Use of Computational Approaches for Genotoxicity Assessment of Pesticides

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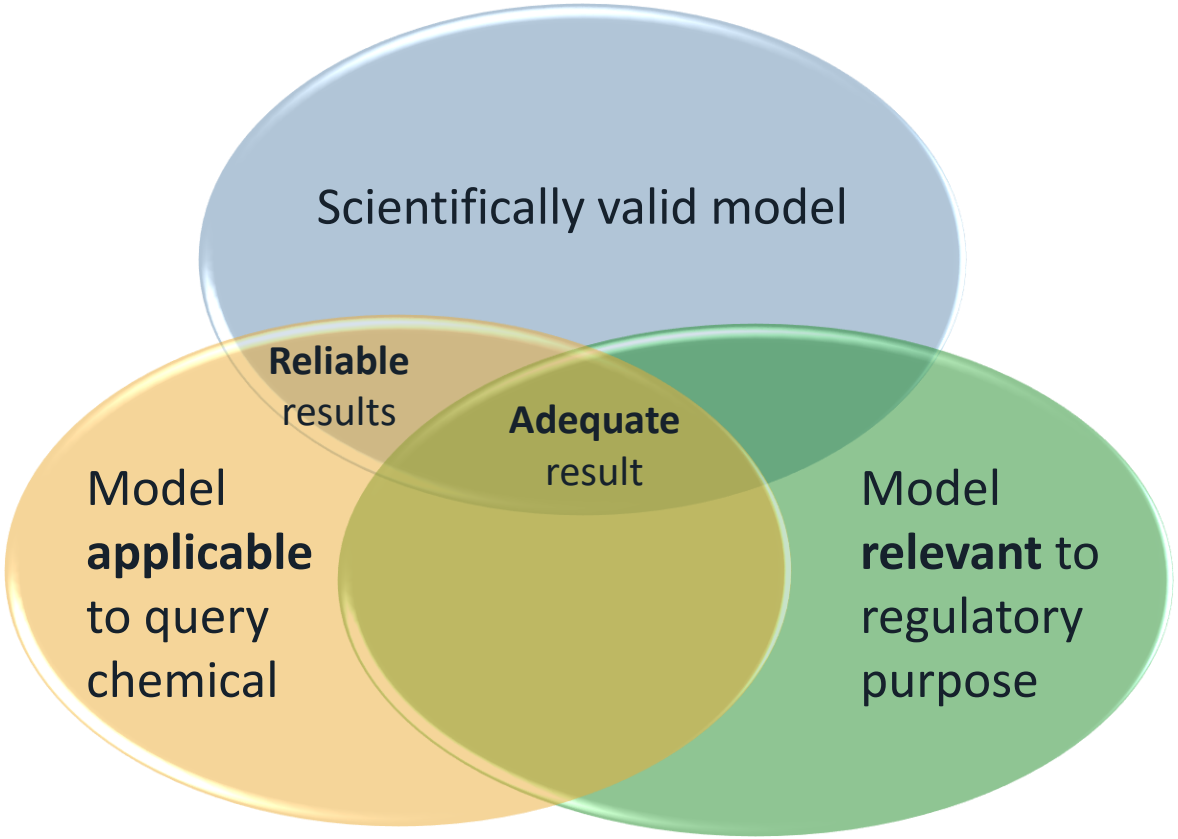
Lecture Outline

- Review of Literature
- Demo of various *in silico* tools
- Our work
- Opportunities for Collaboration

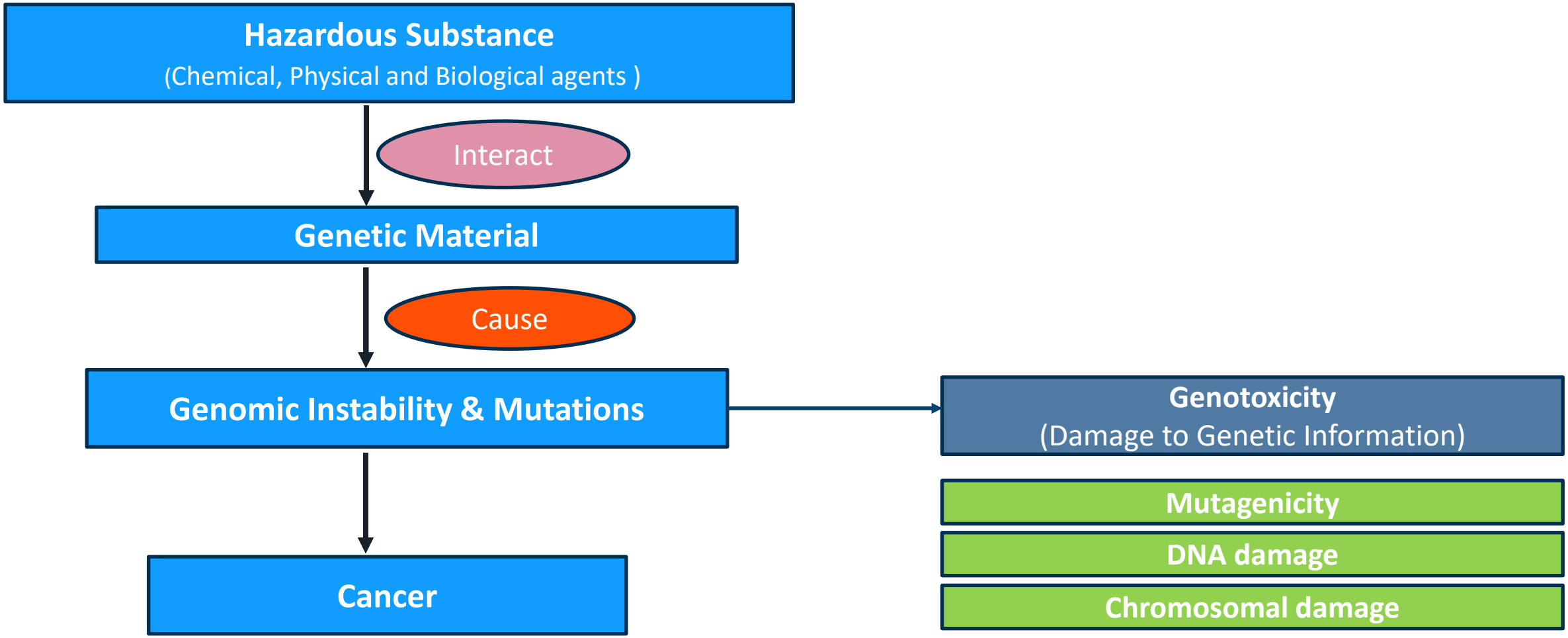
Adequacy of QSAR(s)

Most comprehensive guidance currently available for applying QSAR analysis is provided in the REACH guidance on Information Requirements and Chemical Safety Assessment (ECHA, 2008).



JRC-EU. Applicability of QSAR analysis to the evaluation of the toxicological relevance of metabolites and degradants of pesticide active substances for dietary risk assessment

Genotoxicity



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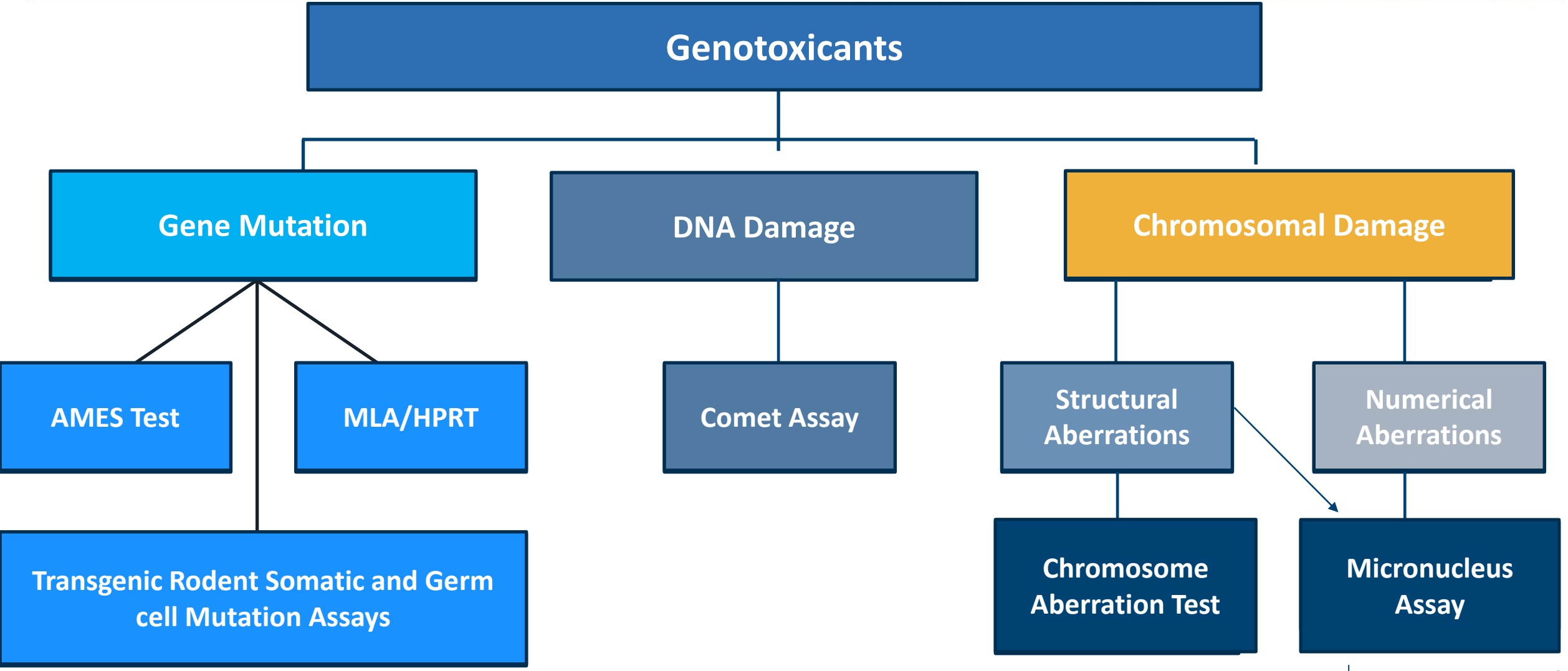
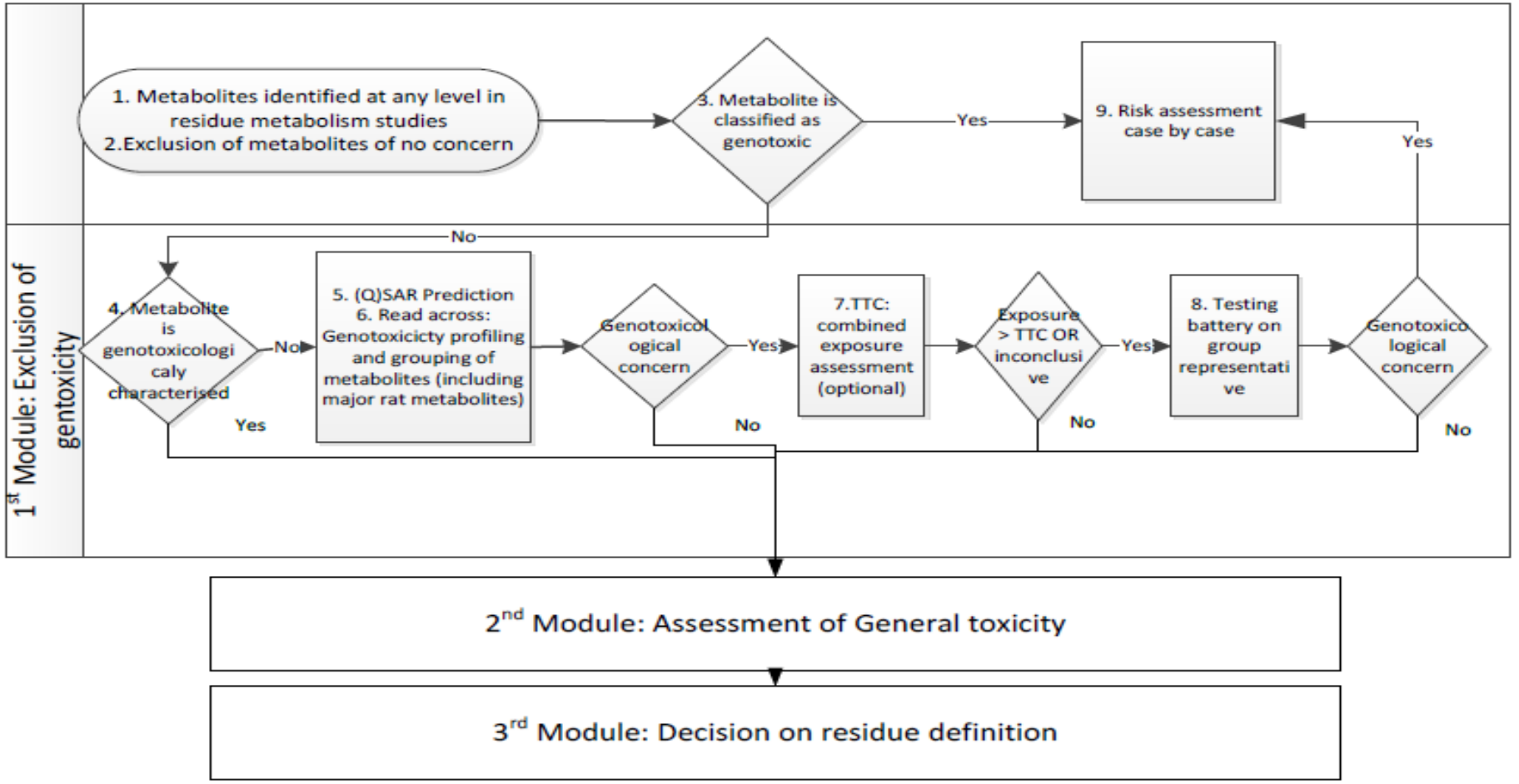
Genotoxicity Testing



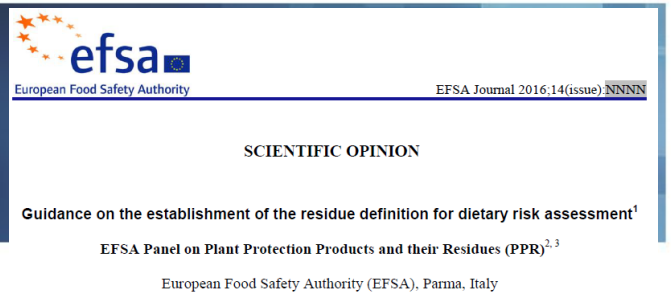
Residue studies for dietary risk assessment (crops, livestock, fish and processed food)



Module 1 exclusion of genotoxicity

EFSA (2016). Guidance on the establishment of the residue definition for dietary risk assessment

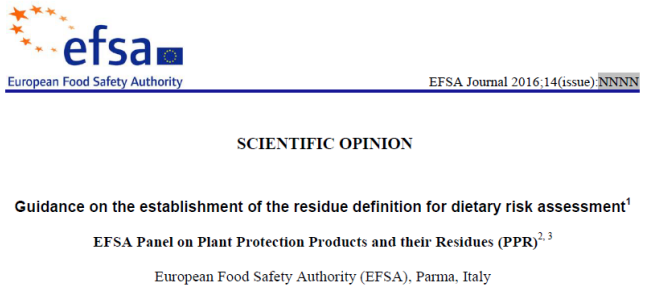
In silico genotoxicity prediction for dietary risk assessment



- Genotoxicity assessment should be assisted by application of (Q)SAR and read across of metabolites.
- Use of computational models for predictions of genotoxicity should not be based on the use of any single model alone, but on a “weight of evidence” approach including all available information provided by the models (e.g. applicability domain, proposed mechanistic information, prediction for the similar substance).
- To maximize the sensitivity and specificity of the prediction, at least two independent (Q)SAR models, where possible, should be applied for each genotoxicity endpoint, including both knowledge based and statistical based models.

EFSA (2016). Guidance on the establishment of the residue definition for dietary risk assessment

In silico genotoxicity prediction for dietary risk assessment


efsa
European Food Safety Authority
EFSA Journal 2016;14(issue):NNNN

SCIENTIFIC OPINION

Guidance on the establishment of the residue definition for dietary risk assessment[1]

EFSA Panel on Plant Protection Products and their Residues (PPR)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

Case Study: Study of genotoxicity potential of Isoproturon and 12 metabolites using QSAR & Read-across

a) In silico:

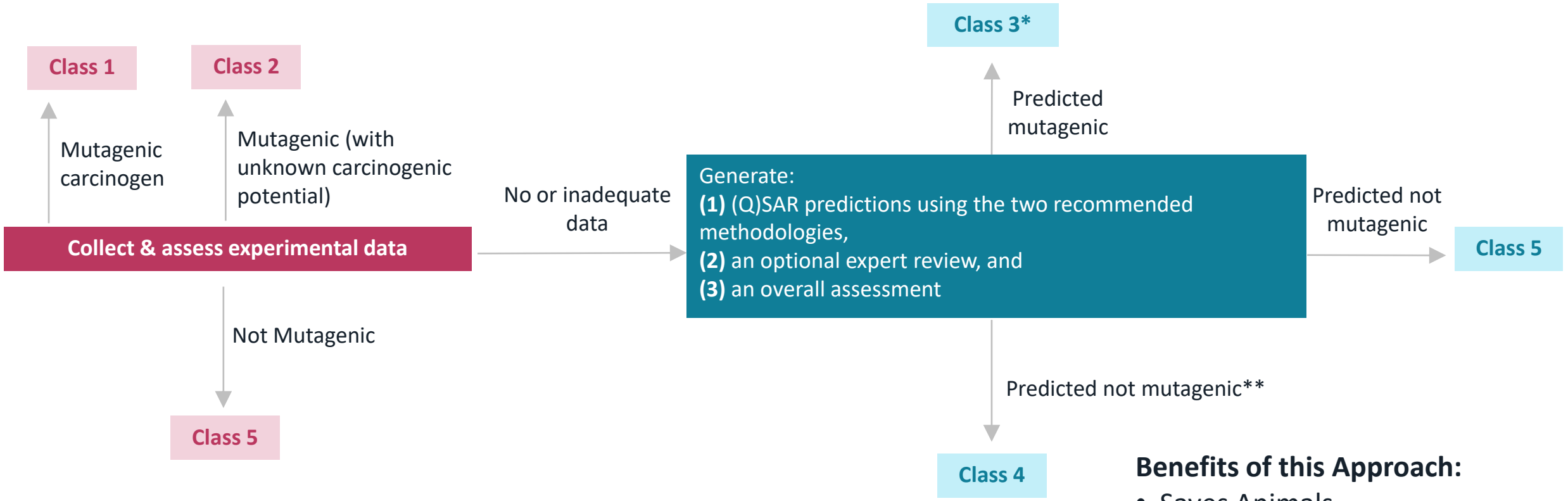
- In order to predict the genotoxic potential (gene mutation and chromosomal aberrations) of the minor rat and plant specific metabolites, four models have been applied: VEGA software, DEREK Nexus, and Toxtree.

b) Read-across:

OECD Toolbox used

EFSA (2016). Guidance on the establishment of the residue definition for dietary risk assessment

Approval of use of in silico tools for Pharmaceutical impurities



*Or perform an Ames test
**Based on a shared alert with a known negative

Benefits of this Approach:

- Saves Animals
- Saves Time
- Saves Money

ICH M7(R1) Assessment & Control of DNA reactive impurities in Pharmaceuticals to limit potential Carcinogenic risk

Approval of use of *in silico tools for* Medical Devices

DRAFT INTERNATIONAL STANDARD
ISO/DIS 10993-17

ISO/TC **194** Secretariat: **DIN**

Voting begins on: **2021-11-18** Voting terminates on: **2022-02-10**

Biological evaluation of medical devices —

Part 17:
Toxicological risk assessment of medical device constituents

- Use of in silico analysis to predict nature of harms is an example when a chemical specific POD is not available.
- When nature of harm is not understood, a computer-based model (also known as in silico analysis) can be used to predict the nature of the harm to health for the identified constituent.

Approval of use of *in silico* tools for Food Contact Material/ Printing Inks

EuPIA Guidance for Risk Assessment of Non-Intentionally Added Substances (NIAS) and Non-Evaluated or Non-Listed Substances (NLS) in printing inks for food contact materials

The use of a combination of rule-based and statistical-based (Q)SAR software is one of the preferred options proposed in the EFSA guidance document.
There are several (Q)SAR software tools available, which allow to predict the DNA reactivity of a substance.

Potential applicable alerts are:
- in vitro mutagenicity (Ames test) alerts by ISS (ToxTree)
- mutagenicity in vitro (Sarah Nexus)
- bacterial mutagenicity OECD 471 (CaseUltra)
- bacterial mutation alerts (Leadscope)

In addition, Annex III of REACH, available on the ECHA website, consists of a compilation of (Q)SAR predicted toxicities for some 33.000 substances, including genotoxicity or carcinogenicity alerts, where applicable

European Printing Ink Association (EuPIA): https://www.eupia.org/fileadmin/Documents/Risk_Assessment/2021-05-11-EuPIA_NIAS_Guidance.pdf

Demo of various computation tools

Derek nexus

Sarah nexus

ICH M7

Toxtree

VEGA

CompTox Chemicals Dashboard-EPA: https://comptox.epa.gov/dashboard/

Test compound: Endosulfan (SMILES: C1C2C(COS(=O)O1)C3(C(=C(C2(C3(Cl)Cl)Cl)Cl)Cl)Cl)

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Our Work

EUROTOX 2023
LJUBLJANA – SLOVENIA
10–13 SEPTEMBER 2023

Predicting skin sensitization of agrochemicals using OECD QSAR toolbox, Derek Nexus, ToxTree, PredSkin and SkinSensPred

Gowrav Adiga.P, Deepa Venkataramulu, Mohan Krishnappa and Varun Ahuja

- *In silico* evaluation of several agrochemicals including inorganic metals, carbamates, chlorinated hydrocarbons, pyrethroids, organophosphate insecticides, fungicides, herbicides, fumigants, nematicides and solvents.

- Three softwares viz. QSAR Toolbox by OECD, Toxtree and TEST by US EPA were used.

- Selection of approximately 60 agrochemicals for *in silico* analysis were based on published data for various endpoints viz. (i) Ames, (ii) *in vitro* mammalian cell gene mutation, (iii) *in vitro* micronucleus, (iv) *in vitro* chromosomal aberration, (v) *in vivo* micronucleus, (vi) *in vivo* chromosomal aberration, (vii) rodent carcinogenicity and (viii) skin sensitization.

- QSAR Toolbox, Toxtree and TEST (for Ames only) had accuracy of 80%, 66% and 77%, respectively. Additionally, QSAR Toolbox and Toxtree had an accuracy of 90% and 69% for carcinogenicity endpoints, respectively.

Syngene Our Work & Opportunities for Collaboration

62nd Annual Meeting & ToxExpo
Nashville, TN • March 19–23, 2023

Predicting genotoxicity and carcinogenicity of drugs and chemicals using OECD QSAR toolbox, Derek Nexus and TEST

EUROTOX 2023
LJUBLJANA – SLOVENIA
10–13 SEPTEMBER 2023

EVALUATION OF PHOTOTOXIC POTENTIAL OF SEVEN SOLVENTS USING *IN SILICO* DEREK AND *IN VITRO* 3T3 NRU METHOD.

M. Shameer P[1], V. Ahuja[1], M. Krishnappa[1], D. Venkataraman[1]

ICT2022
THE XVI[TH] INTERNATIONAL CONGRESS OF TOXICOLOGY
MAASTRICHT, THE NETHERLANDS
SEPTEMBER 18-21,2022

ELSEVIER

Toxicology Letters
Volume 368, Supplement, 1 September 2022, Page S286

Late breaking abstracts

LP-07 In *silico* analysis using Derek and Sarah along with ICH M7 expert review accurately predicts Mutagenicity and Carcinogenicity of Nitrosamines

V. Ahuja, M. Krishnappa

https://www.sciencedirect.com/science/article/abs/pii/S0378427422016770

SOT 61ST ANNUAL MEETING & TOXEXPO • SAN DIEGO, CA MARCH 27–31, 2022

Prediction of Mutagenicity, Genotoxicity, and Carcinogenicity of Drugs and Chemicals Using Derek Nexus

The Toxicologist
Supplement to *Toxicological Sciences*

EUROTOX 2023
LJUBLJANA – SLOVENIA
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Predicting skin sensitization of agrochemicals using OECD QSAR toolbox, Derek Nexus, ToxTree, PredSkin and SkinSensPred

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EUROTOX 2021
VIRTUAL CONGRESS
26 SEPTEMBER – 1 OCTOBER 2021

ELSEVIER

Toxicology Letters
Volume 350, Supplement, September 2021, Page S250

In silico toxicity prediction using Derek Nexus® for skin sensitization, phototoxicity, hepatotoxicity and *in vitro* hERG inhibition

V. Ahuja [1], M. Krishnappa [1], H. Kandarova [2]

https://www.sciencedirect.com/science/article/abs/pii/S0378427421008171

Questions