Assessing and Improving Confidence in a Novel Scheme to Group Chemicals for Ecotoxicological Endpoints

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OBJECTIVES

- The ability to assign compounds to a mechanism of ecotoxicological action allows environmental toxicants to be allocated to QSAR and for read-across to be applied
- This investigation aimed to:
  - Provide a novel, unified, mechanistically-driven scheme for the classification of environmental toxicants
  - Assess the usability and coverage of the new scheme as compared to existing schemes

APPROACH

- Information from existing schemes for the classification of environmental toxicants, and the literature, were compiled for relevant Molecular Initiating Events (MIEs)
- Mechanisms were rationalised and organised
- Structural domains of MIEs were defined using SMARTs
- Using the SMARTs, the scheme based on MIEs was used to assess coverage and compare performance with existing schemes for Mechanism of Action assignment e.g. Verhaar, Russom, MechoA

MAIN RESULTS

- Classes were derived for a broad range of ecotoxicological MoA and organised on the basis of Chemistry, Toxicology and MIE
- The new scheme has greater coverage within the reactive and specific domains compared to Verhaar, Russom and MechoA
- The number of compounds that were unclassified is reduced relative to traditional schemes such as Verhaar

IMPACT

- A novel classification scheme has been presented to support grouping of potential environmental toxicants.
- It unifies existing knowledge into three broad mode of action classifications which are then broken down into individual mechanisms and MIEs
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OBJECTIVES

- A number of schemes classify environmental toxicants such that appropriate QSARs and read-across can be applied
- Existing schemes such as Verhaar [1], Russom [2] and MechoA [3] are well established, but may lack coverage, species definition and relevance to MIEs. A unified scheme has recently been developed [4].
- This investigation aimed:
  - To provide a unified, mechanistically-driven scheme across a broad range of aquatic species for the classification of environmental toxicants, bringing together and enhancing current knowledge
  - To define the novel scheme [4] in terms of chemistry
  - To assess the usability and coverage of the new scheme as compared to existing schemes

[1] Verhaar HJM et al (1992) *Chemosphere* 25: 471– 491 https://doi.org/10.1016/0045-6535(92)90280-5
[2] Russom CL et al (1997) *Environ. Toxicol. Chem.* 16: 948– 967 https://doi.org/10.1002/etc.5620160514
[3] Bauer FJ et al (2018) *Comput. Toxicol*. 7: 36– 45 https://doi.org/10.1016/j.comtox.2018.06.004
[4] Sapounidou M et al (2021) *Environ. Sci. Technol.* 55: 1897–1907 https://doi.org/10.1021/acs.est.0c06551

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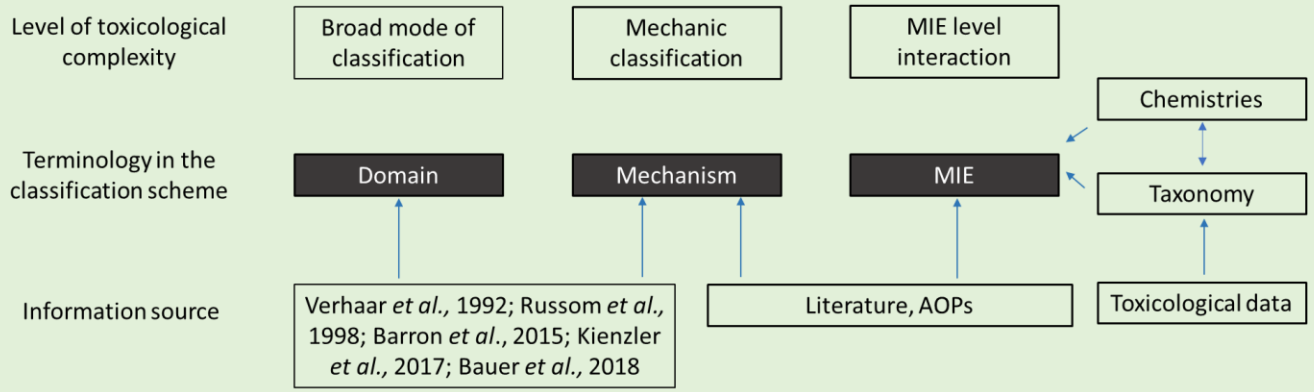
APPROACH

- MIEs from existing classification schemes [1-3] and the literature were reviewed for mechanisms of toxic action relevant to environmental effects

- Various supporting information for each MIE was identified and compiled

- MIEs were grouped into three broad domains, consisting of 24 further mechanistic groups



Domain	Mechanistic group
Unspecific	**Narcosis** (non-polar, polar, polar, Ester, Amine, Other), **Uncoupling**
Chemistry	**Electrophilic** (Soft, Hard, Pre-reactive), **Free radical** (Radical damage of tissues, Mitochondrial damage / disruption), **Redox cycling**
Specific	**Enzyme inhibition** (AChE, Photosynthesis), **Ion channel modulators** (Modulation of ion channels), **Cellular function disruption** (Amino acid biosynthesis, Cell structure, Fatty acid biosynthesis, Nucleic acid biosynthesis, Steroid biosynthesis, Carotenoids synthesis, Developmental disruption), **Mitochondrial** (Mitochondrial electron transport chain inhibitors), **Hormonal function disruption** (Nuclear receptors - ER, AR TR, etc).

- The structural domain of the MIEs was defined in the form of structural alerts and converted to as SMARTs strings

- Alerts were incorporated into a KNIME workflow to allow for the profiling of chemical inventories and to compare the new scheme to existing schemes [1-3]

- A combined dataset was established for profiling consisting of: 1) high quality acute aquatic toxicity data from literature, 2) list of high volume home and personal care ingredients, 3) a list of compounds which are being environmentally monitored for regulatory purposes (5517 compounds)

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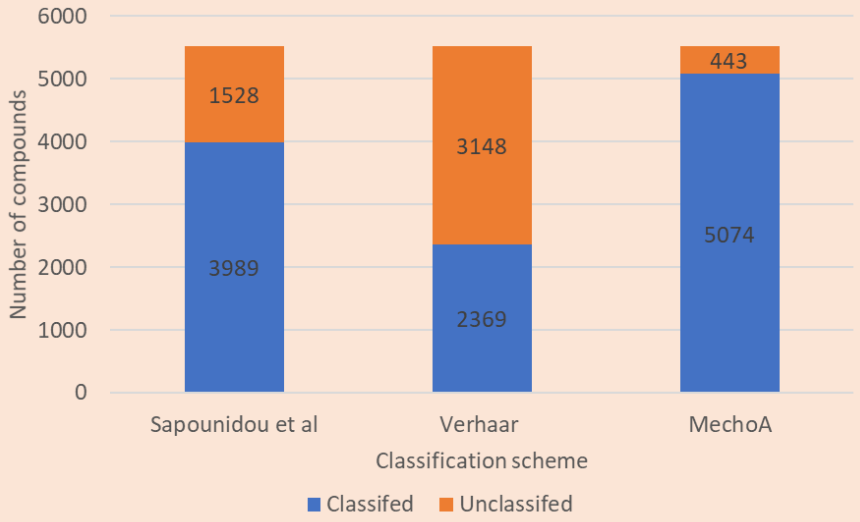
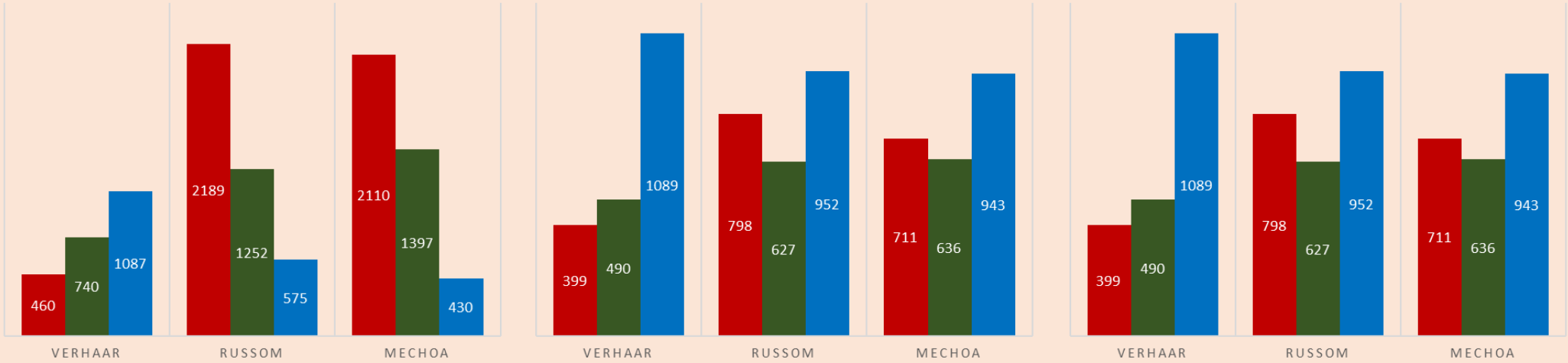
MAIN RESULTS

- The implementation of the novel scheme classifies over 75% of the 5517 compounds from the combined dataset
- Fewer compounds fall into the “unclassified” category with the new scheme as compared to Verhaar
- To allow a comparison, compounds were assigned to broad domains for all three schemes





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IMPACT/SIGNIFICANCE

- A novel classification scheme has been presented to support grouping of potential environmental toxicants
- It unifies existing knowledge into three broad mode of action classifications which are then broken down into individual mechanisms and MIEs
- The new scheme has a greater coverage of compounds within the reactive and specific domains
- The number of compounds that were unclassified is reduced relative to traditional schemes such as Verhaar
- The novel scheme is flexible and updateable, it allows direct linkage to MIEs and potentially AOPs which could provide insight to improve the weight of evidence

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