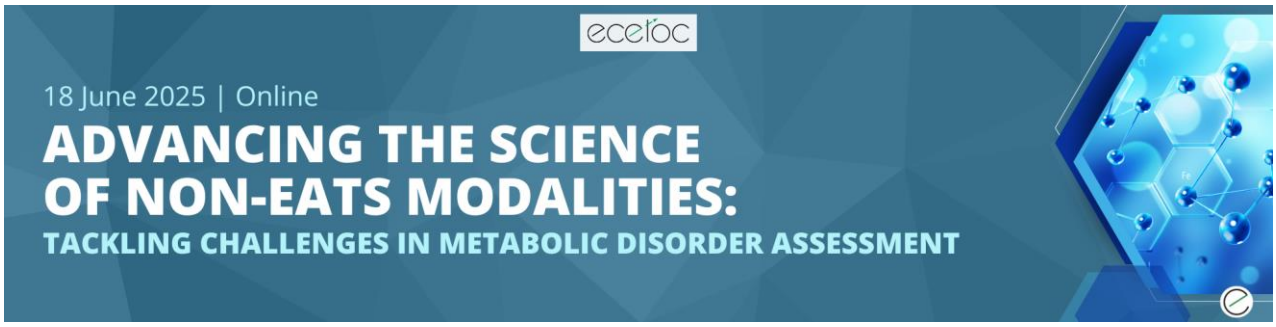


Advancing the Science of Non-EATS Modalities: Tackling Challenges in Metabolic Disorder Assessment

Date and Workshop Format: 18th June 2025, Online

Workshop background and objectives

Background and Scope:

Criteria to identify plant protection products and biocides with endocrine disrupting (ED) properties have been in place since 2018 under Regulation (EU) 1107/2009 and Regulation (EC) No 528/2012, respectively. These criteria are focused on adversity with a biologically plausible link to activity associated principally with the Estrogen, Androgen, Thyroid and/or Steroidogenesis (EATS) modalities, where there is extensive knowledge and validated methods. However, the scope of ED is now broadening to consider also non-EATS modalities. Unlike EATS, the scientific understanding and validated methods for these new areas are much less developed, leading to potential uncertainties and inconsistencies in evaluation.

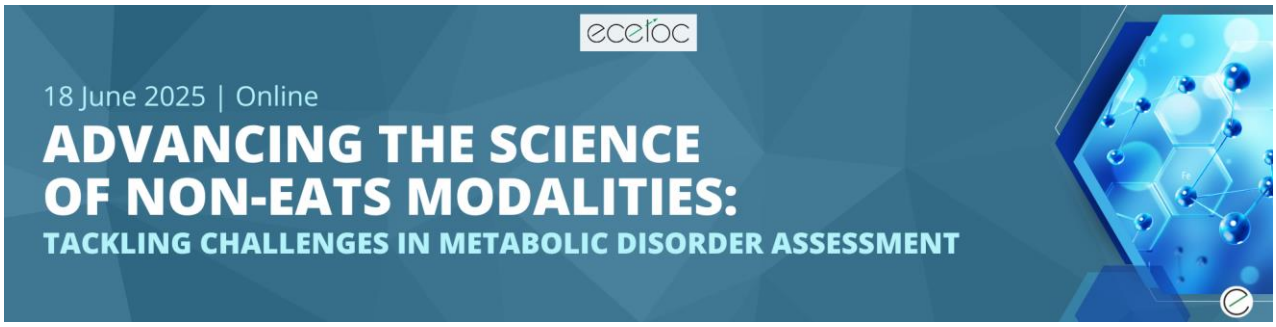
This workshop will bring together experts in toxicology, endocrinology, epidemiology, regulatory science and academia to explore ways to increase confidence in addressing non-EATS-related effects, particularly those associated with metabolic disorders such as diabetes, obesity and non-alcoholic fatty liver disease.

An ECETOC expert group will present their interim findings for discussion and feedback, and other experts working on the topic will be invited to present their insights as well.

Workshop Objectives:

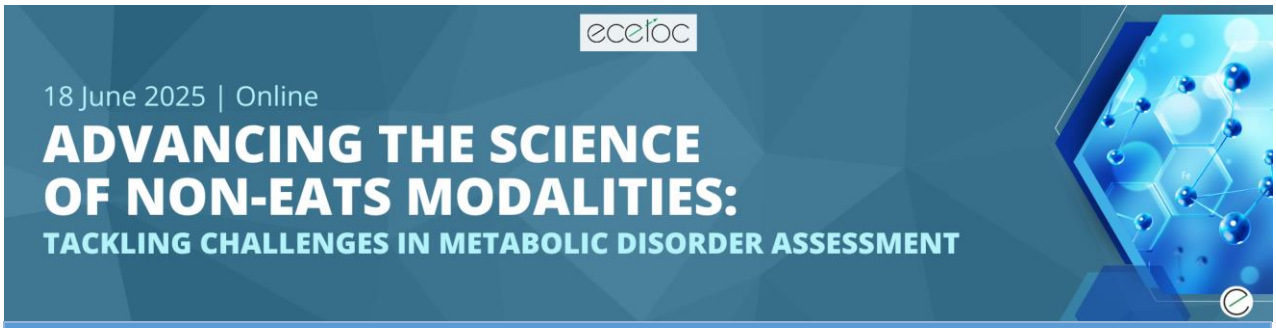
The objectives of the workshop are as follows:

- Understand the state of the science for non-EATS modalities related to metabolic disorders.
- Discuss and address current challenges in identifying non-EATS related effects associated with metabolic disorders. This should include but not be limited to:
    - Method availability
    - Data interpretation and contextualisation
    - How to differentiate between chemical exposure and lifestyle factors.
- Identify and prioritise research and assay development needs to improve confidence and certainty when addressing metabolic disorders.



Online Workshop – Programme:

Day 1: 18 June 2025 – Setting the scene & Discussions [Online]		
Time	**Agenda item**	**Who**
1:00-1:10 PM	**Welcome, introduction and workshop objectives**	***ECETOC***
1:10 - 2:10 PM	***Setting the scene: What's happening in this space?***	
	EURION projects on metabolic disruptors	***Juliette Legler, Utrecht University***
	PARC - Assays and IATA case studies to identify metabolic disruptors	***Philip Marx-Stoelting, BfR***
	ENKORE (NEMESIS)	***Jaana Rysä, University of Eastern Finland***
	ENKORE (EDC-MASLD)	***Matej Oresic, Örebro University***
	PEPPER PLATFORM (Advancement in validation of methods)	***Philippe Hubert, PEPPER***
2:10 - 2:25 PM	***15-min Q&A***	***AUDIENCE***
2:25 - 2:35 PM	***Coffee break***	
2:35 - 2:45 PM	**ECETOC Task Force on State of the Science and Next Steps for Non-EATS Modalities (metabolic disorders) – Scope and timing**	***Helen Tinwell, Bayer***
2:45 – 3:00 PM	**SG4 – Chemical classes implicated to date and knowledge on exposure**	***Kat Sioutopoulou, Syngenta***
3:00 - 3:15 PM	**SG3 – Epidemiology and lifestyle factors**	***Stephanie Kuhn, Syngenta***
3:15 - 3:30 PM	***15-min Q&A***	***AUDIENCE***



Day 1: 18 June 2025 – Setting the scene & Discussions [Online]		
Time	**Agenda item**	**Who**
3:30 - 3:45 PM	**SG1 – AOP status**	***Dries Knapen, University of Antwerp***
3:45 - 4:00 PM	**SG2 – Approaches and methodologies for Screening of Non-EATS Modalities**	***Tushar Mahale, Lubrizol***
4:00 – 4:15 PM	***15-min Q&A***	***AUDIENCE***
4:15 - 4:30 PM	***Coffee break (and time to collect questions)***	
4:30 - 5:30 PM	**Questions, research needs and discussion points raised by the audience**	***AUDIENCE***

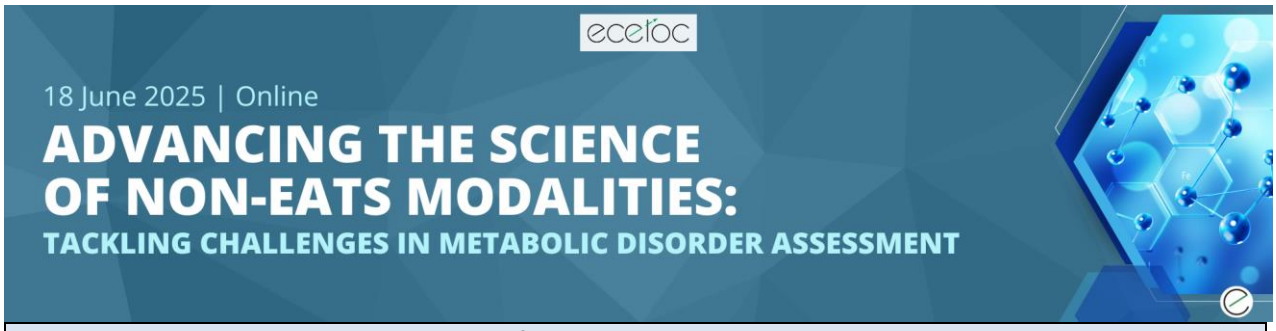
Abstracts and Speakers' bios

EURION projects on Metabolic Disruptors
Dr. Juliette Legler, Utrecht University

The need for reliable, reproducible and relevant tests to identify the potential metabolism disrupting effects of chemicals has been internationally recognized, as without them, comprehensive hazard and risk assessment of this class of chemicals is virtually impossible. Within the European Cluster to Improve Identification of Endocrine Disruptors (EURION), three projects were conducted between 2019 and 2024 with the aim of developing robust methods for the testing and assessment of metabolism disrupting chemicals (MDCs), a class of EDCs which contribute to the development of obesity, diabetes and/or fatty liver in humans. These projects included EDCMET (Metabolic effects of endocrine disrupting chemicals: novel testing methods and adverse outcome pathways), GOLIATH (Generation of novel, integrated and internationally harmonised approaches for testing metabolism disrupting compounds) and OBERON (An integrative strategy of testing systems for identification of EDs related to metabolic disorders). All three projects. These projects brought the field forward by increasing our understanding of the endocrine modes of action of MDCs, developing assay candidates for MDCs, and further developing selected assays into pre-validated test methods. During this presentation I will provide the highlights from these three projects.

These projects have received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825489, 825762, and 825712.

Juliette Legler is Professor of Toxicology and chair of the Toxicology division at the Institute for Risk Assessment Sciences, Utrecht University, The Netherlands. Prof. Legler studies how exposure to environmental contaminants such as endocrine disruptors affect human and environmental health. An expert on the role of EDCs in metabolic disorders such as obesity, her research focusses on elucidating the molecular mechanisms of endocrine disruptors and using these insights as the basis for the development of test methods. She coordinated the European GOLIATH project, which had the objective of developing and validating test methods for the identification of metabolism disrupting chemicals.



PARC - Assays and IATA case studies to identify metabolic disruptors
Dr. Philip Marx-Stoelting, BfR

Abstract

Biography

Horizon Europe Project: NEMESIS
Dr. Jaana Rysä, University of Eastern Finland

Endocrine-disrupting chemicals (EDCs) pose a complex threat to human health by disrupting crucial metabolic pathways in organs such as the liver and pancreas. This interference is associated with the increasing prevalence of obesity, atherosclerosis, and type 2 diabetes, with potential long-lasting effects spanning generations. Despite these widespread impacts, understanding the metabolic effects of EDCs remains elusive and is hindered by a lack of mechanistic data and predictive models. To address this gap, the EU-funded NEMESIS project brings together experts across disciplines to unravel the details of EDC-induced metabolic disruption through diverse research methodologies and advanced data analytics. NEMESIS aims to enhance risk assessment strategies and to develop effective risk communication practices to maximize the science-to-policy impact of the project findings.

Jaana Rysä, *ERT, is a Professor of Drug Toxicology and Director of the master's degree Programme in Toxicology at the University of Eastern Finland. She has extensive experience leading projects that focus on the molecular mechanisms of diseases and toxicity. Her current research interests include the harmful effects of chemicals and drugs on human health, with a particular emphasis on the metabolic impacts of endocrine-disrupting chemicals on placental function. Dr. Rysä is the coordinator of the EU-funded project Novel Effect Biomarkers for Metabolic Disruptors: Evidence on Health Impacts to Answer Science and Policy Needs (NEMESIS).*

Horizon Europe Project: EDC-MASLD
Dr. Matej Oresic, School of medicine, Örebro University (Sweden)

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the condition of excessive accumulation of liver fat unrelated to alcohol intake, ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH). With a 25% prevalence in the general population, MASLD is currently the most common liver disease, and a major healthcare and economic burden. While hyperlipidaemia, obesity and insulin resistance are the major risk factors for MASLD and contribute to its rising prevalence, growing evidence suggests that exposure to endocrine-disrupting chemicals (EDCs) can initiate and/or cause progression of MASLD. The European project EDC-MASLD focuses on investigating the impact of environmental exposure to EDCs on the internal exposome (metabolome, gut microbiome, epigenome, proteome, immunome) and degree of liver damage in MASLD in prospective study settings, with a focus on the period of transition to progressive stages of MASLD. EDC-MASLD is particularly focused on interactions between EDC exposure, sex, genotype, diet, socioeconomic and lifestyle factors, via the data and biosamples available in the unique European Steatotic Liver Disease (SLD) Registry, comprising over 9,000 patients with histologically characterised MASLD. EDC exposure studies are performed in murine models of MASLD, zebrafish models, and human 2D/3D in vitro models, with an aim to understand respective mechanisms-of-action and to develop novel EDC screening tools.

Matej Orešič holds a PhD in biophysics from Cornell University (Ithaca, NY, USA). He is professor of medicine (systems medicine) at Örebro University (Sweden) and a professor of biochemistry (metabolomics) at the University of Turku (Finland). Prof. Orešič's main research areas include exposomics and metabolomics applications in biomedical research and systems medicine. He is particularly interested in the identification of environmental exposures and disease processes associated with different metabolic phenotypes and the underlying mechanisms linking these processes with the development of specific disorders or their co-

morbidities. Professor Orešič currently coordinates Horizon Europe project "Inflammation in human early life: targeting impacts on life-course health – INITIALISE (https://initialise-project.eu/)". He is also Co-Coordinator of the Horizon Europe project "Investigation of endocrine-disrupting chemicals as contributors to progression of metabolic dysfunction-associated steatotic liver disease – EDC-MASLD (https://edc-masld.eu/)".

PEPPER PLATFORM (Advancement in validation of methods)
Dr. Philippe Hubert, PEPPER

The regulatory demand on Endocrine disruptors (EDs) is now quite established (e.g. CLP category). Research has developed methods for characterizing endocrine properties, including in the more recent non-EATS domain. Nevertheless, there is a missing link between research and regulatory science that can be bridged by what is commonly called "validation" (recognition of reproducibility, predictivity and also relevance for regulation), so that regulation can be effective and efficient.

To fill this gap, a non for profit Public Private platform was created in late 2019. The Pepper platform was innovative in two ways; combining the organization and funding of methods validation, and pooling public and private resources. Its operations are described.

First is the search of methods that deserve to undergo validation: scientific quality, but also "Readiness" and "Relevance" (the ability to fill a gap).

Once a method is selected, a "validation experiment plan" (e.g. how many laboratories will participate; how many substances will serve as "test compounds" …) is designed, a call for laboratories that would participate in ring test is launched, a "validation management group" with experts in assays, chemicals, endocrine disruption and validation is assembled, a data manger and a statistician are hired. The next stage (transferability) consists in carrying out the test in the laboratories, on known substances. Finally, a blinded ring test is carried out, with around 30 substances for the 'simpler' tests and fewer substances for the more 'complex' (or expensive) tests.

The analysis of the results bears on reproducibility and predictability. A validation report is drafted and presented to the Scientific Council. Should the results be satisfactory, the method can be proposed, for example to OECD in order to become a "test guideline".

A team of 6 people, out of them 4 are "validation Project Managers" is running the process for 13 methods, involving 26 participating laboratories. The mix of scientific analyses (e.g. scrutinizing the procedure, biology, and results), management/know-how (e.g. selection and contracting of laboratories and support), and contingency planning (availability of consumables, the flow of data communication) is typical of the work of the platform.

The validation process described above is often criticized as being long and costly, but the overall workload within the laboratories is not massive, and a tight management can reduce it drastically.

Philippe Hubert was the first director of Pepper, the Public-private platform for the validation of endocrine disruptors characterization methods, after its creation in 2020. Pepper pools public and private resources and organizes validation of bioassays to bridge the gap between academic research and regulatory science. He worked previously as head of the Chronic Risk Division at INERIS (French National Institute on Industry and Environmental Risk), where toxicology and ecotoxicology on nanos, EMF, EDs, pollutants are performed, as well as chemical analysis, and air pollution forecasting. At the French National Institute for Nuclear Safety and Radiation Protection, he managed the Risk Assessment and Management department (radiation epidemiology, risk analysis, risk perception). He developed methods for low dose effect assessment. After graduating at Ecole Polytechnique in Paris, he specialized in statistics applied to rare events and epidemiology.

ECETOC Task Force on State of the Science and Next Steps for Non-EATS Modalities (metabolic disorders) – Scope and timing

Dr. Helen Tinwell, Bayer

Since the introduction of endocrine disrupting (ED) criteria in Europe in 2018 the assessment of substances for ED properties has expanded in terms of the modalities (EATS and non-EATS) to be considered. This presentation will provide an overview of the increasing regulatory focus on the non-EATS modalities and will highlight the uncertainties and challenges associated with assessing substances for such modalities. In addition, a summary will be provided of an on-going initiative organised by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) to explore ED with respect to non-EATS modalities. The objectives of this resulting global multistakeholder taskforce (TF) will be described and an overview concerning the progress of the TF with respect to understanding our current knowledge on ED related metabolic disorders such as diabetes, obesity and non-alcoholic fatty liver disease will be presented.

Dr. Helen Tinwell is a Distinguished Science fellow at Bayer Crop Science and is the team leader for a group of regulatory toxicologists based at the toxicology laboratory in southern France. She has been studying and publishing on endocrine disruption for nearly 30 years and has been a contributor and partner on several expert working groups and expert panels, as the field has matured and expanded past EATS modalities.

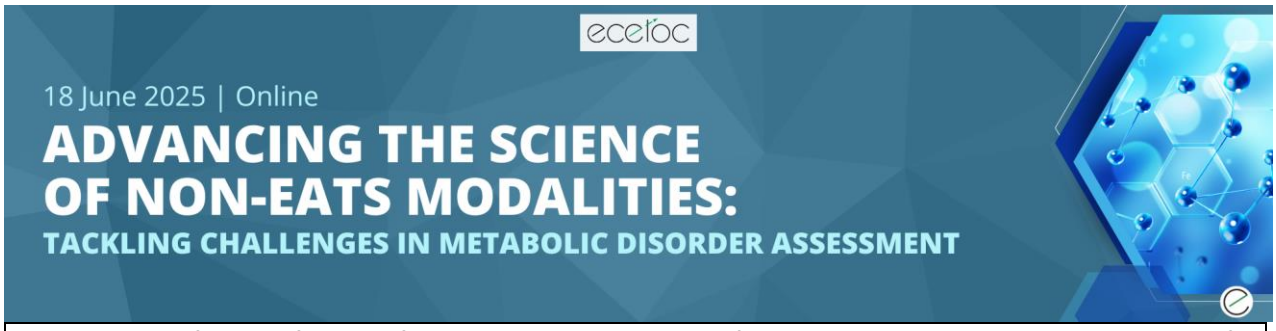
Subgroup 4: Chemical Classes Implicated to date & Knowledge on Exposure
Dr. Kat Sioutopoulou, Syngenta

The global incidence of metabolic diseases, including obesity, type 2 diabetes, and liver steatosis, has risen exponentially, becoming a major public health concern. While the aetiology of these conditions is multifactorial, emerging research suggests a significant role for endocrine-disrupting compounds (EDCs), leading to the proposed term "metabolic disruptors". The objective of the Subgroup 4 is to critically evaluate the evidence supporting the designation of certain chemicals as metabolic disruptors from the literature, focusing on obesity, type 2 diabetes, and liver steatosis. Given the absence of scientific criteria for metabolic disruptors, Subgroup 4 proposes that the scientific criteria for the determination of EDCs, should be applied, i.e., evidence on presence of an adverse effect(s), endocrine activity, and a biological plausible link. Our two-phase approach first identified relevant physiological tissues and processes and reviewed the available toxicological data from regulatory dossiers publicly available on ECHA, EFSA and UPA databases. The second phase, which is still ongoing, mapped relevant Adverse Outcome Pathways (AOPs) and Molecular Initiating Events (MIEs), incorporating bioactivity data from the US EPA ToxCast/Tox21 dashboard. This comprehensive methodology will allow for a thorough assessment of the biological plausibility linking endocrine activity to adverse metabolic effects and the strength of the available evidence.

Kat is a Toxicology - Technical Expert who leads the Endocrine Disruption (ED) team and is part of the Developmental and Reproductive Toxicology (DART) group within Syngenta's Global Toxicology Department at Jealott's Hill Research Centre in the UK. Kat holds a BSc in Biochemistry and Biotechnology from the University of Thessaly, Greece, and an MSc in Toxicology and Risk Assessment from Brunel University, London. Her postgraduate thesis focused on the effects of propylparaben, an endocrine-disrupting chemical, on primary human mammary stromal cells.

Subgroup 3: Epidemiology & Lifestyle factors
Dr. Stephanie Kuhn, Syngenta

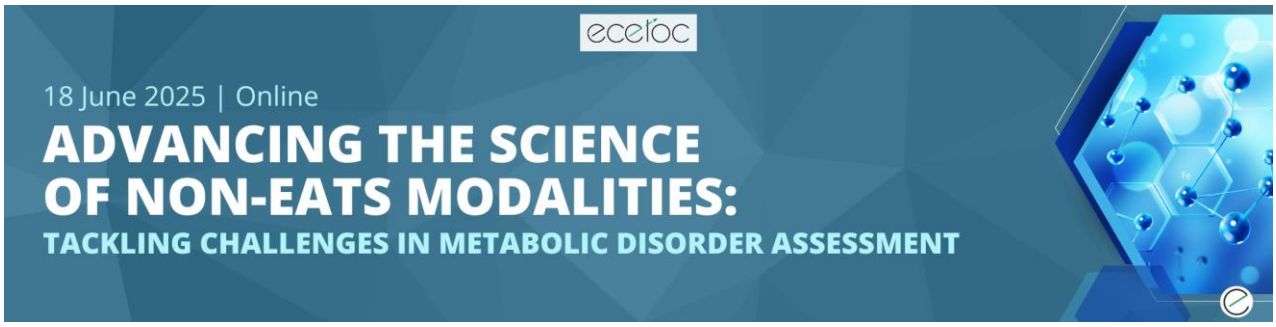
Metabolic disease incidence is affected by many factors, some of which are modifiable (e.g., diet and exercise). Given the role obesity is thought to play in a range of metabolic diseases, the Epidemiology & Lifestyle Factors Subgroup sought to summarize contributory factors for obesity development based on systematic reviews of epidemiological literature. Nearly 600 articles were identified and screened for relevance, resulting in 208 articles for data extraction. Preliminary analysis indicates many contributors, with high complexity based on life stage (fetal, infant, child, and adult), culture (family roles, behaviors, or geographies), and environment (chemical and non-chemical factors). Factors identified in epidemiology studies can be far removed from current adverse outcome pathways (e.g., the key events connecting sleep and obesity are unclear). Additionally, some factors are specific and interrelated, thus work remains to be done in defining precise populations or subgroups of interest.



Similarly, quantifying the fraction of risk attributable to any single factor or assessing the relative contribution of risk factors would require additional data, and likely depends on a number of conditional assumptions.
Stephanie Kuhn has been working in environmental epidemiology for nearly 20 years. Prior to joining Syngenta Crop Protection in Basel, Switzerland, Stephanie worked at the U.S. Centers for Disease Control & Prevention (CDC) and the Colorado Department of Public Health & Environment. Her public health experience has included surveillance for health outcomes associated with environmental contaminants in air, water, and soil, as well as communicable diseases spread through water or insect vectors. Earlier in her career, Stephanie worked as an environmental scientist, focusing on environmental sampling and groundwater hydrogeology. Her graduate research bridged these two fields together by studying the effectiveness of various drinking water treatments in reducing disease-causing microbes.
Subgroup 1: AOP Status **Dr. Dries Knapen, University of Antwerp**
Abstract
Biography
Subgroup 2: Approaches & Methodologies for screening of Non-EATS Modalities **Tushar Mahale, Lubrizol**
Abstract
Dr. Tushar Rajendra Mahale is a seasoned Regulatory Toxicologist at Lubrizol, India with over 14 years of global experience in chemical safety, cosmetics, pharmaceuticals, and medical devices safety assessment. He holds a master's in veterinary science (Pharmacology & Toxicology) from Bombay Veterinary College, Mumbai, India. Dr. Mahale has led toxicology and risk assessments for specialty chemicals, lubricant additives, personal care, medical devices at Lubrizol. His extensive background includes conducting repeat dose, Reproductive and genetic toxicology studies, with a proven track record of, toxicological risk assessments. Dr. Mahale has contributed to ECETOC Technical Reports on Polymer Risk Assessment and Aggregate Exposure Assessment for consumers.

Organising Committee:

Name	Surname	Affiliation
Helen	Tinwell	Bayer, FR
Erik	Rushton	LyondellBasell, NL
Gina	Montoya	Nestle, CH
Paolo	Boffetta	University of Bologna, IT
Philip	Marx-Stoelting	BfR, DE
Juliette	Legler	Utrecht University, NL
Jennifer	Reed	Bayer, US
Daniela	Morias Leme	BfR, DE



Megan D'souza ECETOC

PRACTICALITIES:

Organisation: Online