



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

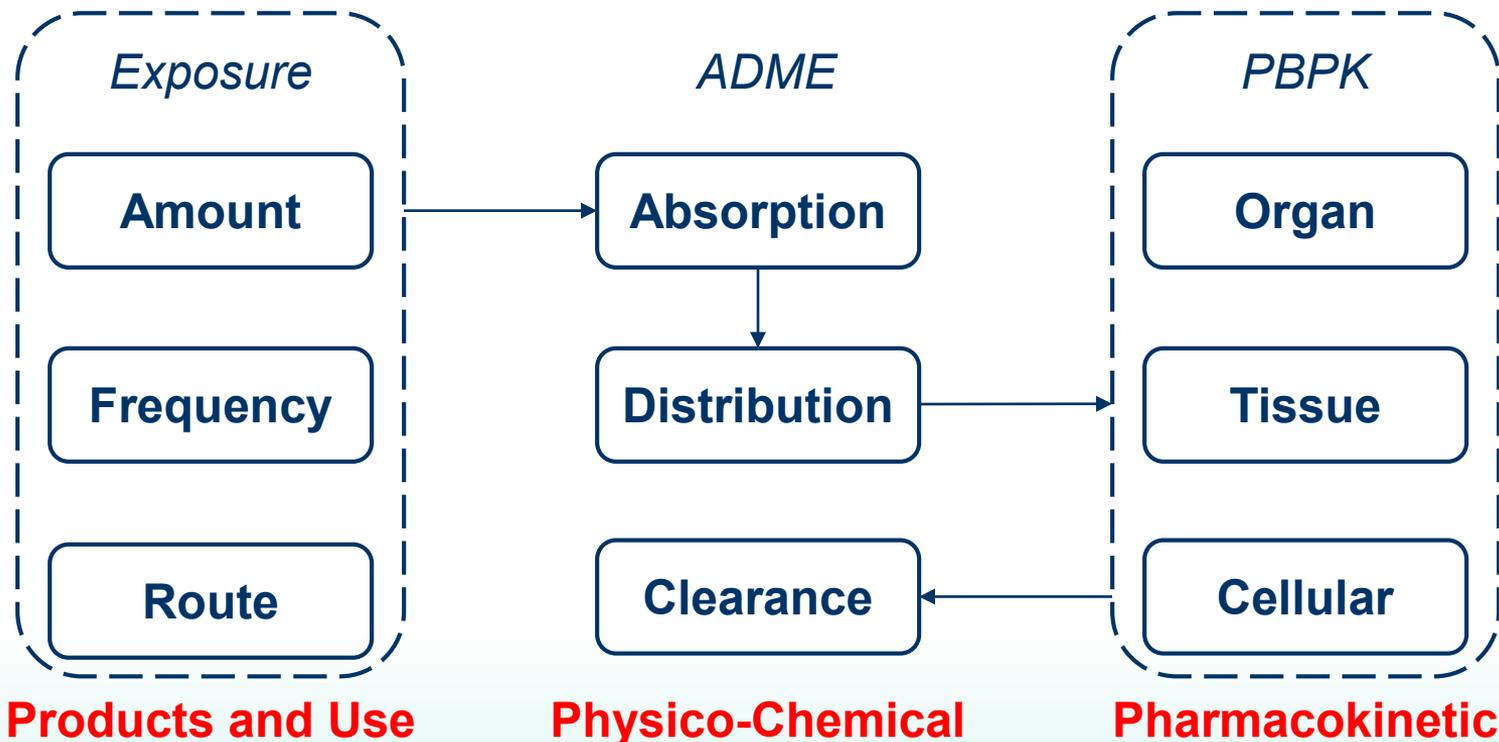


In Silico Safety Assessment—What and Why

- 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

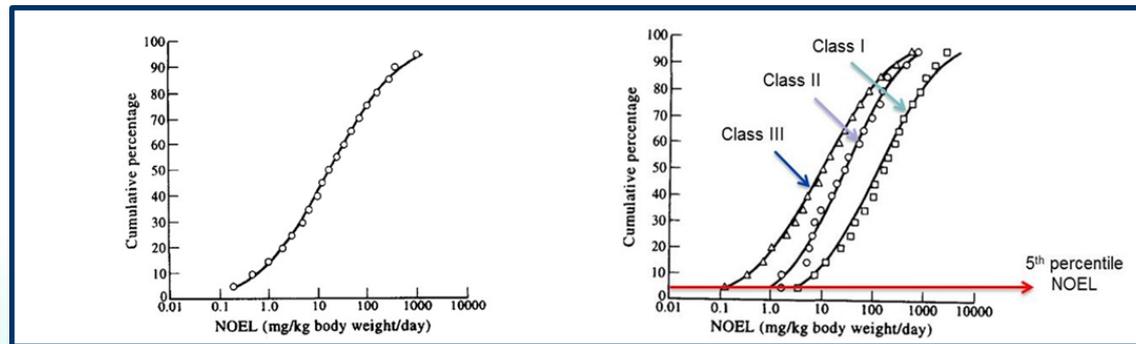


Assessing Safety Needs Knowledge of Exposure: Types of Models and Information Needs



Exposure 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

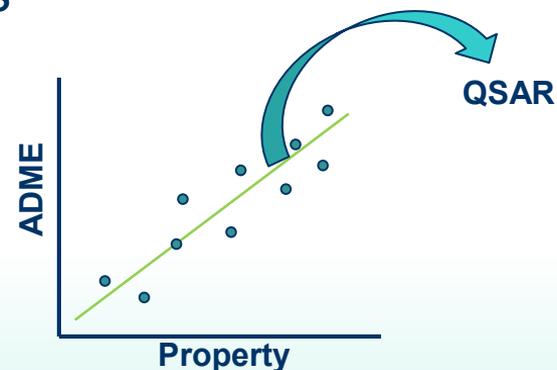


With thanks to Dr.
Corie Ellison (P&G)



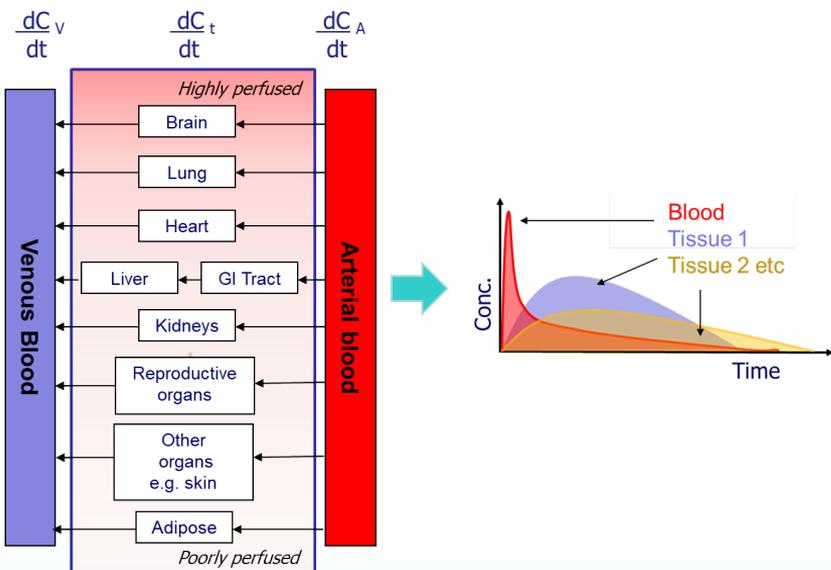
Predicting Absorption, Distribution, Metabolism, and Excretion (ADME) Properties

- “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)

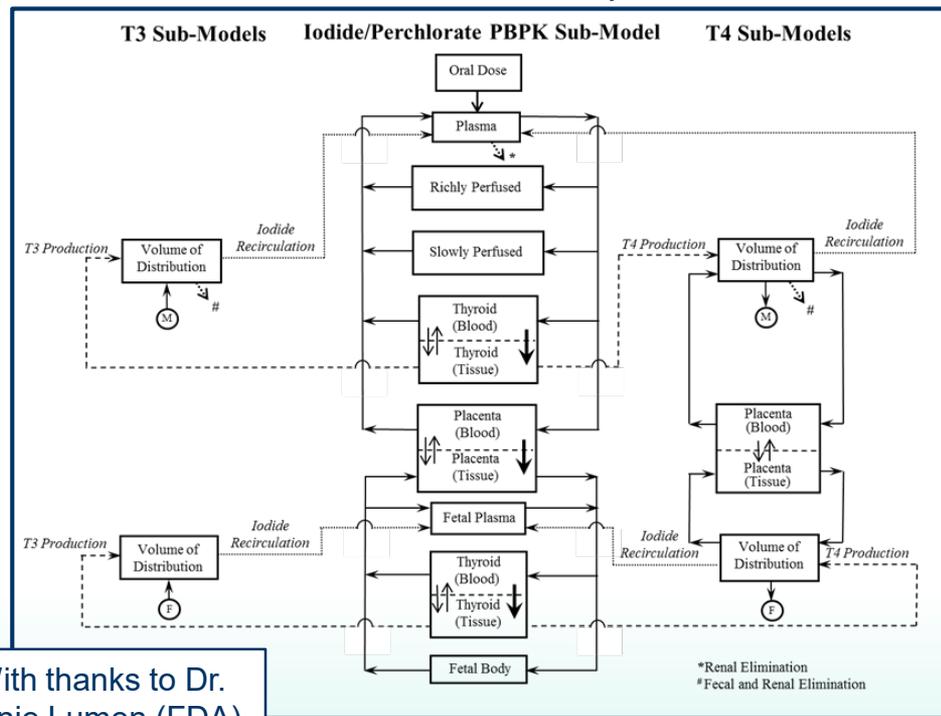


Predicting Concentration at Organ and Tissue Level

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



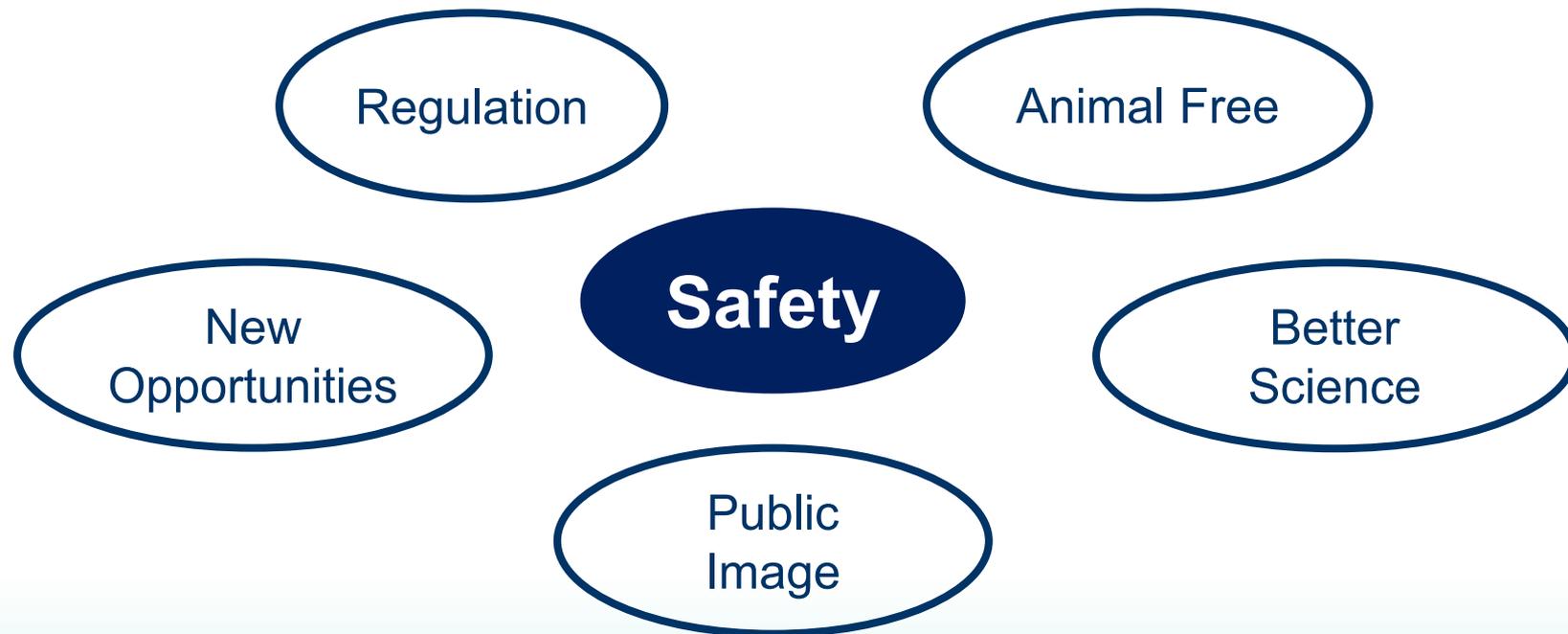
See: Paini et al (2017; 2019)



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



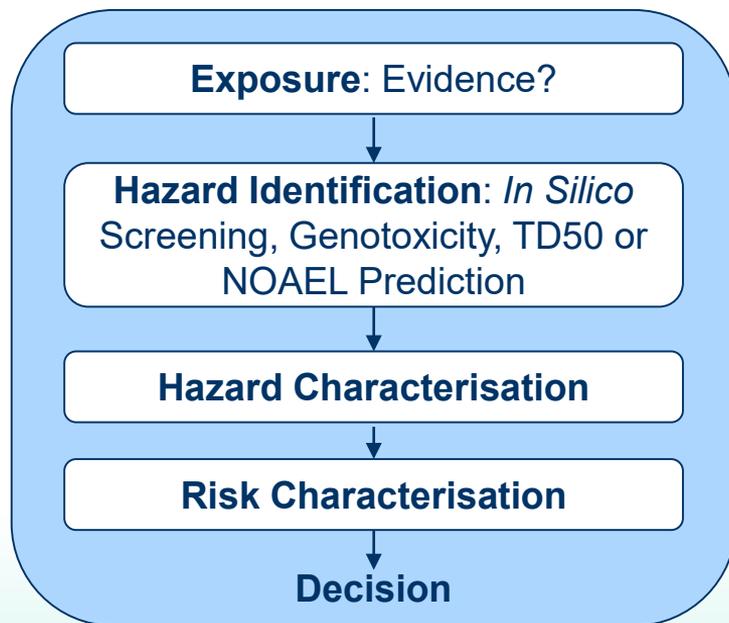
Key Driver 2: Regulation

- 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



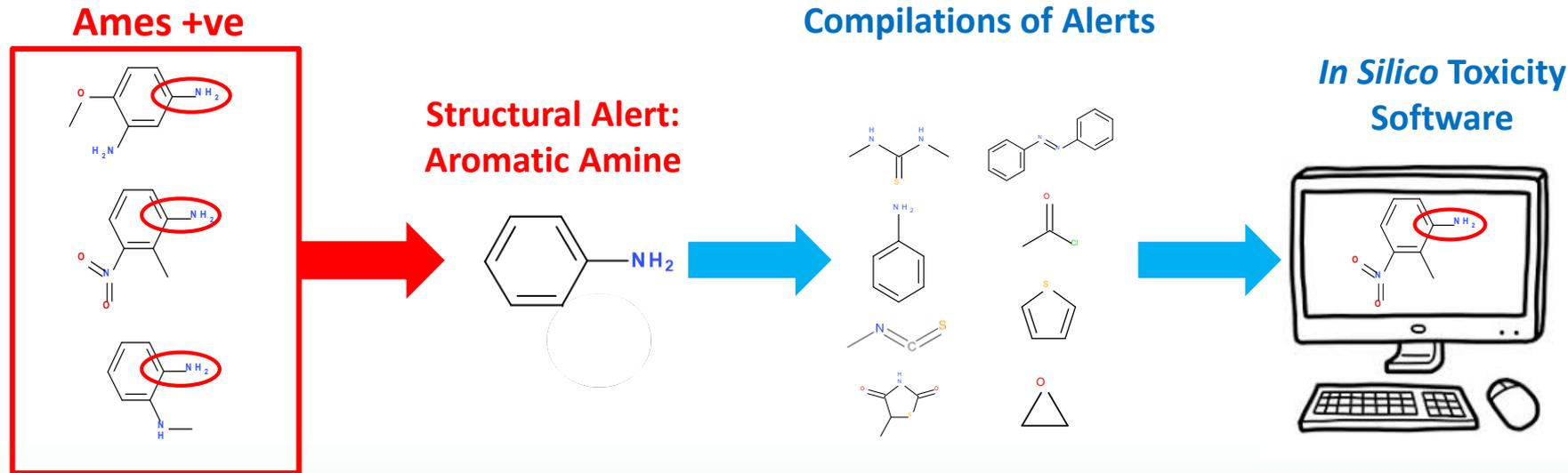
Decision Tree to Integrate Exposure of Toxicological Predictions

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

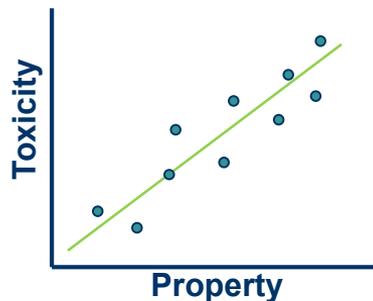


- Including: ToxTree, Derek Nexus *and others*

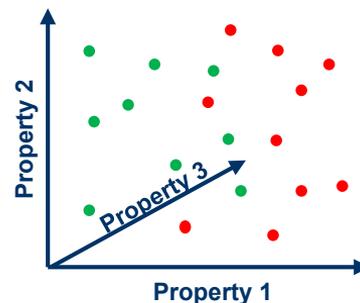


Key Driver 3: Animal-Free Testing

- Use of QSARs
 - Many approaches from simple to complex



Regression-based



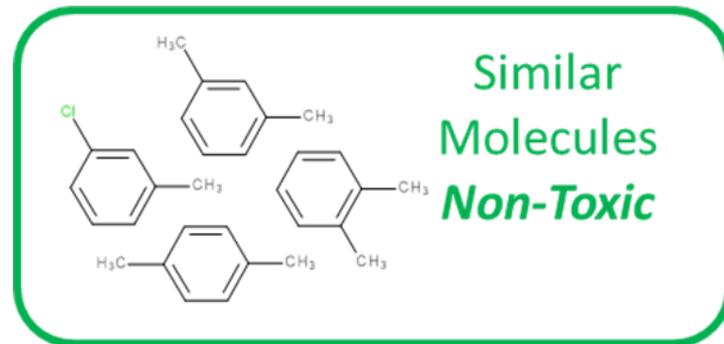
SVM, Neural Networks, etc.

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



Key Driver 3: Animal-Free Testing

- Use of grouping and read-across

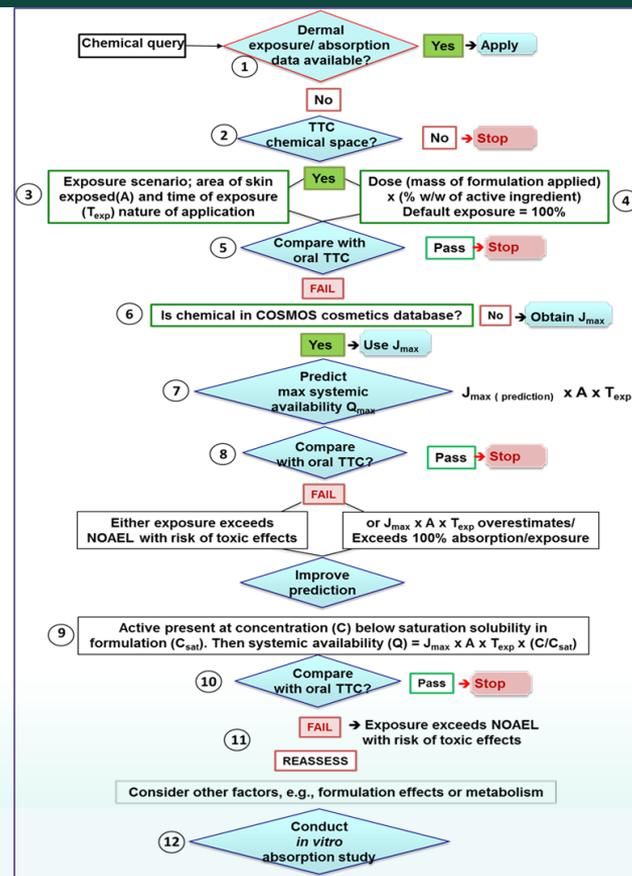


- Including: OECD QSAR Toolbox *and others*



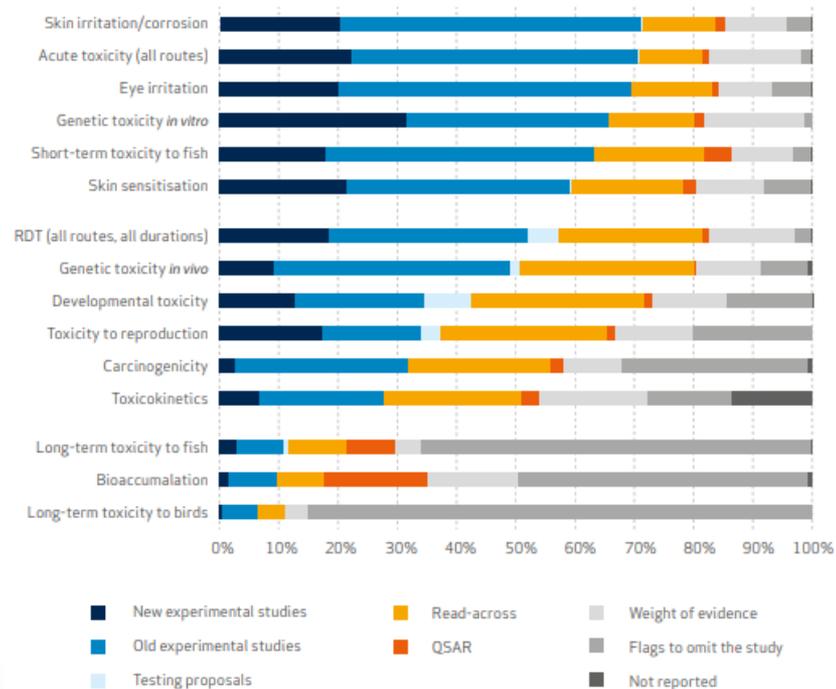
Key Driver 3: Animal-Free Testing

- 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

The screenshot shows the COSMOS NG web application interface. At the top, there is a navigation bar with the COSMOS logo and links for 'About', 'Terms', 'chihae', and 'Help'. Below this is a workflow bar with two steps: 'Find Structures & Data' and 'Calculate TTC'. The main content area is divided into several sections. On the left, there is a 'Data Table' section with tabs for 'TTC', 'Compare', and 'Data Details'. Below this is a 'Compound Summary' section with a 'Data Summary' table. The table has columns for 'CMS ID', 'Daily Intake (µg/day)', 'Cramer Class', 'Warning', and 'Decision'. The 'Daily Intake' column has a dropdown menu set to 'DEFAULT'. Below the table is a 'Query structure' section with a chemical structure diagram. To the right of the structure is a text box labeled 'Enter estimated daily exposure'. Further right is a text box labeled 'TTC Results'. Below these is a 'Data Table' section with a table showing results for 'METHYL 2-NONYNOATE'. The table has columns for 'CMS ID', 'METHYL 2-NONYNOATE', '4 studies', 'High (Class III)', and 'FAIL: Risk assessment requi'. The 'METHYL 2-NONYNOATE' column has a value of '00' and the 'High (Class III)' column has a value of '100'. On the right side of the interface is an 'Actions' menu with options like 'Calculate & Predict', 'Add Chemotype Profiles', 'Calculate Molecular Properties', 'Calculate TTC', 'Database Search', 'Find Structures & Data', and 'Export & Download'.

CMS ID	Daily Intake (µg/day)	Cramer Class	Warning	Decision
DEFAULT	DEFAULT	High (Class III)		
METHYL 2-NONYNOATE	00	High (Class III)	FAIL: Risk assessment requi	

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Key Driver 3: Animal-Free Testing

- TTC Workflow: COSMOS NG

The screenshot displays the COSMOS NG software interface. At the top, a navigation bar includes the COSMOS logo, a progress indicator with steps 'Find Structures & Data' and 'Calculate TTC', and a search bar. A box labeled 'TTC decision tree' points to the 'Calculate TTC' step. Below the navigation bar, there are tabs for 'Data Table', 'TTC', 'Compare', and 'Data Details'. The 'TTC' tab is active, showing a 'Non-Cancer TTC' of 100 µg/day. On the left, there are input fields for 'CMS ID' and 'Query structure', with a chemical structure of a long-chain alkene. The main area displays a decision tree starting from a 'Start' node. The tree branches through several questions (Q1-Q12) based on 'YES' or 'NO' answers. The path taken in the image leads to a 'FAIL' result. The questions and their options are:

- Q1: Is the substance a non-essential metal, or metal containing compound, or a polyhalogenated-dibenzodioxin, -dibenzofuran, or -biphenyl? (NO)
- Q6: Is the compound an organophosphate? (NO)
- Q8: Is the compound in Cramer structural class III? (YES)
- Q9: Does estimated intake exceeds the threshold of 90 µg/day? (YES)
- Q11: Risk assessment requires compound-specific toxicity data (FAIL)

Other questions (Q2, Q3, Q4, Q5, Q7, Q10, Q12) are not explicitly labeled with answers in the image. The 'FAIL' node is highlighted in red. On the right side of the interface, there is an 'Actions' menu with options like 'Calculate & Predict', 'Add Chemotype Profiles', 'Calculate Molecular Properties', 'Calculate TTC', 'Database Search', 'Find Structures & Data', 'Export & Download', 'Export Excel Data Table', and 'Export Chemical Structure File'. At the bottom right, it says 'designed and developed by MN/AM'.

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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)

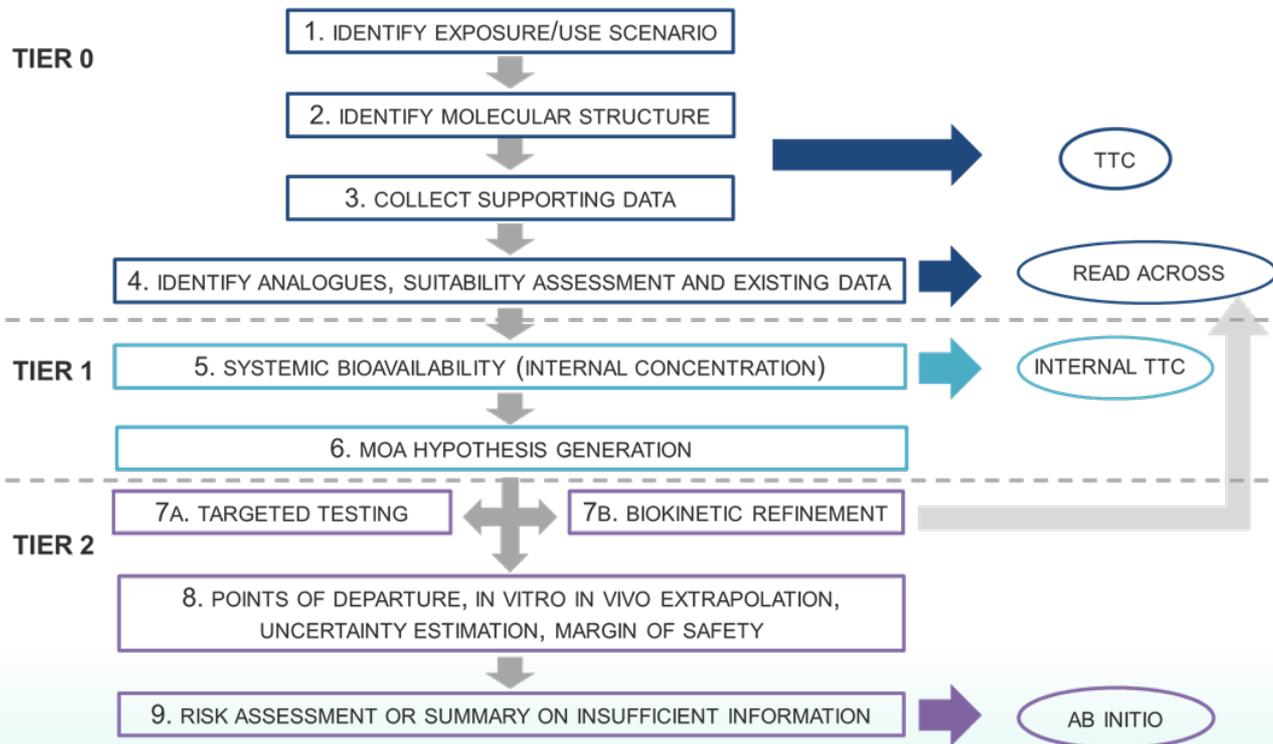


Key Driver 5: New Opportunities

- 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

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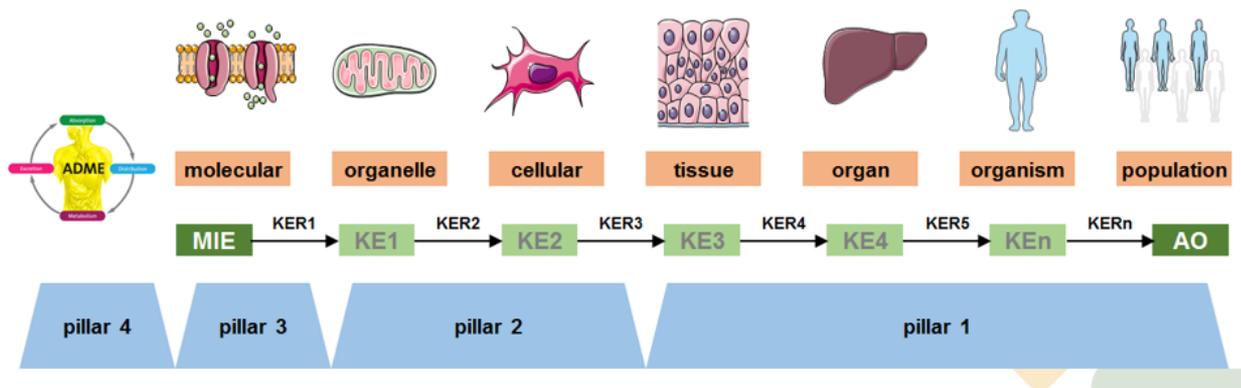
- OECD (2017) Series on Testing & Assessment. No. 275

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/>



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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

