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S19-03
Emerging mitochondrial mechanisms mediating drug-induced cardiotoxicity

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Mitochondria play a central role in cardiac function, providing the energy required for contraction and ion transport. Their dysfunction has emerged as a key contributor to drug-induced cardiotoxicity. This presentation explores the fundamental mechanisms by which pharmacological agents impair mitochondrial function, ultimately leading to cardiovascular pathology.

After reviewing normal mitochondrial bioenergetics, including ATP production, calcium homeostasis, and ROS regulation, the talk delves into the dynamic balance between mitochondrial fission and fusion, essential for maintaining cardiac mitochondrial integrity. Disruption of this balance, often triggered by xenobiotics, predisposes the myocardium to contractile dysfunction and cell death.

A range of drugs – such as doxorubicin, arsenic trioxide, ethanol, diclofenac, and propofol – are examined as case studies. These compounds interfere with oxidative phosphorylation, induce mPTP opening, impair calcium handling, and alter mitochondrial dynamics, culminating in reduced ATP synthesis, increased ROS production, and mitochondrial membrane damage. Experimental data from *in vivo* and *in vitro* models underscore these mechanisms and their pathological consequences, including cardiomyopathy, arrhythmias, and heart failure.

Despite growing knowledge, predicting mitochondrial cardiotoxicity in clinical settings remains challenging. The development of sensitive, specific *in vivo* screening tools is essential to bridge the gap between preclinical findings and clinical outcomes.

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S19-04
Hepatotoxicity in fatty liver disease linked to obesity: role of xenobiotic-induced mitochondrial dysfunction

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Obesity is frequently associated with metabolic dysfunction-associated steatotic liver disease (MASLD, formerly called NAFLD), which encompasses hepatic lesions such as simple fatty liver (steatosis, i.e. fat accumulation), steatohepatitis (MASH) and cirrhosis. It is now acknowledged that mitochondrial dysfunction and oxidative stress are pivotal in the pathophysiology of MASLD [1]. Importantly, some xenobiotics including drugs, environmental pollutants, and alcohol can be particularly harmful in obese patients with MASLD [2,3]. Although different mechanisms could explain this observation, experimental investigations pointed to the important role of mitochondrial dysfunction [1–3]. Acetaminophen (APAP, paracetamol), which can cause liver injury via mitochondrial dysfunction will be given as an example of a drug able to induce more severe or more frequent hepatic cytolysis in patients with MASLD [4–6]. The case of alcohol will also be presented because its excessive consumption can accelerate the transition from fatty liver to MASH, at least in part via an aggravation of mitochondrial dysfunction [3,7]. For APAP and alcohol abuse, an increase in cytochrome P450 2E1 (CYP2E1) activity linked to MASLD could be involved in the worsening of hepatic dysfunction [8,9]. Indeed, CYP2E1 can generate the mitochondrial toxins N-acetyl-*p*-benzoquinone imine (NAPQI) and acetaldehyde from APAP and ethanol, respectively [8,10].

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S20 | ECF session; Towards Inclusive Toxicology: Bridging Diversity in Research and Practice

S20-01
EUROTOX Early Career Forum

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Supporting early career scientists is essential for fostering a dynamic and evolving scientific community. To address this need, the EUROTOX

Executive Committee established the EUROTOX Early Career Forum (ECF) in March 2024 – a dedicated initiative aimed at supporting Early-Career Researchers (ECRs) and building a vibrant, interconnected scientific network. The ECF operates as a collaborative and inclusive platform that embodies the Intersectoral, International, and Interdisciplinary (3I's) nature of contemporary toxicology, providing tailored opportunities for professional development and engagement across sectors.

The ECF is led by a team of eight ECRs with varied backgrounds in academia, industry, and regulatory science. This diverse composition ensures a breadth of perspectives and experiences, and our work is continuously shaped by direct feedback from the ECR community, allowing us to adapt to evolving needs. While operating independently, ECF works closely with the EUROTOX Executive Committee and Subcommittees to align with strategic goals of the society. This cooperation has driven progress in key areas such as the developing European Registered Toxicologist (ERT) info-materials, supporting career exchanges through the EUROTOX Early Career Exchange Program (ECEP), and advancing other career-focused initiatives.

At EUROTOX congresses, ECF offers a portfolio of tailored activities to promote networking and professional growth. Structured networking events, sightseeing-based social tours, poster walkaround presentations with senior mentorship, and the science popularization event "Pub Up Your Poison" have effectively engaged ECRs. Complementing these are our year-round online initiatives, including Talk Shows and blog posts that highlight scientific trends and ECF updates.

At the heart of the ECF is a strong advocacy for inclusion and diversity – not only in representation, but as foundational principles for scientific integrity and relevance. Diversity in research – whether biological, methodological, or cultural, is crucial for generating robust and generalizable scientific knowledge. This philosophy also underpins the rationale for organizing this scientific session, "Towards Inclusive Toxicology: Bridging Diversity in Research and Practice," which explores inclusion across academic, industrial, and regulatory domains.

In summary, the ECF serves as a dynamic platform fostering collaborations with other early-career networks to build a broader community supporting the professional and scientific growth of young toxicologists across sectors and disciplines. Through these initiatives, the ECF is helping shape a more inclusive, connected and forward-looking toxicology landscape.

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S20-02
Sex-specific differences in the immunotoxicity of PFAS

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Background: Per- and polyfluoroalkyl substances (PFAS) are emerging environmental contaminants with multiple hazardous properties including immunotoxicity. This study aimed to investigate sex-specific differences in PFAS-associated effects on human immunity on two levels: 1) immune-mediated disease prevalence and 2) gene expression.

Methods: This study involved 309 adults from the Czech Central European Longitudinal Study of Parents and Children: Young Adults (CELSPAC: YA). Associations between serum concentrations of nine PFAS and nine immune-mediated diseases were assessed using logistic regression. Furthermore, Bayesian kernel machine regression (BKMR) was applied to estimate the effect of the PFAS mixture on immune-mediated disease prevalence. In cases where a statistically significant interaction between PFAS exposure and sex was detected, sex-stratified analyses were performed. To explore transcriptomic profiles, RNA was isolated from participants´ peripheral mononuclear blood cells, sequenced using QuantSeq library and Illumina sequencing, and analysed. Significantly expressed genes associated with perfluorooctanoic acid (PFOA) were identified in a sex-stratified manner and subjected to pathway enrichment analysis using Pathway Studio. All analyses were adjusted for relevant confounders (i.e., sex, age, BMI, smoking, education, and family history of immune-mediated diseases).

Results: Outcomes of both logistic regression and BKMR indicated that sex modifies the effect of PFAS exposure on immune-mediated diseases, particularly for PFOS and atopic eczema. The transcriptomic analysis also revealed sex-specific differences: 511 PFOA-associated genes were identified in women and 756 in men, with only 30 genes (2%) shared between the sexes. Similarly, pathway enrichment analysis showed differences in affected pathways and entities between men and women.

Conclusion: Our findings highlight the immunomodulatory effects of PFAS exposure at both the disease and transcriptomic levels. The observed sex differences underscore the importance of conducting sex-stratified analyses when studying PFAS-associated effects.

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S20-03
AnthroDrugs-Tox: Personalized Toxicology through Population Genetics

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Endocrine-disrupting chemicals (EDCs) are a major concern for human and environmental toxicology because they can cause disruptions in reproductive function, foetal development, thyroid function, and increase the risk of reproductive cancers in men and women. They are also linked to infertility, early puberty, obesity, diabetes, and various cancers *(Mendes 2002, Klanova 2019)*.

Currently marketed and new drugs may exhibit unintended endocrine disruption, which is a concern in drug design and development *(Soverini 2018)*, since this could potentially lead to their market withdrawal or the termination of their development process. Personalized medicine is one of the elements of the P4 medicine of the future, and has already shown its ability to improve patients' lives in an individualized way *(e.g. Soverini 2018, Gambardella 2020)*. However, a series of limitations hinder its widespread implementation in the immediate or short term, which has led to the development of different methods of population stratification *(McGuire 2020, O'Hanlon Cohrt 2021, Litman 2019)*. One of these approaches is stratification based on the biological ancestry of patients, which has seen significant progress in recent years thanks to developments in DNA and ancient DNA analysis.

Stemming from our team's previous work in personalized medicine and drug development *(e.g. Font-Porterias 2021, Bhat-Ambure 2023)*, in this work, we propose to apply personalized toxicology for the optimization of drugs and chemicals considering their endocrine-disrupting potential by leveraging the human population genetics knowledge about

genes related with endocrine disruption. We analyse drug-related genes (DRGs) which are also related to the physiological response caused by EDCs. This contributes to avoiding the current pitfalls of a drug development process specifically focused on people of European descent.

In particular, we analyse a dataset of EDC-DRGs (drug toxicity-related genes) collated from the literature, describe their variability in human populations across the world, and search for potential signatures of adaptive natural selection in specific continental regions (Africa, East Asia, South Asia, Europe, and America). Thus, we analyse how population variability can affect the binding of drugs and chemicals to DRG-EDCs, allowing for the analysis of its effects on the toxicity experienced by individuals when exposed to these drugs and chemicals, and, for selected DRG-EDCs, we propose optimized drugs and chemicals, contributing to newer, optimized, safer-by-design substances for all human populations.

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S20-04
Diversity in PBTK modelling and implications for regulatory application

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The role of diversity in toxicology has gained increasing importance in recent years, as differences in sex, age, and genetics significantly influence toxicological outcomes. Individuals metabolize chemicals differently due to variations in enzyme activity, organ function, and physiological parameters, leading to differences in drug efficacy, toxicity, and overall health risks. Physiologically based toxicokinetic (PBTK) modelling is a valuable tool for supporting risk assessment, as it predicts internal chemical exposure from externally administered doses. With increasing model complexity, internal concentrations can be estimated not only in plasma but also across various organs, providing a more comprehensive understanding of chemical distribution and effects. Understanding the interplay of physiological factors within diverse human populations is crucial for refining PBTK models and improving regulatory safety assessments. This work examines the extent to which diversity is incorporated into PBTK predictions and the potential consequences of neglecting these factors. Ultimately, integrating diversity into PBTK modelling enhances the accuracy and reliability of safety evaluations, ensuring better protection for all populations and reducing health disparities.

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S21 | How safe is cannabidiol (CBD)?

S21-01
EFSA perspective: Cannabidiol (CBD) as a novel food

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Cannabidiol (CBD) is a known cannabinoid that can be either extracted from *Cannabis sativa* L. or synthesised chemically. Following a decision of the Court of Justice of the European Union (EU) that qualified CBD as food, the European Commission received nearly 200 dossiers to be considered under the Novel Foods (NFs) Regulation (EU) 2015/2283. Nineteen of these dossiers are currently under risk assessment by the European Food Safety Authority (EFSA).

Upon initiating the risk assessment process, EFSA identified major knowledge gaps on the safety of CBD. The latter were summarized in a statement published in 2022 (EFSA, 2022), highlighting the limitations of the available studies and identifying areas where additional experimental data were needed. The available literature from human and animal studies indicated primarily potential effects of CBD on liver, gastrointestinal tract, endocrine system, nervous system and psychological functions. In addition, several animal studies triggered concerns of reproductive toxicity, and the extent to which this could occur in humans needed further clarifications.

Since then, EFSA has consistently monitored and assessed newly available data and has endeavoured to update its statement on the safety of CBD as a NF pursuant to Regulation (EU) 2015/2283 by the end of 2025. This presentation will review the status of the data gaps and uncertainties previously identified in light of the new scientific evidence.

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S21-02
UK FSA perspective: CBD consumer guidance

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An announcement was made by the Food Standards Agency (England) that from 31st March 2021 all cannabidiol (CBD) products on the market must have their safety assured with companies submitting a valid safety application. Since then, there have been hundreds of CBD-related novel food applications. Consequently, a significant level of additional data became available *via* applicants that required technical review, together with the evidence available publicly on CBD safety. In considering the new evidence, the FSA's Advisory Committee on Novel