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TOX/2025/13

Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment

Update from FSA Fellow and PhD student

Presentations from the FSA Fellow and PhD Student

Introduction

1. The FSA and COT have been reviewing New Approach Methodologies (NAMs) to scope the best scientific methodologies available to be used in risk assessment of chemicals in foods and the environment, and to understand how these can be incorporated and accepted in a regulatory context.

2. In 2021, the FSA started funding a 4-year computational toxicology postdoctoral fellow Dr Arthur de Carvalho e Silva at the University of Birmingham and a three-year PhD Student Mr Alexander Kalian (London Interdisciplinary Doctoral Program-LIDo-TOX AI) at King's College London.

3. The fellow and PhD student have been working alongside other government departments to understand how NAMs will improve indicative levels of safety in chemical risk assessment.

4. In addition, these new partnerships have helped with networking, research collaboration, training opportunities and furthering our knowledge in this area. The fellowship and studentship also compliment the work set out in the COT FSA UK NAMs Roadmap towards using new approach methodologies in chemical risk assessment.

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5. The Fellow and the PhD student have prepared a yearly review as outlined below and will present their progress to date to the COT Members.

Postdoctoral Fellow Update

Advancing in silico methods of assessing toxicological risk

Why and how are you associated with the FSA?

6. The FSA and COT have been reviewing new approach methodologies (NAMs) and developing a UK NAMs roadmap towards the integration and acceptance of NAMs for chemical risk assessment. One of the activities defined in this roadmap was to actively work on advancing *in silico* methods for assessing toxicological risk, specifically focused on food-related chemicals, but remaining open to work on other classes of chemicals relevant to the FSA's risk assessments. In this context, I was recruited as a computational toxicology fellow and awarded a 4-year fellowship funded by the FSA, whilst supervised by a team of academic and applied NAM experts. The supervisory team is composed of Prof. Mark Viant and Prof. John Colbourne (University of Birmingham), Dr. George Loizou (former Head of Computational Toxicology at HSE Science and Research Centre), and Dr. Olivia Osborne, Ms. Claire Potter, and Dr. David Gott (FSA).

Broad overview of the FSA fellowship and its aims

7. The programme of work of the fellowship consists of (i) scoping the FSA's problem space in chemical risk assessment and mapping this to our computational NAMs solution space, thereby aiding the FSA to develop a strategy for the utilisation of NAMs (months 1-24); (ii) ensuring that the FSA is trained in the use of computational NAMs by delivering training courses, including an introduction to existing and emerging NAM technologies, and topics selected from the FSA's NAM strategy (months 1-48); (iii) developing and evaluating confidence in a new hazard assessment workflow that integrates *in vitro* omics toxicity data, benchmark dose modelling and PBPK modelling to serve as the basis for quantitative risk assessment for human health, i.e. towards generating human health-based safety thresholds for

the FSA and other regulators (months 1-36); and (iv) developing and delivering a second case study that fortifies the community-wide acceptance of 21st century methods in risk assessments, to accelerate the successful application of NAMs within the FSA (months 25-48).

Progress with case studies

8. The latest case study launched is focusing on plant alkaloids of three large classes: tropane alkaloids (TAs), pyrrolizidine alkaloids (PAs), and glycoalkaloids (GAs). The supervisory team decided to start with TAs. In terms of food safety, the first objective of this case study is to support the UK FSA's policy need to determine which TAs are the most potent (neuro)toxicants to prioritise specific substances and inform decisions on the UK's monitoring of these alkaloids in foods. An integral part of this aim is to confirm that neurotoxicity is the primary mode of action of these alkaloids. This aim will be achieved using a tiered-testing strategy of *in silico*, *in vitro* and 'omics NAMs. The second objective of this case study is to derive a HBGV for human exposure for the top priority, i.e. most potent substance within the class of TAs. This will utilise physiologically-based pharmacokinetics (PBPK) modelling and quantitative in vitro to in vivo extrapolation (QIVIVE). From a methodological perspective, a broader third objective of the case study is to evaluate and attempt to build confidence within the FSA in the application of a series of relevant NAMs that have been integrated in a manner to address policy needs. These NAMs are tiered and incorporate existing human *in vivo* data as well as new testing on human *in vitro* cell lines, to maximise the relevance and accuracy to human food safety. A tiered approach was proposed to achieve the objectives of this case study and is depicted in Figure 1.

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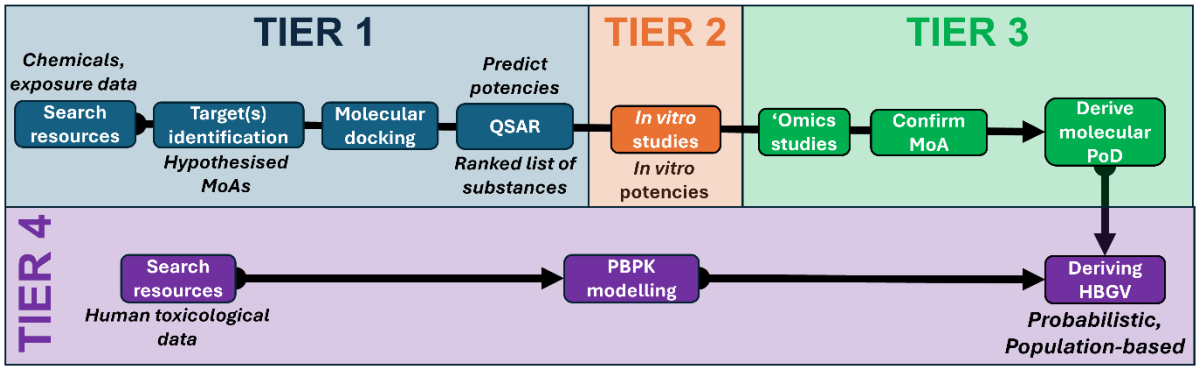

Figure 1. Master workflow describing the proposed tiered approach for the plant toxins case study.

9. The collaborative nature of this case study has been accepted at Accelerating the Pace of Chemical Risk Assessment (APCRA) meeting (Ottawa, CA, 2024) as an international case study; where several potential regulatory partners demonstrated interest and willingness to collaborate.

Progress with papers and conferences

10. Our recent work on PFOA is published (1) and was presented on several occasions. To list a few, PARC Science Day (poster presentation), NURA Dynamic Discussions (oral presentation, online), HSE's workshop (oral presentation, online), EFSA's workshop (oral presentation, online), EUROTOX 2023 (poster presentation), ASPIS Open Symposium 2023 (poster presentation), BTS Annual Meeting (2024, oral presentation). PFOA case study was submitted as a nomination to the Lush Prize under the Young Researcher category and has been one of the five projects awarded in 2022. Furthermore, PFOA case study was used in training sessions delivered to the UK HSA (2024) and to the students of the new MSc course (Human and Environmental Toxicology with Law) at the University of Birmingham (2024).

11. The plant alkaloids case study was presented at the APCRA meeting (Ottawa, CA, 2024) and formally accepted as a case study by its internal committee in the beginning of 2025; tier 1 results will be presented at the upcoming APCRA online meeting (2025) and submitted to EUROTOX 2025.

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PhD Student Update

TOX-AI : Geometric deep learning applied to toxicology, for developing next-generation tools and databases for aiding chemical risk assessment of molecules found in food and drink

Why and how are you associated with the FSA?

12. The Food Standards Agency (FSA) is jointly funding this PhD project, alongside the Biotechnology and Biological Sciences Research Council (BBSRC), as an iCASE (industrial CASE) project under the LIDo (London Interdisciplinary Doctoral programme) consortium, with the PhD project itself based at King's College London, while the FSA is named as an industrial partner. Dr Olivia Osborne, Dr David Gott (now retired) and Ms Claire Potter, of the FSA, are all formally named as part of the supervisory team, in addition to other supervisors. This project shall contribute to the FSA's interests, in developing innovative Artificial Intelligence (AI) based New Approach Methodologies (NAMs) for next-generation chemical risk assessment of molecules found in food and drink, to assist in improving consumer safety while simultaneously reducing reliance on animal testing. It is intended that, in addition to numerous publications of interest, a corresponding database of high-quality predictions for certain food and drink molecules shall be released for the FSA's use, alongside an open-source software tool.

Broad Overview of PhD

13. The primary aim of this PhD project is to develop novel Quantitative Structure-Activity Relationship (QSAR) models, using innovative AI, which may reliably predict toxicological properties of molecules found in food drink, over a diverse range of endpoints of interest. The project started by developing QSAR models of mutagenicity, using relatively simple deep learning approaches, before exploring use of more advanced deep learning approaches for navigating more challenging toxicological endpoints, such as neurotoxicity, developmental toxicity, reproductive toxicity, hepatotoxicity, nephrotoxicity, cardiotoxicity and more. A particular research focus has emerged, on using geometric deep learning algorithms via Graph Neural Networks (GNNs), to construct QSAR models that can directly handle molecular graphs and similar data as inputs. Additionally, specific chemical classes of concern have been investigated via the developed models, as part of targeted case studies; these have so far included Brominated Flame Retardants (BFRs), Selective Androgen Receptor Modulators (SARMs) and Tropane Alkaloids (TAs), while more may be included in the near-future. It is ultimately intended that the final models produced by this project will be as accurate as possible in their predictions, while also providing unique insights into toxicological space, compared to existing models in literature. It is furthermore aimed that the final developed QSAR models will be explainable and easily interpretable, via use of Explainable AI (XAI), along with reliable quantifications of uncertainty on particular predictions. The final QSAR models shall also be made available via open-source, accompanied by open-access datasets of associated predictions for certain molecules. The methods, results and other materials are being developed in close collaboration with the FSA, with a placement within the FSA actively taking place, while all materials are to be published in open-access publications and/or presented at relevant conferences.

Main Work Up to this Point:

14. The main work up to the present is composed of 4 parts: (1) Development of QSAR models of mutagenicity, using feed-forward neural networks and an exploration of dimensionality reduction techniques, before moving on to Graph Convolutional Networks (GCNs) and mining of Structural Alerts (SAs), (2) Case

study on BFRs, using Graph Attention Networks (GATs) to predict *in-vivo* doses and concentrations relevant to neurotoxicity, developmental toxicity and reproductive toxicity, via both graph-regression over molecular graphs and node-regression over knowledge graphs containing numerous molecules; (3) Case study on SARMs, using transfer learning on GCNs to predict Drug-Induced Liver Injury (DILI), Drug-Induced Renal Injury (DIRI) and Drug-Induced Cardiotoxicity (DICT); (4) Exploration of different GNN architectures – GCNs, GATs and Graph Isomorphism Networks (GINs), in order to characterise the most advantageous GNN architectures for navigating varying toxicological assay data environments.

Papers and/or Conferences in Progress:

- Society of Toxicology (SOT) 2025.
- 3 papers in progress, relating to work on BFRs, work on SARMs and work on exploring novel GNN architectures.

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Kalian, A.D., Benfenati, E., Gott, D., Potter, C., Dorne, J.L., Osborne, O.J., Guo, M. and Hogstand, C., 2024. P05-37 Graph attention networks using knowledge graphs, for predicting novel points of departure for brominated flame retardants. Toxicology Letters, 399, pp.S146-S147.

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