8 September 2024 | Copenhagen

TESTING, ASSESSMENT AND CLASSIFICATION OF THYROID HORMONE DISRUPTORS

This workshop is a satellite event of EUROTOX 2024, Copenagen, 8-11-09-2024

Satellite Symposium on the **8th September** ahead of the EUROTOX Congress 2024 (8th – 11th September), Copenhagen, Denmark to take place in the **Copenhagen Island Hotel**

Workshop background and objectives

The ECETOC Thyroid (T4) Task Force has worked on the question of how to assess and investigate compounds, which show effects in the thyroid of laboratory animals, with particular emphasis on the neurodevelopment of offspring following in utero exposure to compounds affecting thyroid hormone balance. In our publications (Sauer et al., 2020[1], Marty et al., 2021[2], Marty et al., 2022[3], Melching-Kollmuss et al., 2023[4])[a] both human evidence for maternal thyroid hormone related neurodevelopmental toxicity as well as an extensive evaluation of rat data (comprising thyroid hormone data in adults and offspring, brain histopathological and observational neurodevelopmental effects of compounds with different thyroid molecular initiating events), using Adverse Outcome Pathway (AOP) approaches, was conducted.

This allowed us to identify relevant neurodevelopmental parameters, potential thresholds for offspring thyroid hormone levels below which no neurodevelopmental toxicity is to be assumed and correlations between levels of thyroid hormone decrements, brain histopathological outcomes and neurobehavioural findings. Moreover, a scheme to assess thyroid active compounds was developed.

ECETOC and RSA have organised this workshop to bring together regulatory toxicologists, pathologists and clinical pathologists with experts from European and North American regulatory authorities, CROs and academia to review the state of the science and its current application in regulatory decision-making. The workshop will also propose future options for improving the evaluation of thyroid hormone related neurodevelopmental toxicity, including the proposed ECETOC testing and assessment scheme.

[a] References can be found at the end of the programme

Symposium programme

Item	Start	End	Agenda item	Who
1	11:30 AM	12:00 PM	Arrival and registration at the Copenhagen Island Hotel	Organising committee
2	12:00 PM	12:30 PM	**Welcome Lunch** (Registration to continue through lunch)	
3	12:30 PM	12:40 PM	**Welcome, introduction and symposium objectives**	Bennard van Ravenzwaay (ECETOC) Christine Walter (RSA)
4	12:40 PM	1:00 PM	**Testing and assessment of thyroid-hormone related neurodevelopmental toxicity – the ECETOC-CLE Thyroid NDT-TAS**	Stephanie Melching-Kollmuss (BASF)
5	1:00 PM	1:20 PM	**Experiences with Thyroid ED assessment – EFSA ED Database**	Martina Panzarea (EFSA)
6	1:20 PM	1:40 PM	**Experiences with Thyroid ED assessment & new CLP ED Criteria**	Niklas Andersson (ECHA)
7	1:40 PM	2:00 PM	**In vitro and in vivo investigation of pesticide effects on the T-axis**	Philip Marx-Stoelting (BfR)
8	2:00 PM	2:20 PM	***Coffee break***	
9	2:20 PM	2:40 PM	**Use of the ECETOC-CLE Thyroid NDT-TAS to Support Identification and Classification of Thyroid Hormone Disruptors**	Helen Tinwell (Bayer)
10	2:40 PM	3:00 PM	**How to identify adverse neurodevelopmental toxicity in laboratory animals**	Heike-Antje Marxfeld (BASF)
11	3:00 PM	3:20 PM	**Decisive new endpoints indicative of abnormal neurodevelopment**	Katie O'Shaugnessy (US EPA)
12	3:20 PM	3:40 PM	**Assessment of thyroid hormone alterations in rat brain and plasma**	Christiane Hindrichs (BASF Metabolome Solutions)
13	3:40 PM	4:00 PM	**Species-specific thyroxine (T4) metabolism and response to nuclear-receptor activators in long-term cultured hepatocytes**	Lysiane Richert (KaLy-Cell) & Laure Asselin (KaLy-Cell)
14	4:00 PM	4:15 PM	**Summarise and closing remarks**	Bennard van Ravenzwaay (ECETOC) Christine Walter (RSA)
15	4:15 PM	4:45 PM	***30 min to EUROTOX opening ceremony***	
16	4:45 PM	6:45 PM	**EUROTOX Congress Opening Ceremony (Tivoli Hotel & Congress Center)**	

[1] Sauer, U. G., Asiimwe, A., Botham, P. A., Charlton, A., Hallmark, N., Jacobi, S., . . . Swaen, G. (2020). Toward a science-based testing strategy to identify maternal thyroid hormone imbalance and neurodevelopmental effects in the progeny - part I: which parameters from human studies are most relevant for toxicological assessments? *Crit Rev Toxicol, 50*(9), 740-763. doi:10.1080/10408444.2020.1839380

[2] Marty, S., Beekhuijzen, M., Charlton, A., Hallmark, N., Hannas, B. R., Jacobi, S., . . . van Ravenzwaay, B. (2021). Towards a science-based testing strategy to identify maternal thyroid hormone imbalance and neurodevelopmental effects in the progeny - part II: how can key events of relevant adverse outcome pathways be addressed in toxicological assessments? *Crit Rev Toxicol, 51*(4), 328-358. doi:10.1080/10408444.2021.1910625

[3] Marty, M. S., Sauer, U. G., Charlton, A., Ghaffari, R., Guignard, D., Hallmark, N., . . . van Ravenzwaay, B. (2022). Towards a science-based testing strategy to identify maternal thyroid hormone imbalance and neurodevelopmental effects in the progeny-part III: how is substance-mediated thyroid hormone imbalance in pregnant/lactating rats or their progeny related to neurodevelopmental effects? *Crit Rev Toxicol, 52*(7), 546-617. doi:10.1080/10408444.2022.2130166

[4] Melching-Kollmuss, S., Bothe, K., Charlton, A., Gangadharan, B., Ghaffari, R., Jacobi, S., . . . van Ravenzwaay, B. (2023). Towards a science-based testing strategy to identify maternal thyroid hormone imbalance and neurodevelopmental effects in the progeny – Part IV: the ECETOC and CLE Proposal for a Thyroid Function-Related Neurodevelopmental Toxicity Testing and Assessment Scheme (Thyroid-NDT-TAS). *Critical Reviews in Toxicology, 53*(6), 339-371. doi:10.1080/10408444.2023.2231033

Organising Committee

Phil	Botham	Syngenta, UK
Stephanie	Melching-Kollmuss	BASF, DE
Bennard	van Ravenzwaay	Wageningen University, DE
Blanca	Serrano Ramón	ECETOC, BE
Andrea	Salvadori	ECETOC, BE
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Sergio	León Pérez	ECETOC, BE
Alison	McCondichie	RSA, UK
Jen	Buchanan	RSA, UK
Liz	Macquarrie	RSA, UK
David	Andrew	RSA, UK

Venue

Copenhagen Island Hotel
Kalvebod Brygge 53
1560 Copenhagen
Denmark

Walking distance from the Tivoli Congress Center at 400 meters.

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Speakers' bios and abstracts

Testing and assessment of thyroid-hormone related neurodevelopmental toxicity – the ECETOC-CLE Thyroid NDT-TAS

Stephanie Melching-Kollmuss, BASF

Normal thyroid function can be impacted by a number of different thyroid modes of actions, e.g. at the level of thyroid hormone synthesis (inhibition of thyroid peroxidase (TPO), inhibition of sodium-iodide symporter (NIS)), and at the level of thyroid hormone metabolism and excretion (liver enzyme induction and interaction with thyroid hormone binding proteins both leading to increased thyroid hormone excretion). A large set of rat studies had been assessed during the ECETOC Task Force work, where compounds - sorted into 4 different case studies (1. TPO inhibition, 2. NIS inhibition / iodine deficiency, 3. Liver enzyme induction / interaction with serum binding proteins, 4. Dio 1 inhibition) - were dosed during gestation / lactation, and thyroid hormone levels measured, as well as data on brain-related parameter and/or neurodevelopmental toxicity were investigated. The main outcomes from this evaluation were, that neurodevelopmental toxicity is correlated to thyroid hormone deficiency in rats, that offspring thyroid hormone levels are more important than adult / maternal levels regarding to predict neurodevelopmental outcomes and that an empirical threshold of about 50% T4 decrement in offspring has been identified to show a correlation between decreased T4 levels and the observation of brain- and/or neurodevelopmental parameters in rats.

The ECETOC-CLE Thyroid neurodevelopmental toxicity Testing and Assessment Scheme (ECETOC-CLE Thyroid NDT-TAS) provides guidance on how to assess mixed thyroid datasets and proposes two general approaches on how to conduct further testing – if needed. On one hand higher tier data could be generated, as e.g. additional testing in offspring animals and / or neurodevelopmental toxicity testing. Alternatively – as there is strong species differences in the extent of (phase II) liver enzyme induction and serum (thyroid hormone) binding protein between humans and rodents – robust substance-specific data shall be provided to show, that thyroid hormone changes seen in rats would not occur in humans. Both approaches require a thorough understanding of underlying thyroid modes of actions provided by in vitro testing. This testing and assessment scheme is presented in the talk followed by future approaches & perspectives.

Stephanie Melching-Kollmuss is working as regulatory toxicologist at BASF SE, in the field of agrochemicals since 2006. She is a German and European Registered Toxicologist and works in the field of Regulatory Toxicology since more than 20 years. Her main interests are in carcinogenicity, mixture toxicity and endocrine disruption assessments; in the last years, the main research focus was in the area of the thyroid. She chaired the ECETOC Thyroid Task Force, publishes in the field and organizes/contributes to Scientific Symposia at Toxicological Conferences, looking for cooperations between industry, academia and regulatory toxicologists, as well as linking between in vitro, in vivo toxicological and modelling approaches. Stephanie was a monitor of the Cefic LRI EMS59 project: "Investigating liver-thyroid-mediated brain developmental toxicity after prenatal exposure in the rat". She is chairing the "Endocrine Effects" working group of the German Toxicology Society, she is member in several Crop Life association endocrine working groups, and the ECHA ED Expert Group.

Experiences with Thyroid ED assessment – EFSA ED Database

Martina Panzarea, EFSA

Following the implementation of the Regulation 2018/605 laying down the scientific criteria for the hazard identification of endocrine disruptors (EDs), to ensure consistency in the assessment carried out since 2018, EFSA built a database in the form of an Excel file. The database collects all the substances assessed for both mammalian toxicology and ecotoxicology. For each substance, the dataset available to reach a conclusion on the T-modality for both the adversity and endocrine activity is reported together with the conclusion and a summary of the assessment driving the conclusion. An overview of the data collected on the T-modality and their analyses will be presented.

M.Sc., Regulatory Toxicologist.

Since February 2020, Scientific Officer in the Mammalian Toxicology Team within EFSA's Pesticide Peer Review Unit.

I am involved in activities regarding the peer review of risk assessment of active substances used in plant protection products and mainly in the assessment of their endocrine disrupting properties. I am also involved in different projects dealing with the application of New Approach Methodologies in chemical risk assessment and development of Adverse Outcome Pathways.

Experiences with Thyroid ED assessment & new CLP ED Criteria

Niklas Andersson, ECHA

In 2018 provided ECHA and EFSA provided guidance on endocrine disrupting (ED) properties for biocidal products (BPs) and plant protection products (PPPs). More specifically, this guidance describes how to gather, evaluate and consider all relevant information for the assessment, apply a weight of evidence (WoE) approach and conduct a mode of action (MoA) analysis, in order to help in establishing whether the substance meets the criteria for approval under the BP and PPP Regulations.

In 2023, ED was introduced into CLP as a hazard class with sub-categorisation. CLP covers classification of hazardous substances and mixtures across regulations and applies (among others) to industrial chemicals, BPs and PPPs.

The presentation will discuss experiences gained from using the ECHA/EFSA guidance to assess the potential for thyroid disruption and explain how the CLP ED criteria relate to the ED criteria applicable to BPs and PPPs.

Niklas Andersson is a senior toxicologist and Scientific Area Leader for Endocrine Disruption at the European Chemicals Agency (ECHA). He brings more than 35 years' experience from academic research, pre-clinical development, and regulatory risk assessment.

Niklas has also contributed to several guidance documents, including the '*Read-across Assessment framework (RAAF)*', the '*ECHA/EFSA Guidance on identification of endocrine disruptors for biocidal- and plant protection- products*' (including Appendix A on the thyroid modality), and most recently, the '*Guidance on the application of the CLP criteria for endocrine disruption*'.

In vitro and in vivo investigation of pesticide effects on the T-axis

Philip Marx-Stoelting, BfR

The presentation will cover results from in vivo and in vitro mechanistic studies on pesticides. It will address questions of thresholds of ED as well as human relevance.

Philip Marx-Stoelting, Dr. rer. nat., ERT, is serving at the German Federal Institute for Risk Assessment (BfR) as a scientific director heading the unit 'testing and assessment strategies' in the pesticides safety department and the BfR working group on endocrine disruptors.

He is involved in several large European research projects on NAM development including PARC, where he is leading the work-package 'hazard assessment'. He is involved in several expert panels on EU and international level and member of the OECD EDTA.

Use of the ECETOC-CLE Thyroid NDT-TAS to Support Identification and Classification of Thyroid Hormone Disruptors

Helen Tinwell, Bayer SAS

Criteria to identify agrochemicals and biocides with endocrine disrupting properties have been in place since 2018 under Regulation (EU) 1107/2009 and Regulation (EC) No 528/2012 respectively. More recently, endocrine disruption has been introduced as a new hazard class in the EU regulation for Classification and Labelling (CLP; 1272/2008) of substances and mixtures, leading to the possibility of substances being classified as known/presumed (Category 1) or suspected (Category 2) endocrine disruptors (ED) for human health and the environment. Guidance on how to identify an ED is detailed in the ECHA/EFSA Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 (2018); however, differentiating between the two categories for this new hazard class under CLP is more challenging particularly when considering the ambiguity of the terms used for justifying Category 2 instead of Category 1 classification (eg "When the evidence for either adverse effect(s) or endocrine activity or both is not sufficiently convincing to place the substance in Category 1, then Category 2 or no classification may be warranted. " or "raises serious doubts about the relevance of the adverse effects to humans"). The current ED pathways considered for classification are the Estrogen, Androgen, Thyroid and Steroidogenesis (EATS) modalities, with the greatest uncertainty for concluding and classifying substances being that for the T modality, especially for thyroid hormone disruption and neurodevelopmental effects.

The ECETOC Thyroid Task Force in conjunction with CropLife Europe (CLE) have recently developed a testing and assessment scheme (TAS) to identify and characterize endocrine disruptors for T-related adversity (focusing mainly on neurodevelopmental effects). Based on knowledge accrued from earlier publications from the Task Force that evaluated the state of the art on thyroid-hormone related neurodevelopmental toxicity in humans and rodents, this scheme allows the user to clarify whether there is sufficient data to conclude on the test substance or if additional data are needed. Examples of data packages from agrochemical active substances, known to be liver enzyme inducers, will be presented to demonstrate how this proposed testing and assessment scheme can be used to determine the relevance, predictivity and specificity of T-related findings and how the outcome of this scheme can then be used to conclude on ED1, ED2 or No ED for human health.

I have a PhD in genotoxicity and more than 30 years' experience in toxicology. I have been with Bayer CropScience for 19 years and am based in the south of France at the Toxicology Laboratory where I currently lead a team of global regulatory toxicologists. I am a Bayer distinguished science fellow with more than 100 publications to my name and I represent Bayer in several key working groups including the CropLife Europe ED expert group; the OECD ED ad-hoc working group; the ECHA ED Partner Expert Group. I have extensive experience in research toxicology particularly concerning modes of action of toxicity (eg liver mediated thyroid toxicity; testicular toxicity) and fundamental aspects of endocrine disruption (eg. low dose effects, mixtures); all of which have required the development of bespoke in vitro and in vivo methodologies. I have also been involved in several OECD validation programmes. I am responsible for developing and refining testing strategies to address ED potential of the Bayer CropScience small molecules pipeline. I am also a member of the scientific advisory board for the PEPPER platform, whose role is to organise the pre-validation of methods for characterising endocrine disruptors and to accelerate the passage from a method developed in an academic environment to a one that can be used in a regulatory context.

How to identify adverse neurodevelopmental toxicity in laboratory animals

Heike-Antje Marxfeld, BASF

Identification of adverse neurodevelopmental findings in laboratory animals has gained in in importance related to the growing concern about thyroid related disturbances in cognitive functions in humans. The applicability of rodent studies will be discussed on the basis of the recently published series of reviews by ECETOC.

Professional experience:

From 2010: BASF SE, Ludwigshafen, Deutschland

Scientific staff member (Pathologist) (since 2010) and team leader of the immunohistology laboratory (since 2011) at the Department of Experimental Toxicology and Ecology of BASF SE, Ludwigshafen, Germany

2005 - 2010: Charles River Laboratories, Preclinical Services, Tranent, UK

2002 - 2005: Combined pathology residency and PhD programme, University of Veterinary Medicine Hannover, Germany and Novartis Pharma AG, Basel, Switzerland

Education

2024: Data Scientist (Sorbonne)

2023: Fellow International Academy of Toxicologic Pathology

2009: Diploma of the European College of Veterinary Pathologists ^ (DiplECVP)

2005: PhD in Veterinary Pathology (Hannover)

2005: Completion of 3.5 year residency training in diagnostic veterinary pathology

1996 - 2002: Qualification as a veterinary surgeon (State exam and Approbation) University of Veterinary Medicine, Hannover, Germany

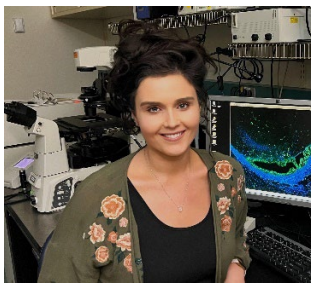
Member of INHAND groups mammary gland

Member of ECVP, ESTP, ESTP expert workshops “Towards Regulatory Acceptance of Digital Toxicologic Pathology', “IT/QA aspects of digital pathology”, co-author for two reviews of the ECETOC thyroid taskforce

Decisive new endpoints indicative of abnormal neurodevelopment

Katie O’Shaugnessy, US EPA

Some standardized developmental and reproductive toxicity studies suggest or require serum thyroxine (T4) measures in pregnant, lactating, and developing rats, to screen for a chemical’s thyroid disrupting activity. However, the developing brain is not often examined concurrently by either histopathology or neurobehavior, making it is unclear when a serum T4 reduction is adverse. To address this knowledge gap, we have worked to identify potential endpoints indicative of thyroid disruption in the brain. In a series of hypothesis-driven investigations, abnormal cell migration and brain barrier disruption are two reproducible effects of TH interference in vivo. Importantly, these mechanisms can be evaluated using specific histopathology or molecular approaches, which could complement serum T4 measures in toxicology studies. In all, directed evaluation of TH targets in the developing rat brain could strengthen the interpretation of serum T4 measures, thus improving chemical assessment. This work does not reflect US EPA policy.



Katie O’Shaughnessy is a Principal Investigator at The United States Environmental Protection Agency (US EPA), where she examines the neurodevelopmental effects of thyroid disrupting chemicals and other pollutants.

Prior to her tenure as Investigator, Katie was a postdoctoral fellow at US EPA under the mentorship of Mary Gilbert. She graduated with her PhD in Genetics and Genomics from the University of Florida in 2015 where she studied how steroid receptors controlled morphogenetic pathways in vivo. Katie’s research philosophy is centered around a Systems Biology approach, and she combines molecular, biochemical, and computational tools to address the complexities of endocrine and developmental toxicity.

	Katie has received numerous research and publication awards, including the Innovator Award from the Society of Birth Defects Research and Prevention, and the Young Investigator Award from the Developmental Neurotoxicology Society.

Assessment of thyroid hormone alterations in rat brain and plasma

Christiane Hindrichs, BASF Metabolome Solutions

The development of the brain from fetal stage to young adulthood can be disturbed by affected thyroid hormone (TH) homeostasis. A correlation between maternal thyroid function during pregnancy and the offspring's gray matter volume and IQ have been described in humans1.Typically, in regulatory studies in rats, disturbances of the TH homeostasis are detected by measuring TH concentrations in adult plasma, in some cases also offspring plasma TH data are available. The target organ of developmental neurotoxicity is, however, the offspring's brain. Measuring TH concentrations in the target organ may be more relevant to developmental neuronal effects due to disturbed TH homeostasis than measuring TH concentrations in the maternal plasma2, 3. Considering standardized study sampling timepoints, we analyzed whole brain as well as cortex and cerebellum regarding their TH metabolite concentrations in adult and postnatal day 4 and 21 (PND4 and 21) rats using an on-line solid phase extraction liquid chromatography tandem mass spectrometer (on-line SPE-LC-MS/MS) method. Currently, we are aiming at generating a database regarding TH concentrations in control rat brain and plasma which would help to improve the differentiation of dose-related effects from biological variation in the given matrix. Age dependent differences in TH concentrations in control rodents in both matrices have been detected which shows dynamic TH variation with increasing age and that emphasizes the importance of knowing the biological concentration.

Besides possible correlation between rat brain and plasma TH levels, we are currently developing a method to analyze free TH concentration in rat plasma samples to potentially identify whether a substance-dependent effect changes total and/or free TH concentration. As effects on free thyroid hormone concentrations are a more accurate indicator for thyroid function impairment in rodents, and in humans usually free thyroid hormones are measured, the correlation of effects on free or total THs to downstream adverse effects (e.g. thyroid histopathology, neurodevelopmental toxicity) will be highly interesting.

After finishing Bachelor Studies (Pharmaceutical Chemistry) at the University of Applied Science in Cologne, Germany in 2018, I started the master studies in Toxicology at the Heinrich-Heine-University in Düsseldorf, Germany from 2018 to 2021.

During my master project in the laboratory of Dr. James at the University of Florida in the USA I worked for the first time on a thyroid-related topic focusing on LC-MS/MS method development to determine possible inhibition of thyroid hormone (TH) formation in animal livers caused by bromodiphenyl ethers. The research on thyroid-related topics continued with the beginning of the doctorate in September 2021 at BASF Metabolome Solutions GmbH in Berlin and on academic side with the University of Kaiserslautern-Landau (RPTU Kaiserslautern-Landau) in Germany. The doctoral project focuses on the analytical quantification of THs from multiple biological matrices to facilitate the prediction of endocrine disruption in the testing and assessment of chemicals and it will prospectively be finished by beginning of 2025.

In parallel to the doctorate project, I attend to various toxicological training courses offered by the German society of toxicology with the goal to become registered as an "European Registered Toxicologist" (ERT) in which field of work I am interested to establish myself in.

Species-specific thyroxine (T4) metabolism and response to nuclear-receptor activators in long-term cultured hepatocytes

Lysiane Richert, KaLy-Cell and Laure Asselin, KaLy-Cell

Since 2018, the European Food Safety Authority (EFSA) has required the evaluation of all pesticide and biocide active substances undergoing (re)-registration for potential endocrine-disrupting (ED) properties for both human health and the environment. More recently, endocrine disruption has been included as a hazard class in the Classification, Labelling and Packaging (CLP) regulation, thus expanding the scope of ED evaluations to all chemicals. Over the past decades, an increasing number of xenobiotics have been shown to interfere with thyroid function in laboratory animals following repeated dosing in toxicology studies, due to one or more molecular-initiating events (MIEs) that may lead to disrupted thyroid hormone (TH) synthesis, transport, metabolism, and signalling. Epidemiology studies strongly support that chemically induced TH perturbations occurring in rats (and mice), secondary to increased hepatic T4 metabolism, mainly T4-glucuronoconjugates and biliary excretion, are mediated by a non-human relevant mode of action (MoA). Nevertheless, assays allowing direct species comparison are limited.

KaLy-Cell has developed an in vitro comparative assay, using 7-day 2D-sandwich (2Dsw) cultured rat and human hepatocytes, in which MIEs following nuclear receptor activation can be assessed (CYP and UGT induction) and the rate of T4 metabolism compared. Here, we highlight a correlation between in vivo and in vitro findings in rats, for UGT induction and increases in T4-UGT activity following exposure to reference inducers, activators of either aryl hydrocarbon receptor (Ahr), constitutive androstane receptor (CAR), or pregnane X receptor (PXR). Additionally, we reveal significant differences in UGT mRNA inducibility, as well as in T4-UGT activity and T4 metabolism, both under basal conditions and in response to inducers, between rat and human hepatocytes, further underscoring the necessity for a species-specific evaluation. We are now extending these tests to hepatocytes from other species such as dogs and mice.

Overall, this work demonstrates that the present standardized in vitro assay can be used in a weight-of-evidence approach to address species differences and allows for a more precise evaluation of the risk of thyroid toxicity in humans following exposure to Ahr-, CAR- and/or PXR- nuclear receptor activators. Inclusion of reference positive and negative controls will help to define the threshold of relative T4-UGT activity increase considered as being compound-related.

Prof. Lysiane Richert is a distinguished professor in cell biology and toxicology and is the founder of KaLy-Cell. She obtained her Ph.D. in Cellular and Molecular Pharmacology from Louis Pasteur University in Strasbourg, France, in 1983. Following her doctoral studies, she completed postdoctoral training at the Weizmann Institute of Science, Rehovot, Israel, focusing on Cell Biology and Immunology. In 1986, Prof. Richert began her career as an in vitro toxicologist with Rhône-Poulenc Santé (now Sanofi). She transitioned to Rhône-Poulenc Agro (now Bayer Crop Science) in 1992 as a regulatory toxicologist. The following year, she became a professor in Cell Biology, and thereafter in Toxicology, at the School of Pharmacy, University of Franche-Comté. In 2003, she established KaLy-Cell through technology transfer, and served as Chief Scientific Officer till the acquisition of KaLy-Cell by the GBA group in 2022, when she started scientific consultancy (via Zylan). KaLy-Cell is a contract research organization (CRO) that has been developing its expertise in liver-related ADME-Toxicology, ex-vivo and particularly in vitro with hepatocytes, helping in optimizing the discovery, development, and approval of drugs, food additives, and agrochemicals. In addition, KaLy-Cell is also actively involved in innovative research in cell biology and in vitro toxicology and has recently set up specific new experimental tests to assess the potential adverse effects of chemicals on thyroid function.

Dr. Laure Asselin holds a Ph.D. in the field of Molecular and Cellular Biology, with a specialization in developmental biology, obtained from the University of Strasbourg. Following her doctoral degree, she joined KaLy-Cell in 2021 for a post-doctoral position. During her tenure, she developed innovative assays to evaluate the potential endocrine-disrupting effects of various compounds. Currently, Dr. Asselin serves as the Scientific Head of KaLy-Cell's test facility.

Today, Prof. Richert and Dr. Asselin will present KaLy-Cell's latest research on species-specific thyroxine metabolism and response to nuclear-receptor activators in cultured hepatocytes.

Co-chairs bios

Bennard Van Ravenzwaay, ECETOC

Bennard van Ravenzwaay is a Doctor of Environmental Sciences/Toxicology from Wageningen University, Netherlands in collaboration with the German Cancer Research Centre in Heidelberg, Germany. He worked for 34 years at BASF SE, Ludwigshafen, the last 20 as Senior Vice President of the Department for Experimental Toxicology and Ecology and BASF Metabolome Solutions.

He is an associate professor for Reproduction Toxicity of the University of Wageningen and had a teaching assignment at the University of Kaiserslautern until 2021.

He is a member the Scientific Committee of the European Centre for Ecotoxicology and Toxicology (ECETOC) – chairman from 2013 to 2023 - and a member of editorial boards of "Archives of Toxicology", "Chemical Biological Interactions" and "Toxicology Letters".

He was member of the board of trustees of the Health and Environment Science Institute (HESI) from 2012 – 2018. He is a member of the German Society for Pharmacology and Toxicology, a European registered toxicologist and SOT-Member.

He is an author more than 250 peer reviewed publications.

Since 2022 he is an independent consultant for environmental sciences.

Christine Walter, RSA

Christine joined RSA in January 2023 as a regulatory scientist with a keen interest in designing toxicology or regulatory strategies to meet clients' needs, making use of more than 15 years of experience in toxicology and regulatory roles in both the agrichemical industry and pharmaceutical consultancy sectors. Her main experience is in active substance toxicology, endocrine disruption, study monitoring, pesticide regulation and AIR. Christine has contributed to multiple human risk assessments including ED assessments, investigative mode of action work and regulatory submissions demonstrating safety and regulatory compliance for EU active substance approvals, renewals, CLH and zonal product registrations. She is experienced in the development of toxicological testing strategies and in the preparation of technical responses to EFSA and Member State authorities.

Christine graduated from the University of Hannover with a Degree in Biochemistry, followed by an international PhD in gene therapy and regenerative sciences.

Rapporteurs bios

David Andrew, RSA

David joined RSA in 2024 as Technical Director and is a highly experienced, board certified (DABT) EU regulatory toxicologist with extensive experience in the areas of plant protection, biocides, general chemicals and cosmetic products, gained over 23 years in senior roles in government and consultancy.

His extensive experience includes providing input into regulatory submissions (pesticides, biocides, REACH), position papers, advice on data waiving and testing strategies including mechanistic data, expert witness statements and client representation, classification and labelling, IUCLID, REACH dossier preparation, and cosmetic safety assessment.

David has been involved in the assessment of ED potential for a large number of pesticide and biocide active substances, according to the 2018 ECHA/EFSA Guidance. He has provided advice to clients on vulnerability to ED classification, designed testing strategies and monitored in vitro and in vivo ED studies including non-standard mode of action/mechanistic studies. He has experience of working with difficult substance types including UVCBs, metals, metal salts and complexes, with extensive experience of working with industry consortia, to reach agreement on testing strategies and study design.

Kathrin Bothe, Bayer

Dr. Kathrin Bothe is a Regulatory Toxicology Expert at Bayer CropScience in Monheim, Germany, since 2017. She is responsible for the development of new agrochemical products and the regulatory defense of existing products covering the area of human safety. Her special focus is on developmental neurotoxicity (DNT) and regulatory implementation of New Approach Methodologies (NAMs) into a Next Generation Risk assessment.

She is a biochemist by training and before joining Bayer, she did her PhD and Postdoc at the Leibniz Research Institute for Environmental Medicine in Duesseldorf, Germany, in the group of Prof. Ellen Fritsche supporting the development of an in vitro testing battery for DNT. Moreover, she worked for two different consultancies as toxicology expert for industrial chemicals and cosmetics.

Kathrin Bothe is chairing the Croplife Europe DNT subgroup and is involved in various international activities, e.g. the EU RiskHunt3R project and the OECD DNT expert group.

Organisers information

ECETOC is a not-for-profit scientific association that provides a collaborative space for leading scientists from academia, governments and industry to develop and promote trusted and practical scientific solutions which ensure a safe, sustainable and healthy world. For more information please visit https://www.ecetoc.org/

RSA (Regulatory Science Associates) was formed in 2007 with a group of experts delivering human health toxicology and regulatory affairs consultancy services. Further information can be found at www.regulatoryscience.com

ECETOC and RSA have significant experience organising workshops and conferences to facilitate the communication of science. Both organisations are working jointly to organise this thyroid hormone related symposium for 2024.