Chronic metal-organic mixture toxicity: quantitative reappraisal and identifications of data-gaps

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Introduction

- The European Union Chemicals Management Strategy for Sustainability[1] calls to integrate the issue of combined exposure into the assessment of substances by the introduction of a Mixture Allocation Factor.
- Toxicity of mixtures have predominantly been studied within broad substance groups, e.g. metals, pesticides, while mixture toxicity between metals and organics has been less well studied.
- This study is part of Eurometaux's comprehensive "Metals Environmental Exposure Data" gathering program (MEED) as project 4.

Objective of the study: Provide scientific evidence on effects of metal-organic mixtures using a literature search and quantitative reappraisal . Null-hypothesis is that metals and organic chemicals act independently from each other, i.e. that the Independent Action (IA) model is an accurate predictor of mixture toxicity.

Methods

Literature search

Chronic metal-organic mixture toxicity to aquatic organisms
- Starting from Martin et al. (2021)[2] extended with more recent WoS-search
- Studies published between 2007 and early 2023

Quantitative reappraisal[3]

3 regulatory questions on chronic organic-metal mixture toxicity to aquatic organisms
Q1: Is Independent Action (IA) a better model to predict metal-organic mixture toxicity than Concentration Addition (CA)?
Q2: What is the frequency of deviations relative to IA and CA?
Q3: How protective is CA on average at low mixture effects (~10% mixture effect)
→ calculation of Mixture Interaction Factor (MIF)

Mixture Interaction Factor (MIF)

$$MIF = EC10_{\sum TU_{EC10}}$$

At low mixture effect levels (~10%), if
- MIF=1: CA is accurate (=additive)
- MIF<1: CA is under-protective
- MIF>1: CA is over-protective

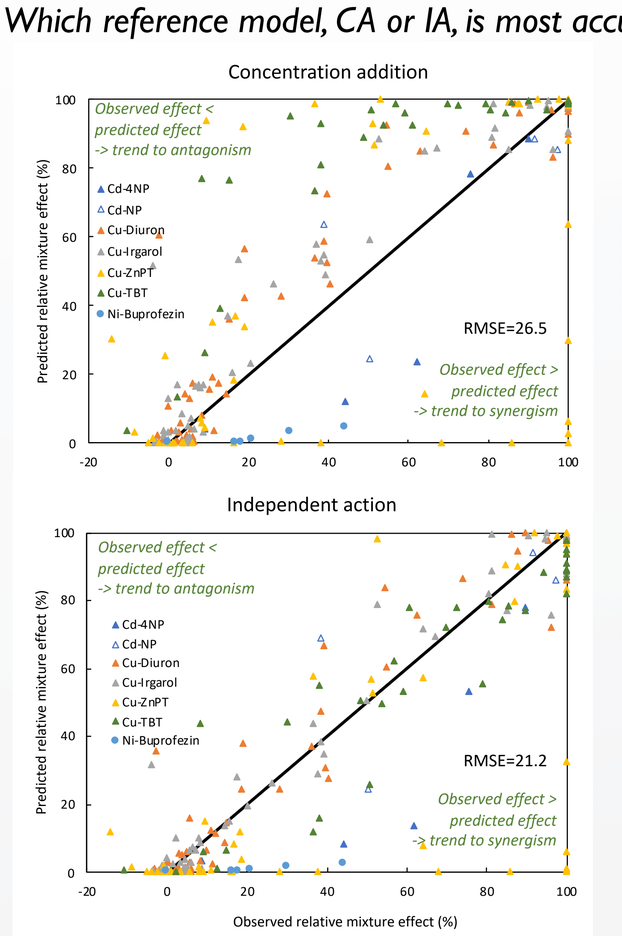
Results & Discussion

Outcome literature search

17 relevant studies identified i.e. regulatory-relevant chronic aquatic endpoints/species. Only 5 studies (14 experiments)[4-8] reported enough data to be reliable for inclusion in the quantitative reappraisal:
- 3 metals (Cu, Ni, Cd) & 6 organics (pesticides, antifouling agent, plasticizer)
- 6 algae species and 1 fish species

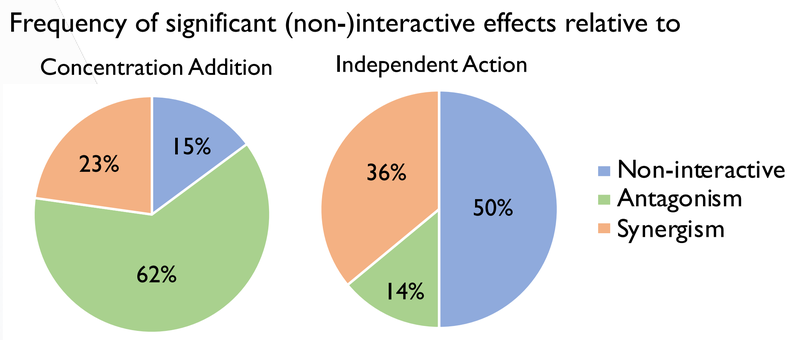
Outcome quantitative reappraisal

Q1: Which reference model, CA or IA, is most accurate?



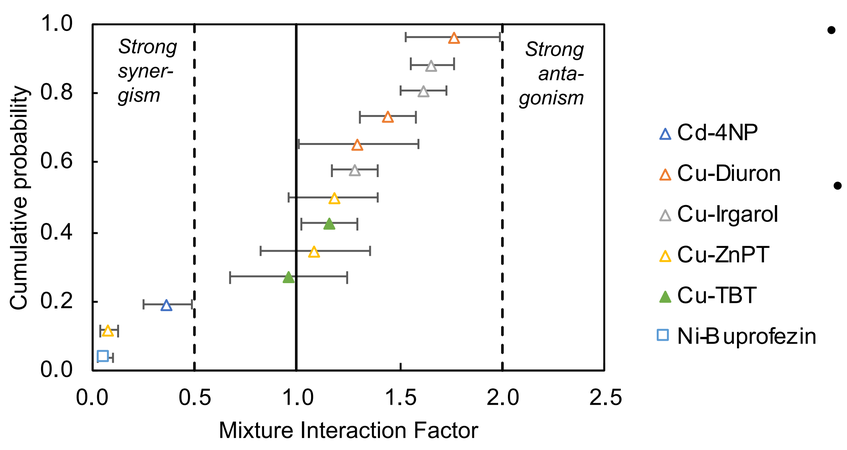
- Chronic metal-organic mixture toxicity is slightly better predicted with IA (lowest RMSE).
- CA is generally the most conservative model

Q2: How frequently do statistically significant deviations relative to IA and CA occur?



- Relative to CA, interactions were mostly antagonistic (62%).
- Relative to IA, non-interactive effects were most frequent (50%).
- Synergisms observed in 23% (CA) and 36% (IA) of the mixture experiments. These could be either related to unreliable test-systems, environmentally non-relevant mixture concentrations or representing complex mixture systems (e.g. Cu-ZnPT), especially when evaluated relative to CA.

Q3: Accuracy of CA for predicting mixture effects at low effect concentrations: what is the magnitude of the MIF?



- CA was on average predictive of mixture toxicity at low effect levels: median MIF is 1.18.
- Three experiments hinted at quite strong synergisms relative to CA, as shown by MIF<0.5. These could either be related to regulatory and/or environmentally non-relevant mixture concentrations, non-simultaneously testing or representing complex mixture systems

Conclusion

- Only few chronic metal-organic mixture toxicity studies were identified that allowed a systematic quantitative reappraisal.
- Among those, IA seemed to perform somewhat better than CA. Alternatively, CA was on average predictive of mixture toxicity at low effect levels (~10% mixture effect), with median Mixture Interaction Factor (MIF) equal to 1.18.
- Most identified chronic metal-organic mixture studies have been conducted outside of environmentally or regulatory relevant mixture concentrations, or both. It is therefore currently not possible to draw any meaningful conclusions with respect to our null hypothesis. Hence, there is a **need to investigate metal-organic mixture toxicity at environmentally and regulatory relevant concentrations, with appropriately sensitive species and endpoints.**

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References: [1] European Comission. 2021. EU Chemicals Strategy for Sustainability. https://environment.ec.europa.eu/strategy/chemicals-strategy_en; [2]Martin et al. 2021. Environ Int 146, 106206; [3] Nys et al. 2018. Environ Toxicol Chem 37: 623-642; [4]Wang et al. 2018. Ecotox Environ Safe 154: 145-153; [5] Dupraz et al. 2018. Chemosphere 209: 801-814; [6] Ku et al. 2015. Environ Sci Technol 49: 4600-4608; [7] Yi et al. 2017. Mar Pollut Bull 124: 839-846; [8] Ke et al. 2022. Environ Sci Pollut R 29: 78913-78925.