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Viewpoint

Enhanced Risk Assessment of Transformation Products through Chemical Similarity Analysis

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Chemical pollution is one part of the triple planetary crisis, alongside climate change and biodiversity loss. To better address this complex issue, it is essential to recognize that chemicals undergo various transformations over their life cycle. These transformations can occur through metabolism within organisms, treatment operations (e.g., wastewater and drinking water treatment), and natural processes in the environment (e.g., photolysis and hydrolysis). They generate new chemical pollutants [transformation products (TPs)] that can be structurally related to the respective parent compounds. The importance of characterizing TPs in the aquatic environment has been emphasized.[1] Many commonly used chemicals are designed to be biologically active, such as pharmaceuticals (e.g., antibiotics), pesticides, and biocides, and TPs of these substances are likely to exhibit similar effects, particularly when the toxophore remains intact. Thus, they pose potential risks to environmental organisms and human health.

TPs have long been included in ecological risk assessment of pesticides; e.g., the European Food Safety Authority (EFSA) guidance on aquatic organisms included a tiered approach with (non)testing methods more than a decade ago.[2] For industrial chemicals, covered by European Union Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulations, assessing the risks associated with TPs is more challenging. The formation of TPs typically involves a variety of complex mechanisms (e.g., biotic and abiotic), which are not systematically identified during regulatory risk assessment of the parent compound. Many TPs are discovered through nontarget screening studies that may not always provide quantitative results. Moreover, the lack of commercial chemical standards for most TPs hampers ecotoxicological testing and development of analytical methods to identify and quantify TPs. Laboratory-scale synthesis of potential TPs could be also very costly and time-consuming.

In a recent article,[1] we developed and applied an *in silico* approach for evaluating the ecotoxicity of TPs of antimicrobial chemicals. The approach is based on the analogy frequently used in medicinal chemistry that chemical similarity indicates a similar or even identical mode of action. We used this approach to explore a potential structural similarity threshold for TPs and the respective antimicrobial parent compound. Above this threshold, we cautiously assumed a similar mode of action and used toxicity end points of the parent compound for risk assessment purposes (termed the "read-across approach"). Extending this method with predictive *in silico* techniques could provide valuable insights into TP risks, effectively bridging the current data gap in risk assessment studies.

The core of our proposed *in silico* method is the calculation of structural similarity, for which there are multiple approaches available depending on, e.g., the research question, chemical space, and required precision of prediction. Typically, a cheminformatic representation of the molecule is derived by calculating its fingerprint using a path-based, substructure, or circular approach. The distance between fingerprints is then evaluated to assess the similarity between two molecules, and depending on the established similarity threshold, TP-parent pairs may be deemed similar or different.

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The Tanimoto distance is the most commonly used distance metric in similarity assessment[3] and is also mentioned in OECD guidance on grouping chemicals.[4] We utilized the PubChem's open-access transformation database to illustrate the different approaches, using different fingerprints to encode the molecular structures. The proportion of TP-parent pairs classified as similar varied widely, highlighting the importance of selecting an appropriate algorithm (Table 1). Because no algorithm is universally superior, the choice should reflect the context and objectives of the analysis.

Table 1. Proportion of TP-Parent Pairs Classified as Similar Using Different Fingerprinting and Similarity Methods from ChemmineR (R package) and RDKit (Python module)[a]

method	TP-parent pairs classified as similar (%)
ChemmineR MCS	21.35
RDKit Path-based fingerprint	14.92
RDKit Avalon fingerprint	9.25
RDKit MACCSKeys fingerprint	7.39
RDKit Topological fingerprint	0.79
RDKit Daylight-like fingerprint	0.44
RDKit Morgan fingerprint	0.36

[a]The TP-parent dataset (n = 7241) was obtained from PubChem's Transformations section (DOI: 10.5281/zenodo.5644561), and the similarity threshold is based on the work of Löffler et al.[1] Code available via https://github.com/paloeffler/TP_Similarity.

This approach has some limitations. For instance, Tanimoto coefficients emphasize the presence over the absence of fragments, leading to a larger overlap between complex query fragments and database compounds than between simple queries and the same target. Other distance metrics or similarity metrics should be evaluated and their limitations considered when developing the appropriate methodology for risk assessment of TPs.

The most appropriate method and similarity threshold depend on the research questions, specifying, for example, how conservative the analysis should be. This involves considering whether it is preferable to include more chemicals as similar, rather than adopting an overly restrictive approach, requiring careful evaluation for each investigation. In the context of risk assessment, the precautionary principle calls for a conservative approach in cases in which experimental toxicity values for validation are lacking. In our recent study of antimicrobial TPs,[1] we used literature data to determine the activity of known TPs and set the similarity threshold in accordance with the findings.

While chemical similarity often serves as a useful and valuable predictor for toxicological end points, the predictions can exhibit some variabilities; e.g., exchanging an NH moiety for an oxygen atom (OH moiety) can sometimes lead to shifts in affinity constants of 3 orders of magnitude.[5] A complementary approach hence involves studying the interaction of the parent compound and respective TP with the relevant target protein using molecular docking, yielding a more resource-intensive but potentially more precise estimation of potential TP activity.[6] Given the general structural similarity of TPs and their parent compounds, more comprehensive exploration of TP activity relative to that of the parent compound might be achievable using molecular dynamics simulations coupled with free energy perturbation.

All of these proposed read-across approaches assume, at a minimum, the same mode of toxic action of the TP and the parent compound, but it is crucial to acknowledge that other toxicity mechanisms of the TP may exist. In addition, transformation may change physicochemical properties, such as the solubility or partition coefficient, influencing the environmental fate and ecotoxicity.

The issue of TPs demands urgent attention. Chemical pollution continues to affect the environment, and the intricate nature of TPs conceals the potential threats that must be understood and addressed promptly. Collaborative efforts by scientists and policymakers are crucial in deciphering the complexities of TPs and protecting life on Earth. Only through collective action can we preserve the environment for future generations and ensure a sustainable future. The incorporation of additional predictive *in silico* techniques into current technical guidelines may be a necessary and essential step in addressing existing data gaps, particularly in risk assessment studies of TPs. It is crucial to highlight the fact that *in silico* methods must undergo validation through laboratory studies to confirm their robustness. The existing information about pesticides, including their active substance and TPs, could also be used to verify and enhance the reliability of *in silico* techniques. Institutions such as the EFSA and the U.S. Environmental Protection Agency regularly publish comprehensive information about the toxicity of active substances and their TPs, which can serve as a valuable reference for the validation and refinement of mathematical models. We believe that our suggested approach to characterizing chemical similarity could be a useful complementary tool in assessing the potential hazards of TPs in the absence of experimental data.

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Notes

The authors declare no competing financial interest.

Biographies

Paul Löffler is a Ph.D. candidate at the Swedish University of Agricultural Sciences investigating the impact of antimicrobial transformation products on aquatic environments. Holding a bachelor's degree in chemistry from the University of Stuttgart and a master's degree in ecotoxicology from the University Koblenz-Landau, he integrates his expertise together with multidisciplinary colleagues from, for example, medicinal and computational chemistry to enhance *in silico* methodologies.

Foon Yin Lai is a senior lecturer in the field of analytical and environmental chemistry. Her group is researching chemical use in society (wastewater-based epidemiology), water pollution, source elucidation, and (waste)water reuse related to emerging contaminants. In these topics, her group develops new analytical methodology for chemical detection and also workflows with *in silico* tools and new approaches for prioritizing chemicals of concern and for chemical risk assessment. She is interested in studying transformation products and other chemicals associated with negative health effects, e.g., antimicrobial resistance and endocrine disruption. She obtained her Ph.D. in environmental forensic chemistry from The University of Queensland (Australia) in 2014 and has been an Associate Professor at the Swedish University of Agricultural Sciences (Sweden) since 2020.

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