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FSA-funded Computational Toxicology Fellowship and LIDo PhD student in AI

15. 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 understand how these can be incorporated in a regulatory context with validation approaches.

16. The FSA have recruited a computational toxicology fellow at the University of Birmingham and a PhD Student (London Interdisciplinary Doctoral Program-LIDo-TOX AI) at King's College London. The aims of the projects are to develop *in silico* tools (*i.e.* artificial intelligence machine learning) for toxicological prediction of chemicals through case studies and proof of concept studies. The fellow and student will also work alongside other government departments to understand how NAMs will improve indicative levels of safety in chemical risk assessment.

17. The programme of work in 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; (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; (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 FSA and other regulators; 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.

18. The postdoctoral fellow continues to work on the internationally accepted case study (APCRA meeting, Ottawa, CA, 2024) Utilising in silico, in vitro and 'omics New Approach Methodologies (NAMs) for priority-setting and safety assessment of tropane alkaloids (TAs) as potential food contaminants.

19. This study aims to generate toxicity data for several more TAs, determine the most potent TA, and prioritize substances to inform UK monitoring decisions. A four-tiered approach was implemented to tackle these objectives. Tier 1 focuses on literature and databases searches, in silico target identification and potency prediction; tier 2 focuses on in vitro potency estimation; tier 3 focuses on multi-omics technologies applied to a subset of TAs to derive molecular PoDs; and tier 4 focuses on quantitative in vitro to in vivo extrapolation to derive health-based guidance values.

20. Preliminary results in Tier 1 revealed (a) neurotoxicity-related pathways such as neuroactive ligand-receptor interaction, signalling pathways (calcium, sphingolipid and cAMP), synapses (cholinergic, serotonergic, and dopaminergic), chemical carcino-genesis and pathways of neurodegeneration; (b) neurotoxicity-related MIEs such as muscarinic acetylcholine receptors (mAChRs) subtypes M1, M2, M3, M4, and M5; sodium-dependent transporters for dopamine, serotonin, and noradrenaline; sigma non-opioid intracellular receptor 1; and 5-hydroxytryptamine receptor 3A. Potential interactions between the TAs and all relevant targets were analysed using molecular docking.

21. Additionally, binary and regression QSAR models were generated and validated in compliance with OECD principles to predict the potency of each TA against all mAChRs subtypes, enabling ten TAs (atropine, 2-hydroxymethyl

atropine, scopolamine, anisodine, aposcopolamine, convolvine, fillalbine, convolamine, noratropine, and O-acetylscopolamine) to be prioritized for progression to tier 2.

22. Our recent work on tropane alkaloids (Silva et al., 2025) has been presented at QSAR Milan 2025 and was short-listed for the Alfonso Lostia Award on Food Safety research at EuroTox 2025.

23. The programme of work in the PhD 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 (Kalian et al., 2024); (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) (Kalian et al 2025); (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. (Kalian et al 2025).

24. The PhD student presented this work at QSAR Milan 2025 and SOT 2025.

FSA Research Programme

25. The FSA research strategy has seen the consolidation of all research in the portfolio into a series of programmes by area of research interest.

26. Current projects in the Chemical, Radiological and Hypersensitivity Research Evidence Programme include:

- Determination of the bioavailability of hydrogen cyanide following consumption. This project aims to determine the bioavailability of hydrogen cyanide from a range of foods.
- Method development for PFAS in fruit and vegetables. The aim of this project is to develop analytical techniques to measure 30 pre-identified PFAS in a range of fruit and vegetable matrices.