# MechoA+
## a significant update to the MechoA classification scheme

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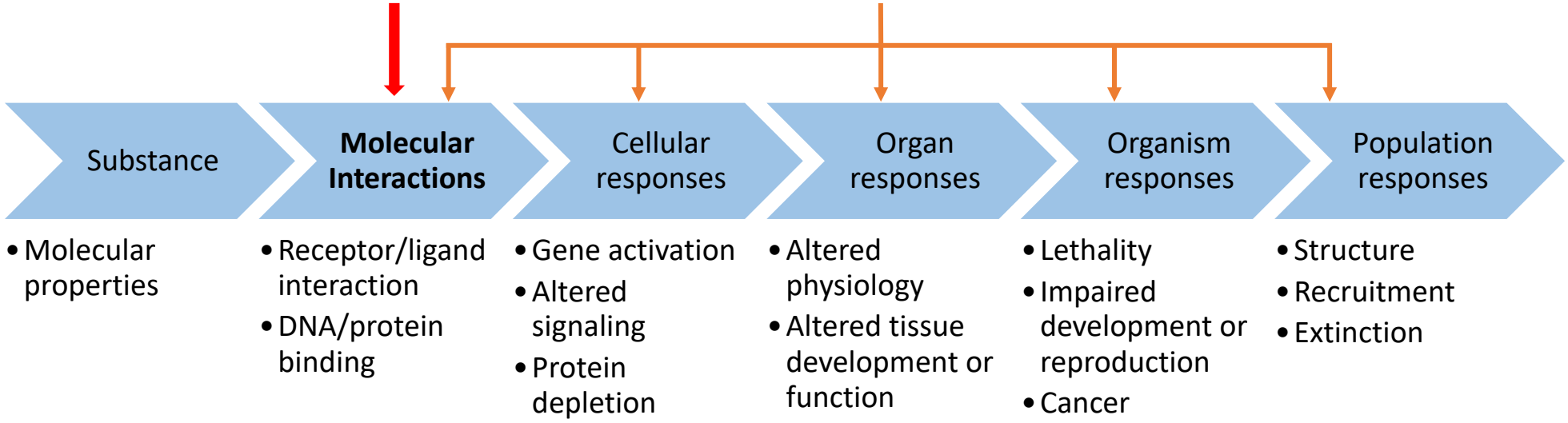
# MechoA definition

Mechanisms of Toxic Action (MechoA) scheme → structure-activity relationships (SAR) tool which predict molecular initiating events (MIE) by which a substance induces adverse effects to an organism.

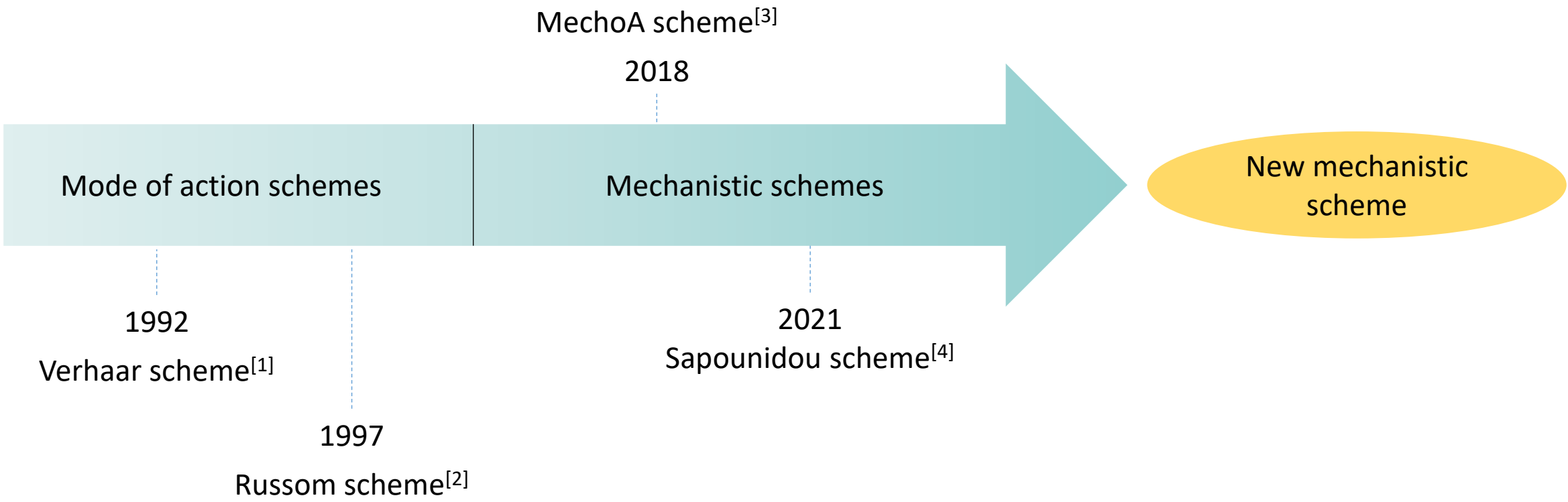
MechoA ➡ Molecular initiating event (MIE) Mode of action (MOA)




Adverse Outcome Pathway (AOP)

Adapted from Ankley, G. T. et al. Environ. Toxicol. Chem. 29, 730–741 (2010).

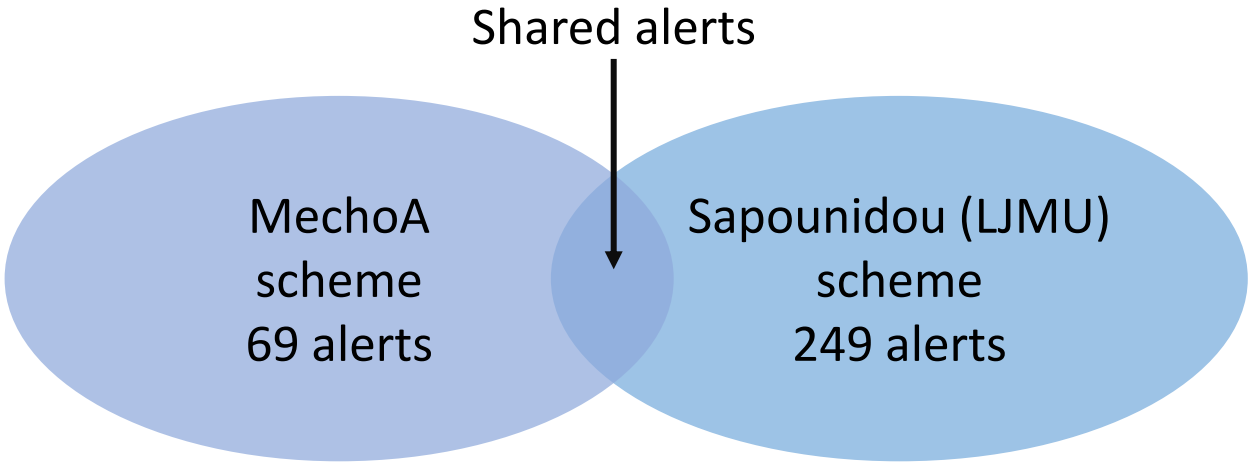
# Classification schemes




[1] Verhaar HJM, van Leeuwen CJ, Hermens JLM. 1992. Classifying environmental pollutants. Chemosphere. 25, 4, 471-491.
[2] Russom CL, Bradbury SP, Broderius SJ, Hammermeister DE, Drummond RA. 1997. Predicting modes of toxic action from chemical structure: Acute toxicity in the fathead minnow (Pimephales promelas). Environ. Toxicol. Chem. 16, 948-967.
[3] Bauer FJ, Thomas PC, Fouchard SY, Neunlist SJM. 2018. High-accuracy prediction of mechanisms of action using structural alerts. Comput. Toxicol. 7, 36-45.
[4] Sapounidou M, Ebbrell DJ, Bonnell MA, Campos B, Firman JW, Gutsell S, Hodges G, Roberts J, Cronin MTD. 2021. Development of an Enhanced Mechanistically Driven Mode of Action Classification Scheme for Adverse Effects on Environmental Species. Environ. Sci. Technol. 55, 1897-1907.

# What is behind MechoA+ development?

- Merging of the most recent MIE schemes



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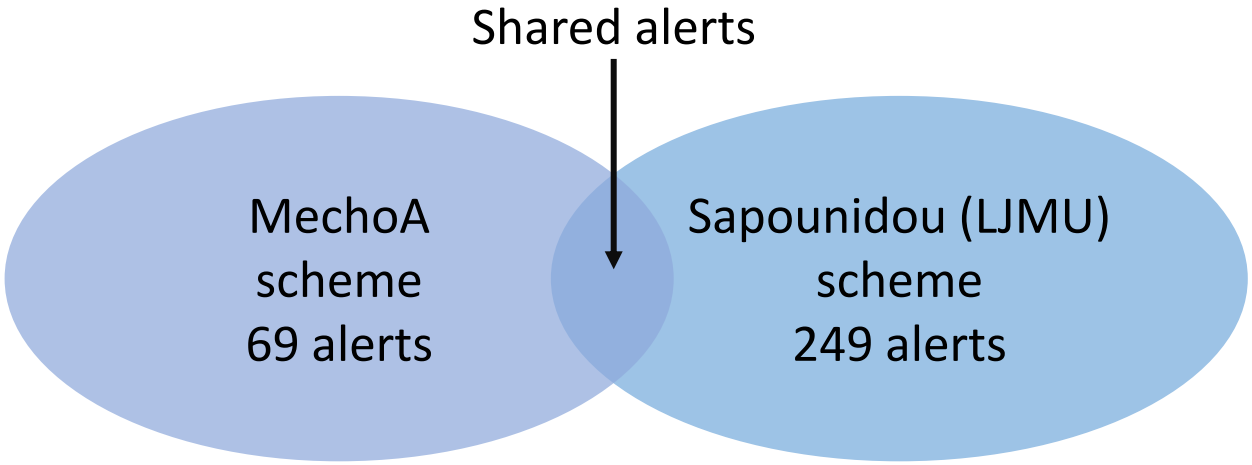
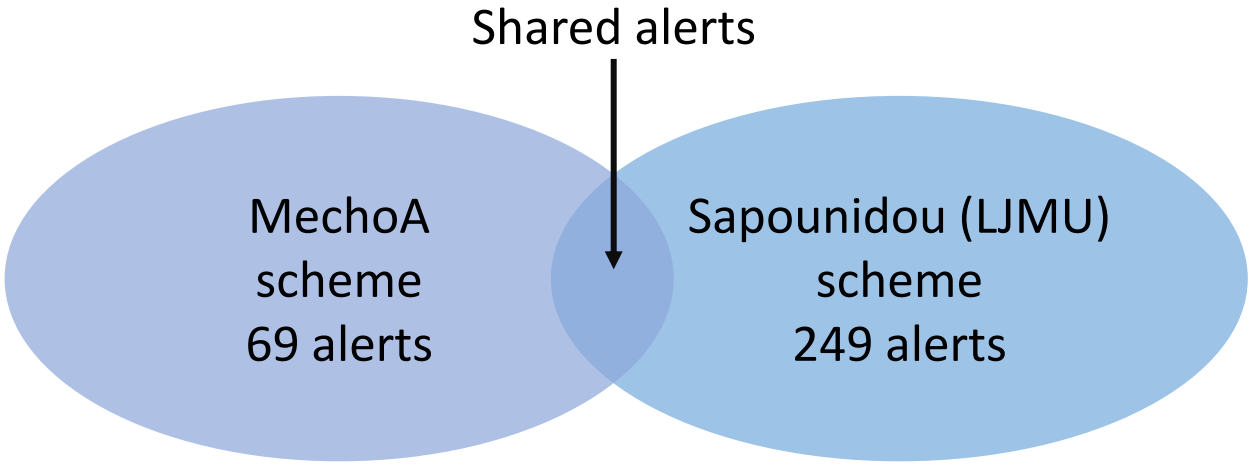
- Merging of the most recent MIE schemes
- Replace the older schemes



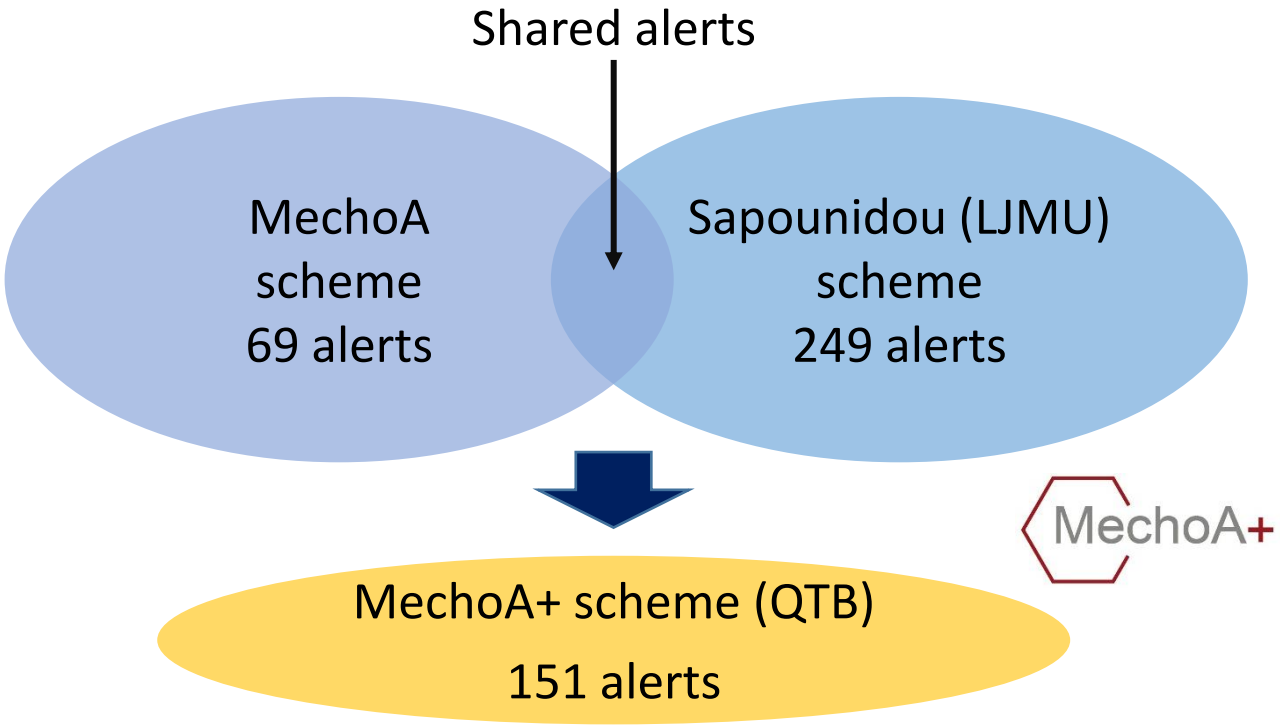
# What is behind MechoA+ development?

- Merging of the most recent MIE schemes
- Replace the older schemes
- Build on the advantages of both
  - Based on MIE
  - Free and published
  - Species indications (e.g. fish, mammals, plants, etc.)
  - Description of the MechoA
  - Automated
  - And more !



# What is behind MechoA+ development?

- Merging of the most recent MIE schemes
- Replace the older schemes
- Build on the advantages of both
- MechoA+ scheme:
  - Collaborative work : KREATiS, LJMU, Unilever
  - Profiler in OECD QSAR Toolbox (2023)
  - Covers a wider mechanistic domain
  - Covers a wider structural domain
  - Better species differentiation
  - Automated



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- MechoA+ scheme:
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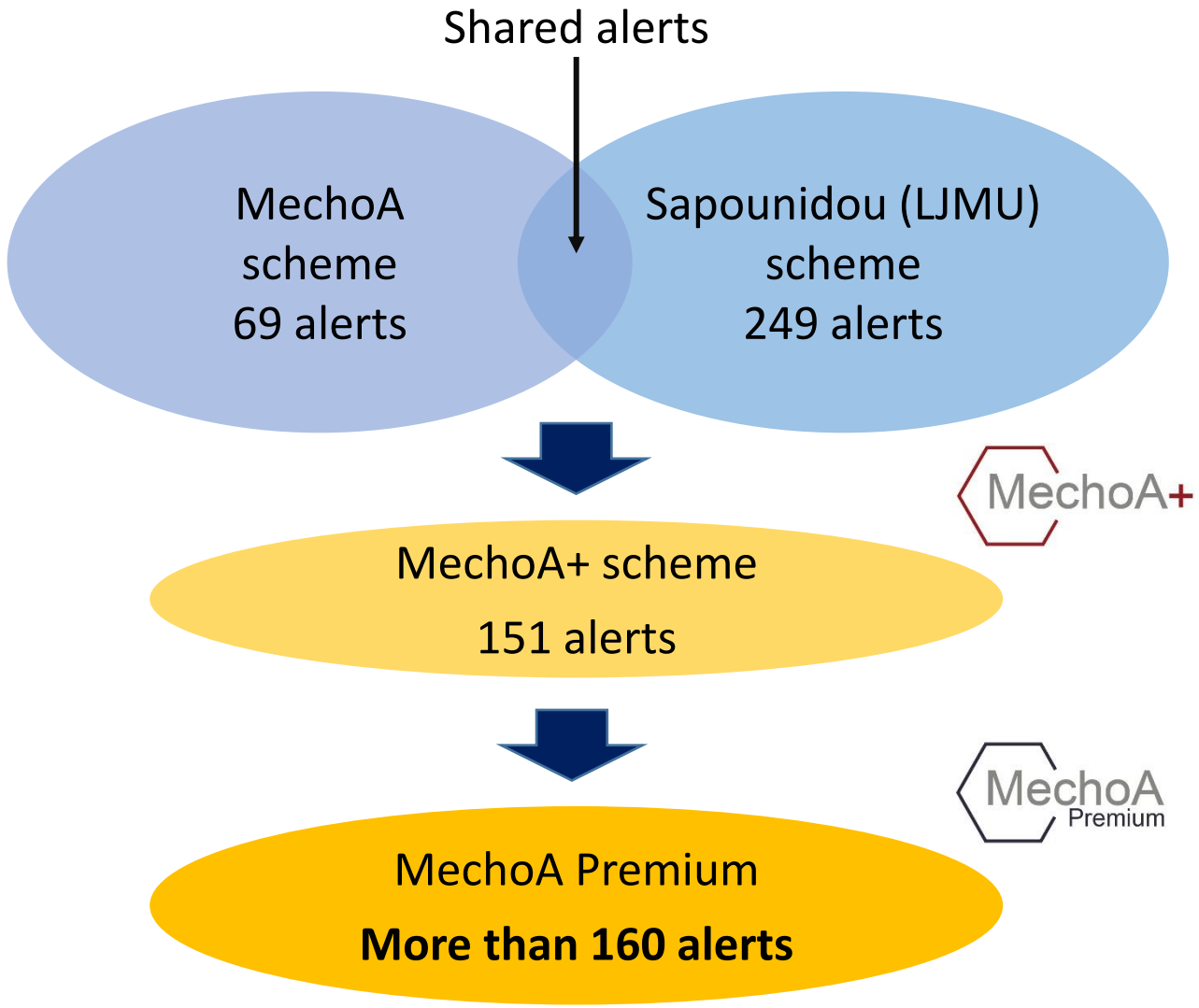
  - Profiler in OECD QSAR Toolbox (2023)
- MechoA Premium:
  - Further independent work (iSafeRat® by KREATiS)



# Alerts refinement workflow

Existing Sapounidou and MechoA alerts

- **Sapounidou alerts**
  - 26 Narcotic
  - 119 Reactive
  - 104 Specific
- **MechoA alerts**
  - 5 Membrane destabilization
  - 4 Enzymatic hydrolysis
  - 10 Spontaneous reactivity
  - 18 Pro-activity (metabolism)
  - 3 Indirect biological systems disruption
  - 27 Specific interaction with endogenous macromolecules
  - 1 Exclusion rule

# Alerts refinement workflow

Existing Sapounidou and MechoA alerts

Literature search on the MechoA for classes of molecules, check if there are observed effects in experimental studies

- Refining the alert:
  - Confirm/Unconfirm the alert
  - Widen or restrict the structural domain of the alert
  - Check for substances in the literature

# Alerts refinement workflow

Existing Sapounidou and MechoA alerts

Literature search on the MechoA for classes of molecules, check if there are observed effects in experimental studies

Characterisation of the applicability of structural alerts to various species

- Extrapolate to most species (e.g. orthology database) when possible

# Alerts refinement workflow

Existing Sapounidou and MechoA alerts

Literature search on the MechoA for classes of molecules, check if there are observed effects in experimental studies

Characterisation of the applicability of structural alerts to various species

Refinement of the structural alerts and the MechoA text

- Design a new structural alerts
- Design a sentence to explain shortly the expected MechoA for each species
- **Exactly 151 alerts were validated → MechoA+**

MechoA+

# Alerts refinement workflow

Existing Sapounidou and MechoA alerts

Literature search on the MechoA for classes of molecules, check if there are observed effects in experimental studies

Characterisation of the applicability of structural alerts to various species

Refinement of the structural alerts and the MechoA text

Develop/Refine the existing decision tree

- Define sets of priority rules in function of the “expected” toxicity
- Continue MechoA search if “all” species are not considered yet

# Alerts refinement workflow

Existing Sapounidou and MechoA alerts

Literature search on the MechoA for classes of molecules, check if there are observed effects in experimental studies

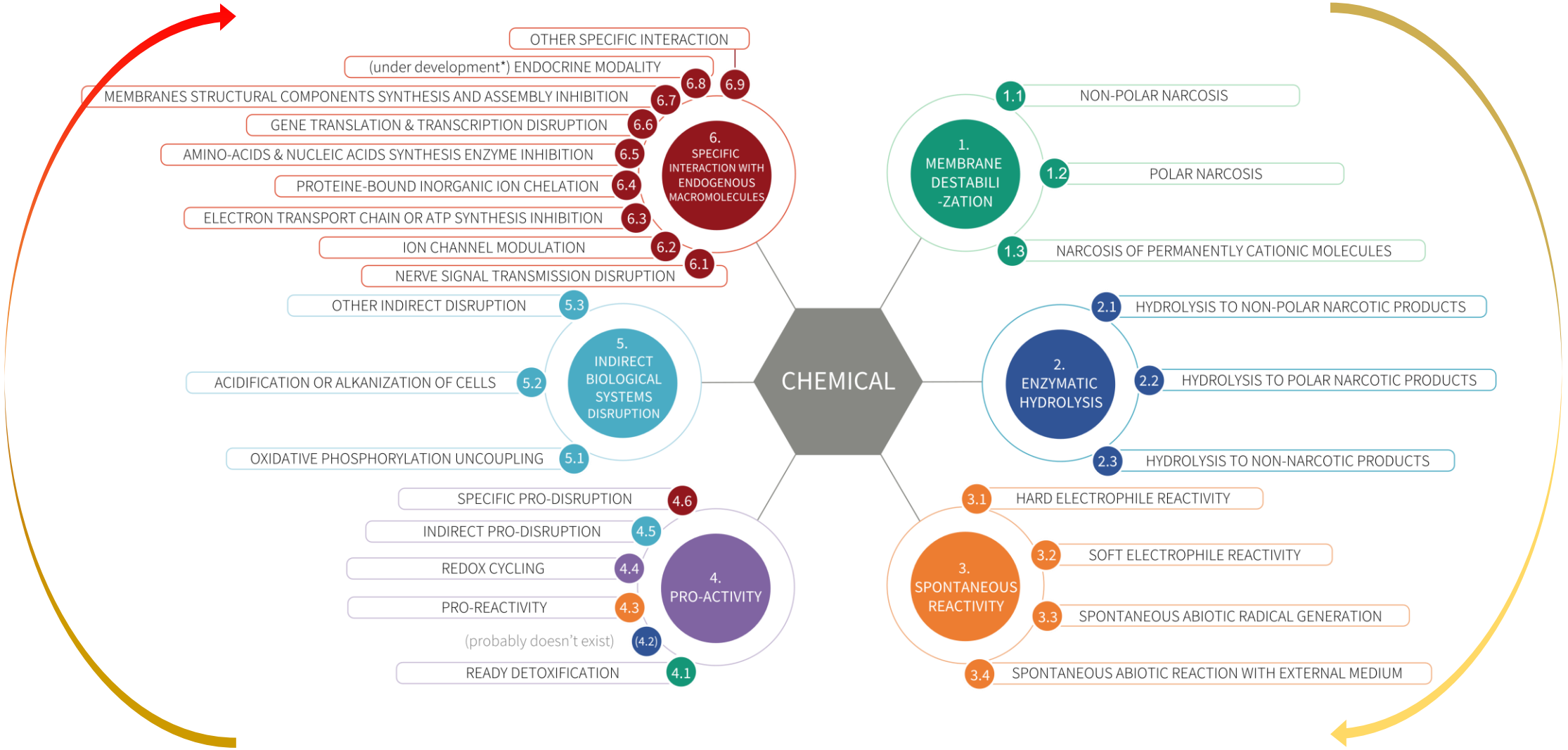
Characterisation of the applicability of structural alerts to various species

Refinement of the structural alerts and the MechoA text

Develop/Refine the existing decision tree

Implement all the alerts in iSafeRat® Desktop by KREATiS (and MechoA+, shortly available in the OECD QSAR Toolbox)

# Finalised MechoA+/Premium scheme



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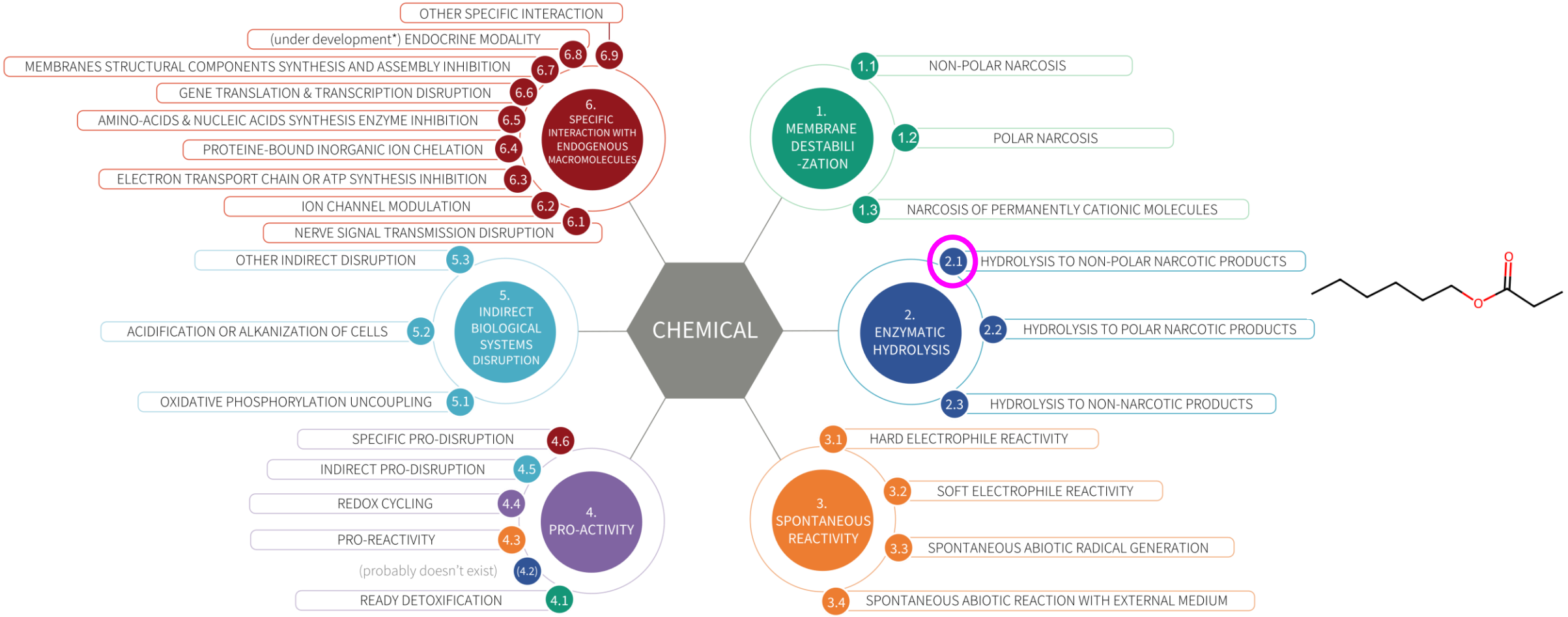

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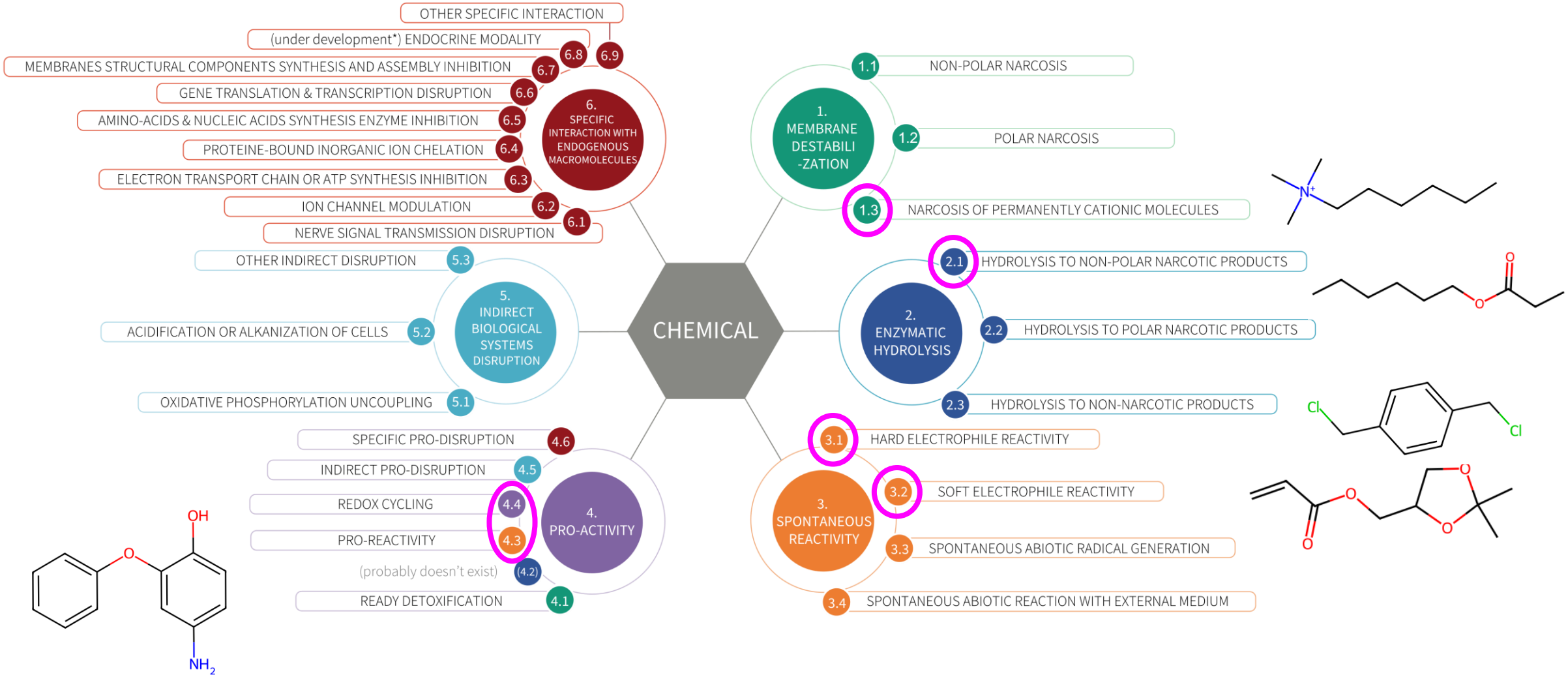
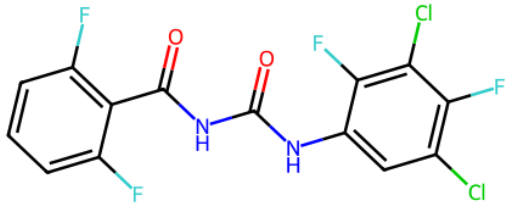
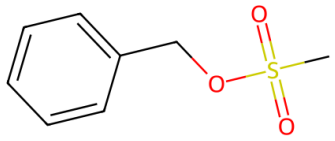


# Comparison between MechoA VS Sapounidou VS MechoA+: two examples

| Name | Teflubenzuron | Benzyl Methanesulfonate |
|---|---|---|
| Structure |  |  |
| MechoA scheme | MechoA 2.1 & p6.5: Enzymatic hydrolysis for all species & blocking of electron transfer at the photosystem II for plants. | NA: Out of applicability domain |
| Sapounidou Scheme | Specific: Inhibition of chitin synthase for *Daphnia magna* | Reactive: Nucleophilic substitution leading to protein/DNA adducts for eukaryota |

Note:
Results of the schemes were shortened for the slide

MechoA + differences

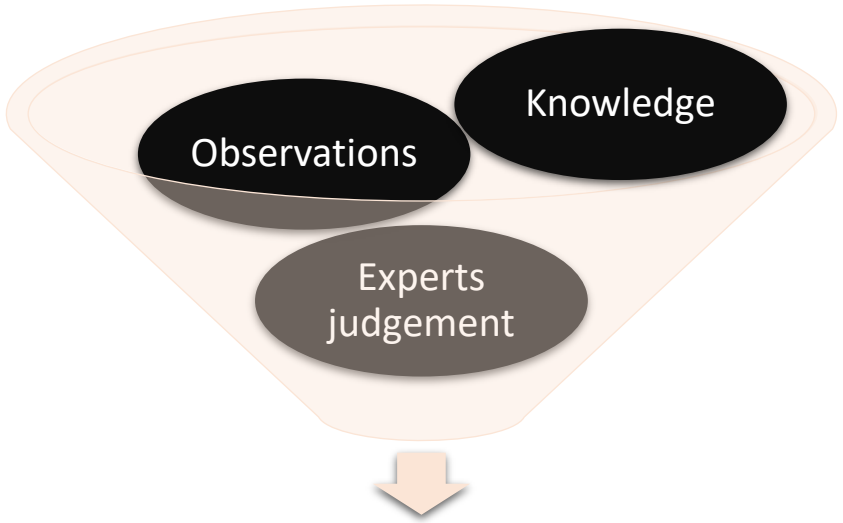
MechoA fu+ps+fi6.7 & 2.2: inhibition of chitin synthase & enzymatic hydrolysis to polar narcotic

MechoA 3.1 & 3.4: reaction with proteins and DNA & abiotic hydrolysis for all species

# Advantages and limitations of MechoA+/Premium

| Advantages | Limitations |
|---|---|
| • **More accurate for mechanistic interpretation**<br>➢ Helpful for (eco)toxicology endpoint (Q)SARs (e.g. aquatic acute/chronic, skin sensitisation, genotoxicity, neurotoxicity)<br>➢ Read-Across justification / Analogue search<br>• **Species relevance better defined**<br>➢ fish, daphnids, algae, mammals, bacteria, fungi, etc.<br>• **Applicability domain increases**<br>• **Automated**<br>➢ Visual: MechoA wheel<br>➢ User-friendly<br>➢ Related to acute/chronic ecotoxicity and a sensitisation model (iSafeRat Desktop®) | • **Toxicokinetics not considered (e.g. absorption)**<br>• **Weaknesses of the decision tree**<br>➢ Need a balance between the level of detailed information VS short and exploitable results for high-throughput use<br>➢ Some detection problems can occur for molecules bearing several functional groups which are relatively close to each another<br>• **Validation on going**<br>• **Species extrapolation requires further refinement** |

# Conclusion - Take-home messages




- **MechoA+ scheme: 151 alerts**
  - wide applicability domain
- **MechoA Premium scheme:**
  - >160 alerts, addition of new alerts
  - Refine the decision tree
  - Better definition of the structural applicability domain

# Acknowledgments


- Franklin J. Bauer, Etienne Bourgart, Floriane Larras, Antoine Charmeau, Carole Charmeau, Jora Omva, Paul C. Thomas
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- Jayne Roberts, Steve Gutsell, Bruno Campos, Geoff Hodges
- Mark Bonnell

Government of Canada / Gouvernement du Canada

MechoA+

MechoA Premium

# Thank you for your attention

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