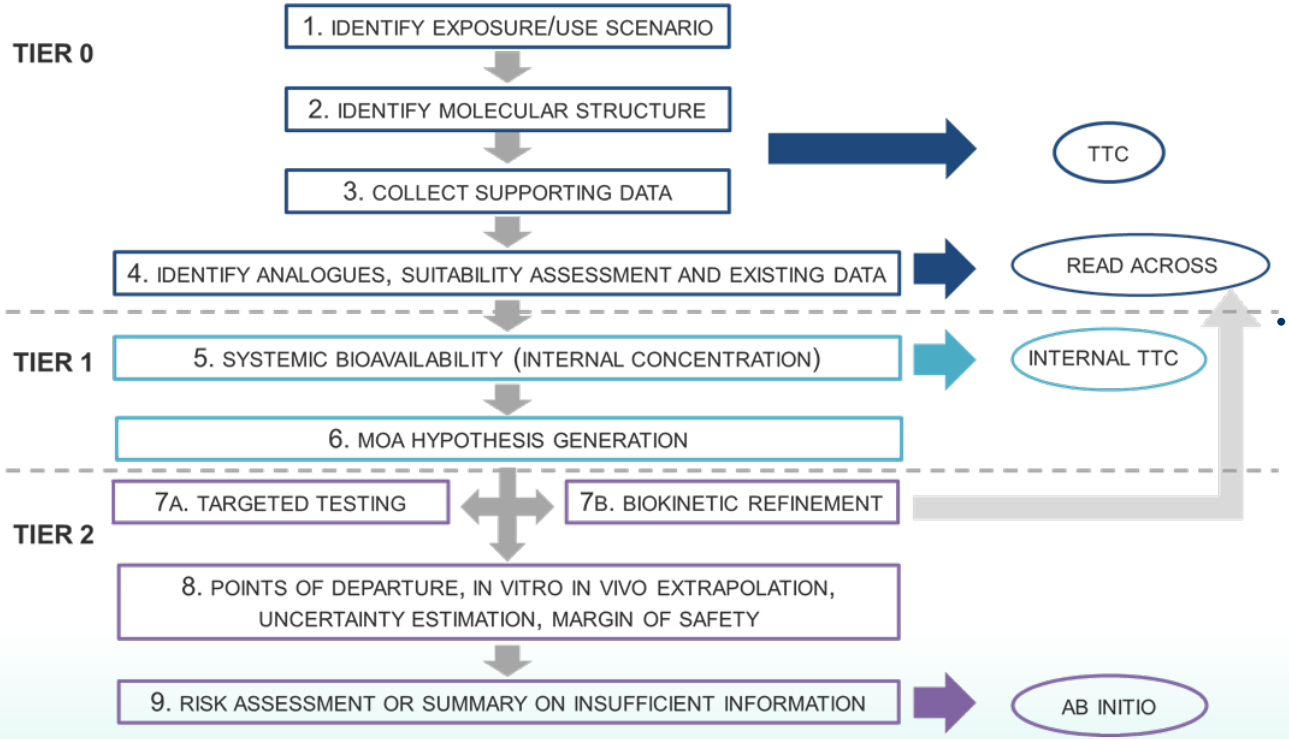
Key Driver 4: Better Science

- 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

- Berggren E et al (2017) *Computational Toxicology* 4: 31-44

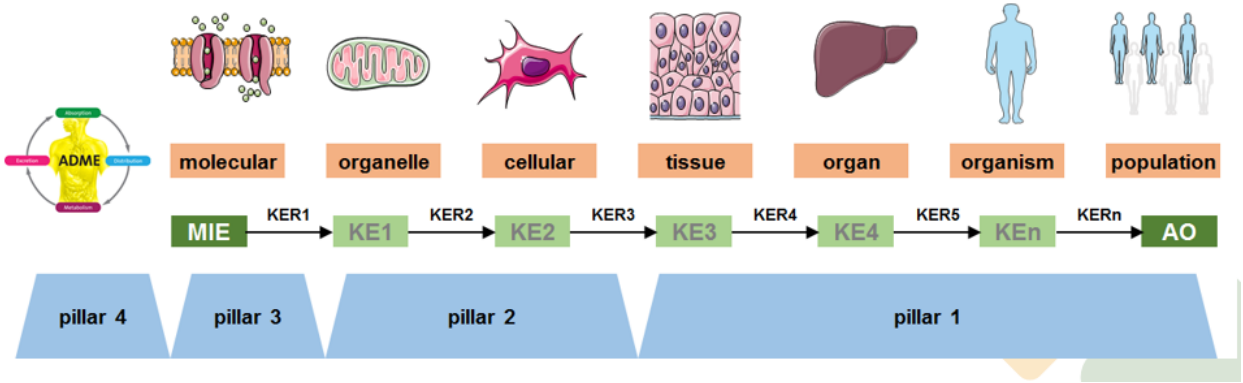
&

- OECD (2017) Series on Testing & Assessment. No. 275

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

- Publically 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/

References

- Berggren E et al (2017) *Ab initio* chemical safety assessment: A workflow based on exposure considerations and non-animal methods. *Computational Toxicology* 4: 31-44
- Dent M et al (2018) Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients. *Computational Toxicology* 7: 20-26
- Desprez B et al (2019) A mode-of-action ontology model for safety evaluation of chemicals: outcome of a series of workshops on repeated dose toxicity. *Toxicology in Vitro* 59: 44-50
- European Chemicals Agency (ECHA) (2017) The use of alternatives to testing on animals for the REACH Regulation. ECHA-17-R-02-EN. Available from: https://echa.europa.eu/documents/10162/13639/alternatives_test_animals_2017_en.pdf
- Laroche C et al (2018) Finding synergies for 3Rs – Toxicokinetics and read-across: Report from an EPAA partners' Forum. *Regulatory Toxicology and Pharmacology* 99: 5-21
- Madden JC et al (2019) *In silico* resources to assist in the development and evaluation of physiologically-based kinetic models. *Computational Toxicology* 11: 33-49
- OECD (2017) *Chemical Safety Assessment Workflow based on Exposure Considerations and Non-Animal Methods*. Series on Testing & Assessment. No. 275

References

- Paini A et al (2017) Investigating the state of physiologically based kinetic modelling practices and challenges associated with gaining regulatory acceptance of model applications. *Regulatory Toxicology and Pharmacology* 90: 104-115
- Paini A et al (2019) Next generation physiologically based kinetic (NG-PBK) models in support of regulatory decision making. *Computational Toxicology* 9: 61-72
- Patel M et al (2018) Assessment and reproducibility of Quantitative Structure–Activity Relationship models by the nonexpert. *Journal of Chemical Information and Modeling* 58: 673–682
- Pawar G et al (2019) *In silico t*oxicology data resources to support read-across and (Q)SAR. *Frontiers in Pharmacology* in press
- Przybylak KR et al (2018) Characterisation of data resources for *in silico* modelling: benchmark datasets for ADME properties. *Expert Opinion On Drug Metabolism and Toxicology* 14: 169-181
- Schilter B et al (2014) Establishing the level of safety concern for chemicals in food without the need for toxicity testing. *Regulatory Toxicology and Pharmacology* 68:275–296
- Williams FM et al (2016). Assessing the safety of cosmetic chemicals: Consideration of a flux decision tree to predict dermally delivered systemic dose for comparison with oral TTC (Threshold of Toxicological Concern). *Regulatory Toxicology and Pharmacology* 76: 174–186

Acknowledgements

- COSMOS Project - funding from the European Community's 7th Framework Program and Cosmetics Europe
- Cosmetics Europe CE-TOXGPS Project
- Cosmetics Europe Mode-of-Action Ontology Project
- The funding of the CEFIC LRI B18 Project