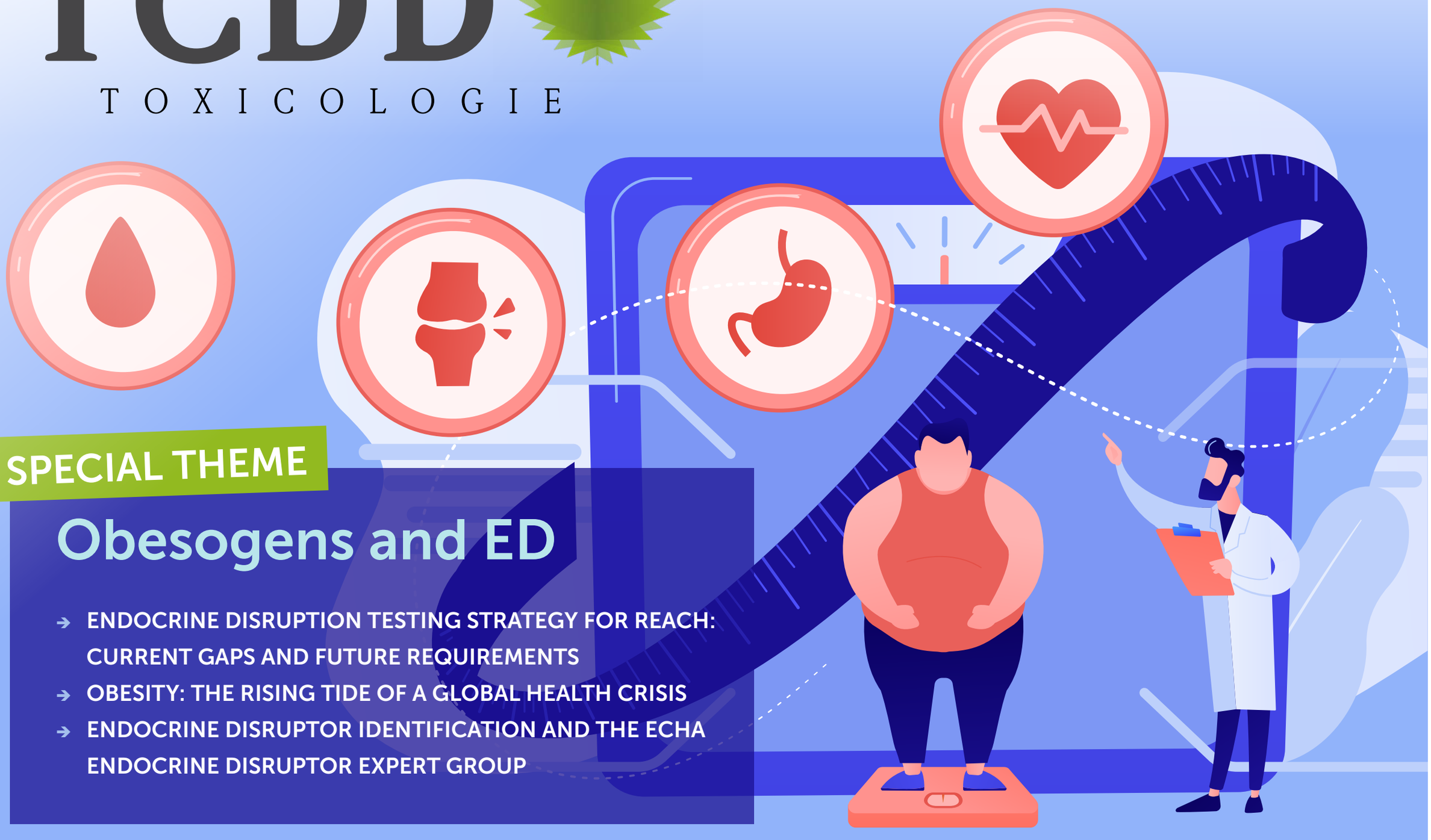
TCDD
TOXICOLOGIE

NUMMER 45
OKTOBER 2025



SPECIAL THEME

Obesogens and ED

- ENDOCRINE DISRUPTION TESTING STRATEGY FOR REACH: CURRENT GAPS AND FUTURE REQUIREMENTS
- OBESITY: THE RISING TIDE OF A GLOBAL HEALTH CRISIS
- ENDOCRINE DISRUPTOR IDENTIFICATION AND THE ECHA ENDOCRINE DISRUPTOR EXPERT GROUP

NEDERLANDSE VERENIGING VOOR TOXICOLOGIE

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Het lidmaatschap wordt automatisch verlengd tenzij de NVT-ledenadministratie vóór 1 december van het lopende jaar schriftelijk of per e-mail een opzegging heeft ontvangen. Hiervan ontvangt u een bevestiging.

Contributie NVT
Incl. abonnement TCDD 50,= euro
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Indien u ervoor kiest zelf uw contributie over te maken, dan worden € 5,- administratiekosten in rekening gebracht.

Sluitingsdata kopij 2025
November 14, 2025

Kopijbus
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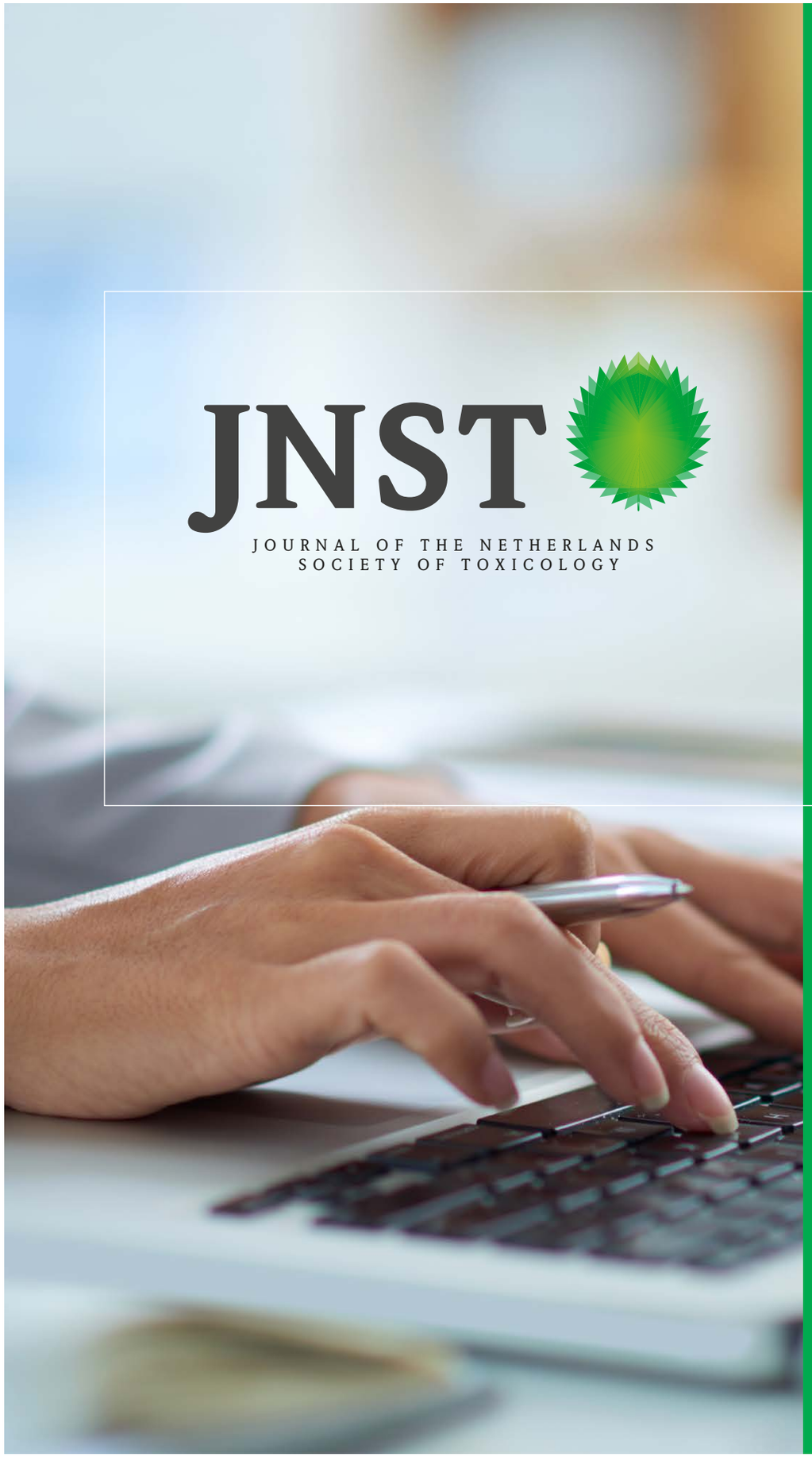
TCDD
TOXICOLOGIE

Inhoud



JNST

JOURNAL OF THE NETHERLANDS SOCIETY OF TOXICOLOGY

Submit your paper!

Call for submissions

to the Journal of the Netherlands Society of Toxicology

- Submissions can be made through ScienceOpen.
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- There is no deadline for submission.
- Once the submitted papers are accepted and have completed the peer review process, they will be available online and the journal entries will be appended to the TCDD.

TERUG NAAR INHOUD

Editorial

The theme for the current edition of the TCDD is “Obesogens and Endocrine Disruption (ED)”. The current testing strategy for ED to comply with REACH is discussed, with special focus on gaps and future requirements. Also, insights are provided into the role and structure of the ECHA Endocrine Disruptor Expert Group that provides advice to EU Member States on matters related to ED. There is an article on the obesity pandemic, including a discussion on its mechanisms and the potential relationship between obesity and chemicals (i.e., obesogens) that might predispose people to its development. Besides articles related to the special theme, an article also discusses exposure to pesticides among French residents living near a vineyard (which in some parts of France may be the whole population). Finally, titanium dioxide features in two articles, one is a presentation of a PhD thesis (with the fascinating title “Whiteout”), and the other is a historical overview of the recent annulment of the classification of TiO2 for carcinogenicity, by the European Court of Justice.

We hope you enjoy the issue and wish you a pleasant autumn.

Damiën van Berlo

Photo by Jess Bailey on Unsplash

Updates from the NVT Board

Back to Work! After the summer holidays, working life has started up again, and so has the NVT agenda...

The 46th and 47th Annual Meeting

The 46th NVT Annual Meeting, held on June 4–5, 2025 at the Reehorst in Ede, was a great success with a record-high attendance of almost 200 participants each day!

The theme *From Lab to Law: Bridging the Gap from Science to Policy* proved highly relevant, and the program clearly demonstrated how toxicological science can shape and influence policy. The board wishes to **thank the organizing team** - senior and especially junior members - for their dedication and energy, which made this meeting such a success.

Preparations for the next Annual Meeting have already started. In 2026, we will change scenery and have our **47th NVT Annual Meeting on 23-24 of June at the Eenhoorn in Amersfoort.**

Please save the date and block these dates already in your agenda!

To reduce pressure on the program of the Annual Meeting, the NVT Board has decided to organize an **online Business Meeting** before the Annual Meeting next year, to allow everyone to join without creating a conflict with other activities during the Annual Meeting. If needed, the Board will still plan a face-to-face meeting to discuss specific topics.

Future Proofing the NVT

The working groups on future proofing have made solid progress. Together with the section liaisons, they have reported to the board on communication, the website, and the structure of the sections. A new **communication approach is needed**, aiming to make our outreach more professional, stimulating, and engaging. Central to this is also a **new website** which is very needed: user-friendly, future-proof, and tailored to the needs of the NVT and its sections. We are now entering the design and technical development phase and are already in contact with a web developer.

We now need to take this a step further. We are looking for one or two **junior toxicologists** to help us shape the website in the coming months. Please reach out to us!

Collaboration with German Toxicologists

We are excited to announce that the 11th German Pharm-Tox Summit (GPTS 2026) will be organized in cooperation with the NVT! The joint meeting with the German Society of Toxicology (GST) will take place on March 17–20, 2026, in Düsseldorf. More information here: https://gpts-kongress.de/

Call for submissions to the JNST

We warmly remind you to submit your articles to the Journal of the Netherlands Society of Toxicology (JNST).

Looking Ahead

Now that summer is behind us, it is time to gear up again and continue our important work: advancing toxicology, contributing to a cleaner environment, and protecting all living creatures - including ourselves.

Open Positions

Several positions on the board and in the sections will soon become vacant (see the overview below). If you are interested, please consider applying. The Board is especially looking for a treasurer who can work alongside our current treasurer, Laura, for one year. If you are interested, please get in touch!

Prof. Dr. F.J. van Schooten

Where	Open position	Description
NVT Board	Treasurer	As the NVT Board Treasurer, you will play a key role in ensuring the financial health of our society. The main responsibilities include: • Preparing the annual budget (1 year ahead and 3 years in advance). • Presenting the annual financial report and coordinating its review by the audit committee. • Managing income and expenses, including processing invoices and reimbursements (together with an administration office of KNCV). • Overseeing the financial aspects of the annual NVT Congress. Please contact Laura (l.hondebrink@umcutrecht.nl) for more information
NVT Board/ communication team	New NVT Website - design support	The NVT Board, supported by the Future Proofing Communication group is currently preparing for a new website. We recently have come to an agreement with a designer to help us with that. At the moment we are looking for 1-2 junior toxicologists to join our team and help us with the design of our new website. Do you have experience with or interest for web design, and are you interested to offer your support, please contact us! Please contact Yvonne (yvonne.staal@rivm.nl) for more information
Registration Committee	Member	Support with ERT (re-)registrations Please contact Walter (Walter.Brand@rivm.nl) for more information
TCDD and JNST editorial team	Editor	Join a team of editors to gather, edit and write content for the NVT's quarterly newsletter and journal. Please contact Barae (redactie@toxicologie.nl)

TERUG NAAR INHOUD

SECTIE MILIEUCHEMTOX

TERUGBLIK

Analytical Solutions

Op 3 juni vond wederom het door de MCT-sectie mede georganiseerde Analytical Solutions symposium plaats in de Reehorst in Ede, voorafgaand aan de jaarlijkse NVT-meeting.

Keynote Anneli Kruve liet zien hoe machine learning non-target screening in milieuanalyse revolutioneert – met tools zoals MS2Tox, die toxiciteit voorspellen zonder dat de chemische structuur bekend is. Frederic Béen, Saer Samanipour en Leonieke van den Bulk, toonden concrete AI-toepassingen in wateronderzoek, exposoomanalyse en voedselveiligheid. De MCT Proefschriftprijs 2025 ging naar Annika Mangold-Döring voor haar onderzoek naar temperatuur- en chemische effecten op verschillende biologische niveaus. De dag werd afgesloten met inzichten van Jeroen Jansen over hoe AI bijdraagt aan robuustere labs en efficiëntere productieprocessen.

Zie de volledige terugblik op Analytical Solutions 2025 op de MCT website: https://mct.kncv.nl/en/activities/3-june-2025-analytical-solutions/analytical-solutions-2025

SECTION GENETIC TOXICOLOGY

INVITATION

Webinar - Novel DNA sequencing technologies revolutionize mutagenesis assessment

Tuesday November 4, 2025, 15:00-16:30 CET

Genetic toxicology is a crucial part of safety assessment of novel pharmaceutical products, chemicals, cosmetics and food products. The potential of a substance to induce gene mutations is a key part of the genotoxicity testing strategy. Gene mutations in somatic cells can lead to cancer and other severe diseases. Mutations in the germ line can cause hereditary diseases.

The mutagenic properties of substances are currently measured *in vitro* by the bacterial reverse mutation (Ames) test and various gene mutation assays in mammalian cells. Different transgenic rodent models, like Big Blue and Mutamouse, as well as the PigA assay are applied to assess the mutagenic potency of compounds *in vivo*. Although these assays have proven their value in mutagenicity risk assessment, the relevance of some of these models for humans, assay availability and the (social) pressure to reduce animal testing pushes the development and implementation of next-generation methods for mutagenicity assessment, such as DNA sequencing.

Error-corrected DNA sequencing (ECS) dramatically improves the accuracy of next-generation sequencing technologies. ECS is based on deep sequencing of both DNA strands that can be combined to distinguish between genuine gene mutations and DNA sequencing errors that occur during the amplification and sequencing reactions. ECS can detect rare gene mutations that are caused by chemical exposure at a frequency of 1 in 10 million. ECS can be applied using various tissues from any *in vivo* tox study, eliminating the necessity to run a dedicated TGR mutation study. ECS can also be applied *in vitro* in any relevant cell line.

TERUG NAAR INHOUD

ECS is currently under evaluation by numerous academic and industry laboratories as alternative approach for mutagenesis assessment. First results confirm the accuracy and sensitivity of ECS to detect chemically-induced mutations in animals and in cell lines. ECS is currently under review by OECD to explore regulatory applications.

During the webinar, you will learn about ECS and its latest developments, *in vivo* and *in vitro* applications of the ECS technologies and case studies.

Presenters

- Dr Sujath Abbas- Principal scientist at GSK
- Dr. Francesco Marchetti – Research professor at the Environmental Health Centre, Health Canada
- Dr. Inger Brandsma, Director genetic toxicology at Toxys

SECTION RISICOBEOORDELING

Minutes Autumn symposium 2024

Making uncertainties in risk assessment visible: A journey towards informed decision making

With this autumn symposium, organised by the section Risk Assessment from the Dutch Society for Toxicology (NVT), it was aimed to demonstrate the latest methodology and model development in the management of uncertainties in risk assessment. Speakers from RIVM, KWR and EFSA were invited to show their applications.

The symposium was started with an introductory presentation on probabilistic approaches, presented by Bas Bokkers a risk assessor and toxicologist from the National Institute for Public Health and the Environment (RIVM, NL). With this presentation insight was provided on probabilistic risk assessment (PRA) compared to deterministic risk assessment. The differences, advantages and disadvantages of both approaches were explained, showing that PRA can provide more informative conclusions including variability and uncertainty.

The applicability and usage of APROBA-Plus tool was subsequently demonstrated by Judith de Heer. Judith is a researcher working at the National Institute for Public Health and the Environment (RIVM, NL). During this session the usage of APROBA-Plus for deterministic compared to a probabilistic risk calculations was given. Multiple examples were showed on how to use and interpreted APROBA-Plus retrieved results.

The usage of APROBA-Plus for probabilistic risk assessment in a drinking water case study was presented by Renske Hoondert. Renske is a researcher and project manager working at KWR. During this case-study presentation the steps taken in PRA were explained to characterise the uncertainties and support better risk assessment to improve risk management.

During the final session Ullrika Sahlin an Associate Professor from Lund University provided an introduction to the need and methodology of expert knowledge elicitation (EKE), and how this can be used to support the characterisation of uncertainty in risk assessment. Ullrika has been an independent expert in EFSAs cross cutting working group on uncertainty and is currently providing trainings and support in EKE for EFSA. The audience were told that EKE was developed to counteract bias in expert judgement, as a systematic documented and reviewable process and uses probability to express uncertainty.

Endocrine Disruption Testing Strategy for REACH: **Current Gaps and Future Requirements**

By *Barae Jomaa*

The European Union's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation is undergoing significant revision to address knowledge gaps in endocrine disruption assessment. Endocrine Disrupting Compounds (EDCs) are substances that interfere with the endocrine system and cause adverse effects on the health and/or reproduction of humans and other animals. The European Commission's Chemicals Strategy for Sustainability placed special emphasis on endocrine disruption and proposed to establish legally binding hazard identification for EDCs, a ban on certain products containing them, and aimed to protect workers by including endocrine disruptors as substances of very high concern (SVHCs) under REACH[1]. This approach is the result of years of public concern over suspected endocrine disruptors, including substances that have been formally identified as endocrine disruptors by European Chemicals Agency (ECHA) Endocrine Disruption Expert Group, such as 4,4'-isopropylidenediphenol (bisphenol A), dicyclohexyl phthalate, phenol, dodecyl-, branched, 2,2-dibromo-2-cyanoacetamide, cyanamide, bisphenol B, and butyl 4-hydroxybenzoate, among others.

Bisphenol A (BPA) was banned from baby bottles in the European Union in 2011 due to concerns about its endocrine-disrupting effects (photo courtesy of Vyacheslav Argenberg, CC BY 4.0)

Endocrine disruption is among a select group of hazards, alongside sensitizers and genotoxicants, that can exert effects at very low concentrations. Some endocrine disruptors demonstrate potencies in the nanomolar or even picomolar range. Moreover, the effects of such low concentrations of EDCs may go unnoticed in the general population, while exerting outsized impacts on babies and children during critical windows of development.

Currently, REACH standard information requirements do not provide comprehensive data on endocrine-disrupting properties, despite some existing studies, such as reproductive and developmental toxicity studies (e.g., OECD 421, 414, and 443), which include relevant endpoints for fertility, sexual development, and fetal growth. A combination of testing methods, both in vitro and in vivo, is usually required to generate data relevant to both the adverse effect and the endocrine activity, following the approach outlined in the OECD Conceptual Framework for Endocrine Disruption Testing and Assessment[4].

The ongoing REACH revision aims to update information requirements in order to allow for better identification of endocrine disruptors, following the horizontal approach already implemented for plant protection products and biocides through Commission Regulation (EU) 2018/605 and Commission Delegated Regulation (EU) 2017/2100 respectively. Such a revision of REACH would add consistency in endocrine disruption identification regardless of the regulatory framework under which a substance is assessed.

CLP Regulation and Endocrine Disruption Classification

The Commission Delegated Regulation (EU) 2023/707, which entered into force on 20 April 2023, sets the scene for the widely anticipated REACH revision by introducing

specific hazard classes for endocrine disruption under the Classification, Labelling and Packaging (CLP) regulation[3]. The new classifications establish two categories (1 and 2) for endocrine disruption based on the strength of evidence rather than potency, similar to the approach used for carcinogenic, mutagenic, and reproductive (CMR) hazards. When there is sufficient evidence, classifications can be set for both endocrine disruption to human health (ED HH) and endocrine disruption to the environment (ED ENV). As these classifications are not implemented in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), they don't have H-codes but rather get the EU specific EUH-codes.

The classification criteria follow the approach established in the ECHA-EFSA guidance[2], requiring evidence of both endocrine activity and adverse effects, with a plausible link between the two. This ensures that substances are not classified as endocrine disruptors based solely on their ability to interact with the endocrine system, but rather requires demonstration that such interaction leads to adverse effects in vivo, which are relevant to human health or the environment. Conversely, an adverse effect alone cannot be conclusively attributed to endocrine disruption without mechanistic evidence, which can often be more readily established under controlled in vitro experiments.

The CLP amendment requires new substances and mixtures to comply from 1 May 2025 and 1 May 2026, respectively, while existing substances and mixtures must comply by 1 November 2026 and 1 May 2028, respectively.

Proposed REACH Testing Strategy

The development of enhanced testing requirements for endocrine disruption began at the third meeting of the Competent Authorities for REACH and CLP (CARACAL) Sub-Group on Endocrine Disruptors (CASG-ED) in October 2020.

Table 1: Table 1: Proposed Endocrine Disruption Testing Requirements Under REACH. Proposals I, II as well as the latest Weight of Evidence (WoE) determination approach

Test Method	Proposal I	Proposal II*	WoE (Latest)**
Annex VII (1-10 tpa)			
Estrogen receptor transactivation assay (OECD TG 455)	X	X	X
Androgen receptor transactivation assay (OECD TG 458)	X	X	X
H295R steroidogenesis assay (OECD TG 456)	X	X	X
Aromatase assay – human recombinant (OPPTS 890.1200)	X	X	X
WoE determination using all available data	—	—	X
Annex VIII (10-100 tpa)			
HH: Uterotrophic bioassay in rodents (OECD TG 440) or ToxCast ER Model	If concerns	X	X
HH: Hershberger bioassay in rats (OECD TG 441)	If concerns	X	X
ENV: Fish short term reproduction assay (OECD TG 229)	If concerns	X	—
ENV: Amphibian metamorphosis assay (OECD TG 231)	If concerns	X	X
Annex IX (100-1,000 tpa)			
HH: Uterotrophic bioassay (TG 440) or ToxCast ER Model	X	See VIII	X
HH: Hershberger bioassay in rats (OECD TG 441)	X	See VIII	X
ENV: Fish short term reproduction assay (OECD TG 229)	X	See VIII	—
ENV: Amphibian metamorphosis assay (OECD TG 231)	X	See VIII	X
ENV: Fish sexual development test (OECD TG 234)	X	X	X
Annex X (> 1,000 tpa)			
ENV: Medaka extended one-generation reproduction test (OECD TG 240)	X	X	X
ENV: Larval amphibian growth and development assay (OECD TG 241)	X	X	X

* Proposal II: Positive results trigger testing relevant to the following Annex.

** WoE (Latest): In vivo testing at all tonnage bands only if WoE is positive. Positive WoE triggers Annex VIII human health (HH) ED testing. If these tests result in ED HH Cat. 1 classification with RMMs applied, no further ED HH or ED ENV testing needed. However, if ED HH Cat. 1 classification is based only on WoE, environment tests may still be required. ED ENV tests may be waived at all tonnage bands if classified ED ENV Cat. 1 with RMMs applied. For Annex VII, in vivo testing may be waived if substance shows no long biological half-life and no potent toxicity.

Two proposals emerged from these initial discussions.

Proposal I followed a concerns-based approach where in vitro mechanistic assays would be mandatory at Annex VII, but progression to higher-tier studies would depend on case-by-case evaluation of whether the data indicated sufficient concern to warrant additional testing. This approach offered regulatory flexibility and allowed for expert judgment in determining testing needs, though Member States expressed concerns about potential inconsistencies in implementation across different substances and registrants.

Proposal II incorporated a systematic triggering framework where positive results at each testing tier would automatically initiate testing at the next level. This approach found favor with ECHA and several Member State competent authorities due to its predictability and the consistency it would bring to endocrine disruption assessment. While the automatic progression mechanism eliminated subjective interpretation, it raised concerns about proportionality, particularly for substances with limited exposure potential.

Industry stakeholders, led by the European Chemical Industry Council (Cefic), consistently argued that both proposals would impose disproportionate administrative and testing burdens. Small and medium enterprises highlighted the existential threat posed by testing costs that could exceed the commercial value of many specialty chemicals. On the other hand, Non-Governmental Organisations (NGOs) maintained that comprehensive testing was essential given the serious implications of endocrine disruption.

On the 7th of February 2025, the Commission circulated a new approach centered on weight-of-evidence evaluation. The weight-of-evidence approach places the responsibility for determining testing needs on registrants, who must justify their decisions through systematic evaluation of all available data including existing toxicological studies, structural alerts, read-across from analogues, and exposure considerations. Unlike the automatic progression of Proposal II or the concerns-based evaluation of Proposal I, the Weight of Evidence (WoE) framework requires registrants to develop comprehensive justifications for their testing strategies.

This shift emerged from the substantial opposition encountered during impact assessment, particularly the findings of Burden et al.[5] demonstrating that systematic testing requirements could cost the European chemical industry over €22 billion and require testing on nearly 26 million animals. The economic analysis revealed that implementation of Proposal II would be particularly challenging for the substantial number of substances in the 10-100 tonne band, where mandatory progression to in vivo studies would represent a doubling or tripling of registration costs. The shift also aims to align with the European Union's simplification agenda aimed at boosting competitiveness.

The presentation of the weight-of-evidence approach at the CARACAL-54 meeting on April 3, 2025, triggered unprecedented industry opposition. Cefic's response that "the Commission services are living in a different world than their own political leadership" reflected deep frustration with what industry perceived as a failure to align regulatory proposals with broader EU competitiveness objectives. The requirement that all in vivo studies, including those at Annexes VII and VIII, would require testing proposals would represent a fundamental departure from REACH's established framework where lower-tier studies are standard information requirements.

In contrast, NGOs expressed concerns that the WoE approach would enable industry to avoid necessary testing through subjective data interpretation.

As of the date of publication, the Commission continues to review stakeholder submissions received during the consultation period that closed on April 25, 2025. The final legislation remains scheduled for adoption in the fourth quarter of 2025, though the depth of stakeholder disagreement and the fundamental nature of the concerns raised suggest that further modifications may be necessary to achieve a viable regulatory framework.

A limiting factor for implementation is the global shortage of laboratories capable of conducting specialized endocrine disruption studies. Most critically, standardized thyroid assays remain unavailable, with placeholder methods awaiting development and validation.

Scientific and Technical Gaps

The thyroid system represents the most significant gap in current testing capabilities. The complexity of thyroid hormone regulation involves multiple potential targets for disruption, including thyroid peroxidase inhibition affecting hormone synthesis, sodium/iodide symporter interference disrupting iodine uptake, alterations in serum transport proteins and cellular transporters affecting hormone distribution, deiodinase enzyme inhibition affecting peripheral hormone activation, and direct interference with thyroid hormone receptors. Currently, no validated OECD test guidelines adequately address these diverse mechanisms, with placeholder assays awaiting development that may not be available until 2026-2028.

Most in vitro assays lack metabolic activation systems, creating a fundamental limitation in their predictive capacity. Many substances require biotransformation to become endocrine active, while others that appear active in vitro may be rapidly metabolized to inactive forms in vivo. This limitation significantly affects the predictive value of screening assays and contributes to the high false positive rates.

Industry analysis suggests that the proposed in vitro battery could generate positive results in 15-50% of tested substances, triggering expensive follow-up animal testing. The International Fragrance Association (IFRA) highlighted that for thyroid assays currently under validation, 28 out of 30 chemicals tested positive in at least one assay, with only divanadium pentoxide showing negative results across all assays[6]. This extraordinarily high positive rate raises serious questions about the specificity of the proposed testing battery.

Conclusion

Success in implementing enhanced endocrine disruption requirements will require continued investment in method development and validation, particularly for thyroid disruption assessment and metabolically competent in vitro systems. Expansion of global testing capacity through strategic investment in laboratory infrastructure and personnel training is essential to avoid implementation bottlenecks. Development of pragmatic implementation guidance that balances scientific rigor with practical feasibility will be crucial. Most importantly, achieving an appropriate balance between protection goals and economic feasibility will require continued dialogue between regulators, industry, and civil society stakeholders.

References:

1. European Commission. (2020). Chemicals Strategy for Sustainability. Towards a Toxic-Free Environment. COM(2020) 667 final.
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Obesity: **the rising tide of a global health crisis**

Obesity represents a major global health challenge and is now recognized as a chronic, relapsing, and multifactorial disease. Its prevalence has been steadily increasing worldwide and is projected to continue rising in the coming decades[1]. This trend poses a profound threat to public health, given its association with a wide spectrum of comorbidities, including type 2 diabetes mellitus, cardiovascular diseases, certain cancers, musculoskeletal disorders, and overall reduced life expectancy[2].

By *Héloïse Proquin*

Defining obesity

Obesity is commonly defined using the body mass index (BMI), with values above 30 kg/m² typically classified as obese. However, BMI is an imperfect diagnostic tool, as it does not account for body composition, fat distribution, bone density, ethnicity, or muscle mass. Consequently, it may both overestimate and underestimate metabolic risk at the individual level. More precise approaches, such as waist-to-hip ratio, visceral fat imaging, and metabolic biomarkers, are increasingly being explored to provide deeper insights into obesity-related health risks.

Origins of obesity

Historically, higher body weight was considered a marker of wealth, abundance, and social status. In contrast, in modern societies, obesity is more closely associated with socioeconomic disadvantage. Populations with limited access to fresh and diverse foods are more likely to rely on inexpensive, energy-dense, and nutrient-poor processed foods, leading to an increased prevalence of obesity. Importantly, obesity cannot be explained solely by dietary diversity; it results from a complex interplay of biological, environmental, behavioral, and socioeconomic factors.

Current situation

For the first time in history, global childhood overweight and obesity rates exceed the prevalence of underweight. Data from UNICEF involving more than 190 countries show that childhood obesity increased from 3% in 2000 to 9.4% in 2020, while underweight prevalence decreased from nearly 13% to 9.2%[3]. This epidemiological shift underscores the urgency of addressing obesity through effective prevention and intervention strategies.

Biological mechanisms

Obesity arises from the interaction of genetic, epigenetic, and environmental factors that influence energy homeostasis and adiposity. Environmental drivers include diet, physical activity, microbiome composition, circadian rhythm disruption, and exposure to chemical obesogens. These factors act on a complex network of organ systems, including the liver, adipose tissue, pancreas, gastrointestinal tract, skeletal muscle, adrenal glands, and the central nervous system.

Obesity is strongly linked to dysregulation of adipose tissue biology. Adipocyte differentiation and lipid storage are orchestrated by transcription factors such as PPARγ and RXR, which act either independently or as heterodimers to promote adipogenesis[4]. Nuclear receptors—including LXR,

PXR, CAR, FXR, and AhR—further regulate lipid metabolism, glucose homeostasis, bile acid synthesis, immune responses, and cholesterol transport[5]. Dysregulation of these pathways may manifest as hyperinsulinemia, leptin resistance, and weight gain. Hormonal factors, particularly insulin, glucocorticoids, sex steroids, and thyroid hormones, also play pivotal roles in modulating metabolism and fat accumulation.

Obesogens in consumer products

A growing body of evidence suggests that synthetic chemicals, termed obesogens, can disrupt endocrine and metabolic pathways, predisposing individuals to obesity. Obesogens are commonly found in consumer products such as cosmetics, toys, detergents, plastic food-contact materials, and even medical devices[4,6,7].

Substances suspected to act as obesogens include:

- Phthalates and bisphenols (plastics, packaging, cosmetics)
- Parabens, phenols, benzophenone-3, octocrylene (personal care products, sunscreens)
- Organophosphates (pesticides)
- Heavy metals (usually contamination in products)
- Perfluorooctanoic acid (non-stick cookware, packaging)
- Monosodium glutamate (MSG) (food additive)
- Synthetic compounds such as dioctyl terephthalate, acetyl tributyl citrate, and cyclohexanone (industrial chemicals, plasticizers)

Chronic exposure to these substances, even at low levels, may contribute to long-term alterations in metabolic function and obesity risk.

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Endocrine Disruptor Identification and the ECHA Endocrine Disruptor Expert Group

By *Gaby Eliesen*

Identification and regulation of endocrine disruptors in the EU

As outlined in our recent paper (Bouwmeester et al., 2025), identification and regulation of endocrine disruptors (EDs) has been an important topic in the EU for over the past decades. In the EU, EDs can be identified under the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation, Biocidal Products Regulation (BPR), and the Plant Protection Products Regulation. Under REACH, twelve chemicals have currently been identified as a Substance of Very High Concern (SVHC) based on their ED properties for human health. In 2020, the Chemicals Strategy for Sustainability (European Commission, 2020) emphasized the need to consolidate and simplify the EU regulatory system with regard to EDs, by introducing new hazard criteria for EDs under the Classification Labeling and Packaging (CLP) Regulation to enable appropriate regulation of these chemicals in consumer products (European Commission 2020 and 2023). In 2023, new hazard classes for ED came into effect under the CLP Regulation (European Commission, 2022).

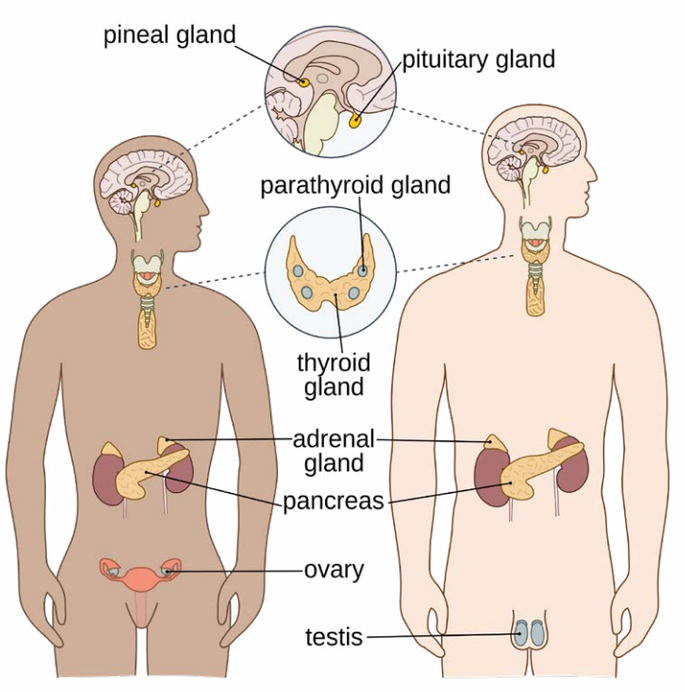
The abovementioned regulations are based on the WHO definition of an ED: “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations” (WHO IPCS, 2002). Although this definition covers all types of endocrine disrupting effects, most substances discussed in the ED expert group have concerns for estrogenic, androgenic, thyroid and steroidogenic (EATS) modalities. This is due to a fairly good mechanistic understanding of how these disruptions cause adverse effects.

ECHA ED Expert Group

The ECHA ED Expert Group is an advisory body which can be consulted by Member States of the European Union that are working on ED identification or classification of substances under REACH and CLP or the Biocidal Product Regulation[1]. Additionally, the ED expert group is also consulted as part of a Substance Evaluation under REACH, where additional studies can be requested by the reviewing Member State to address a concern for ED effects.

The goal of the ED expert group is to provide informal and non-binding scientific advice related to the identification of endocrine-disrupting properties of chemicals. In summary, the discussions during the ED expert group meeting address in particular[2]:

- “Matters related to screening methods or activities to identify potential endocrine disruptors (e.g. for the CoRAP list or the Candidate List).
- Matters related to the development of integrated approaches to testing and assessment of endocrine-disrupting properties.
- Feedback and recommendations on complex (specific/generic) scientific issues related to information and (tiered) testing needs for potential endocrine disruptors



Endocrine system diagram within a human body.
By OpenStax & Tomáš Kebert & umimeto.org - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=95250832

(e.g. under dossier or substance evaluation, or under biocidal active substance evaluation).
- Specific questions on the interpretation of test data or other relevant information in relation to the identification of endocrine-disrupting properties (e.g. during SVHC dossier development, CLP dossier development or a biocidal active substance evaluation)."

Structure and Meetings

The ECHA ED expert group convenes three times a year, of which two are remote sessions and one is an in-person meeting in Helsinki. Members of the ED expert group include scientific experts from EU Member States, ECHA and the European Commission. Supporting experts can be invited by members on a case-by-case basis. The group also includes observer organizations representing industry or NGOs. The list of current members can be found at https://echa.europa.eu/cs/list-of-ed-members. All meeting minutes are publicly available at https://echa.europa.eu/endocrine-disruptor-expert-group-meeting-dates-and-reports/ .

Additional information

For more information on the identification of EDs and the type of studies and parameters that inform on ED activity and adversity, the following guidance documents are useful:

- The ECHA/EFSA guidance for identification of endocrine disruptors (ECHA/EFSA, 2018);
- The CLP guidance, Chapter 3 on health hazard (ECHA, 2024),
- OECD guidance document 150 (OECD, 2018).

Furthermore, a recent paper by Holmer and colleagues, well describes the current regulatory framework on regulation of EDs (Holmer et al., 2025).

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[1] Of note is that the consulting body for ED identification of plant protection products is the EFSA Working group on Endocrine Disruptors.

[2] Quoted and adapted from the website of the ED Expert Group: https://echa.europa.eu/endocrine-disruptor-expert-group

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From vine to home: PestiRiv, a French study of plant protection substances exposure in vineyard communities

By *Héloïse Proquin*

The PestiRiv study demonstrated that people living near vineyards are more highly exposed to plant protection substances used in viticulture compared to those living further away from any crop fields. This heightened exposure is particularly notable during periods when treatments are applied to the vines.

Study Design

The participants were 1946 randomly-selected adults (18-79 years old) and 750 children (3-17 years old), either living within 500 meters of vineyards or more than 1,000 meters from any agricultural land. The participants were from 265 varied study zones in six major wine-producing regions (from Bourgogne to Rhone including Bordeaux).

Samples were collected between 2021 and 2022 from urine, hair, dust, indoor and outdoor air, and home-grown fruits and vegetables, with accompanying questionnaires on behaviours, environmental context, and agricultural practices. The first set of samples were taken between October 2021 and February 2022, a period without treatments and between March 2022 and August 2022, a period with different treatments. A total of 3484 urine samples, 1890 hair samples, 333 indoor air samples, 790 dust samples, 106 home-grown fruits and vegetables samples, 1557 outdoor samples.

Key plant protection substances tested

Vineyard-Specific Substances:

- Folpel: A fungicide commonly used in viticulture, frequently found in both environmental and biological samples.
- Metiram: Another vineyard-targeted fungicide measured in the study.

Other Frequently Detected Pesticides:

- Glyphosate: A very widely used herbicide, detected in samples even though not exclusive to vineyards.
- Fosetyl-aluminium: Used as a fungicide, often applied on vines.
- Spiroxamine: A systemic fungicide detected in sampled areas.

Broader-use plant protection substances:

- Pyrethroids: Insecticides that may originate from multiple sources (not just agricultural use).
- Copper-based products: Also detected, but these have other uses beyond vineyards.

Other substances of note (from related research):

- Tebuconazole (fungicide), trifloxystrobin, pyraclostrobin, benalaxyl, and boscalid have also been reported as relevant to vine treatments in similar studies.

Key Findings

As expected, people living near vineyards had consistently higher levels of plant protection substances exposure (measured by biomarkers in urine and hair, and environmental samples) than those in control areas. Additionally, exposure peaks during treatment periods in the vineyards and affects both adults and children. The distance to the vineyard with the quantity of plant protection products are the main factors driving exposure.

Both vineyard-specific substances (e.g., folpel, metiram) and more widely used chemicals (e.g., glyphosate, fosetyl-aluminum, spiroxamine) were detected. Some substances, such as pyrethroids and copper, did not show a strong difference because they are used in other contexts as well.

Scientific and Public Health Implications

The results provide robust, nuanced data across several types of biological and environmental samples, supporting the link between proximity to vineyards and plant protection substances exposure. The findings confirm the need for interventions targeting the source (vineyard practices) to reduce exposure for those living near crops.

The study's data establish a baseline for monitoring and provide resources for further research; the conclusions are also relevant for other crops and support national policies recommending stricter regulation of plant protection substances use and improved public notification prior to spraying.

Limitations

PestiRiv provides the most accurate snapshot possible of the exposure of local populations during pesticide spraying. However, it does not provide any further information on the degree of danger posed by the products or their impact on health.

Another limitation of the study is that it does not allow for the establishment of exposure thresholds for a product. Here too, work remains to be done to properly characterise and measure the risk of developing diseases for exposed individuals, particularly children. To date, these studies have been conducted when there has been an increase in cancer cases, for example in municipalities that suddenly deviate from the national average for the occurrence of a particular disease. These 'clusters' currently serve as warning signs, without any formal link to the environment having been established.

Inschrijving Register

Voorletters	Achternaam	Datum inschrijving	Datum afloop registratie
K.	Nierman	28-05-2025	28-05-2030
M.	Graumans	28-05-2025	28-05-2030
C.	Henstra	28-05-2025	28-05-2030
H.	Proquin	28-05-2025	28-05-2030
P.	Bao	28-05-2025	28-05-2030
F.	Widjaja	21-08-2025	21-08-2030
N.	Ruijter	21-08-2025	21-08-2030
T.	Nolte	21-08-2025	21-08-2030
J.	Fang	21-08-2025	21-08-2030

Inschrijving TiO

Voorletters	Achternaam	Datum inschrijving	Opleider
D.	Roelofsen	21-05-2025	Dr.ir. P.T.J. Scheepers
P.	Roos	21-05-2025	Prof.dr. R. Masereeuw
M.M.	Oldenburger	21-05-2025	Prof. dr. F.R. Cassee
R.	van der Linden	21-05-2025	Prof.dr. R. Masereeuw
A.A.	Kan	20-08-2025	Prof.dr. D.W. de Lange
F.R.	Makarim	20-08-2025	Prof.dr.ir. Nico van den Brink
L.	Gan	20-08-2025	Prof.dr.ir. I.M.C.M Rietjens
M.M.	Faber	20-08-2025	Prof. dr. F.R. Cassee

EU Court of Justice annuls harmonized classification for Carcinogenicity (Cat. 2) of TiO_2

By *Damiën van Berlo, Petra van Kesteren*

Hazard classification is a cornerstone in the regulation and management of chemical substances, stimulating protection of human health and the environment by hazard identification and communication. Such hazards include physical hazards (e.g., flammability or metal corrosivity), health hazards (e.g., acute toxicity, carcinogenicity) and environmental hazard (such as toxicity to aquatic organisms).

Since 2008, the "Regulation on classification, labelling and packaging of substances and mixtures" (CLP; Regulation EC/1272/2008) is effective. CLP is complementary to the EU chemicals regulation REACH (EC/1907/2006) and incorporates classification criteria for a number of hazard categories, recently expanded to include novel hazard classes endocrine disruption and persistent, bioaccumulating and toxic (PBT). When a legally binding harmonized classification applies to a certain substance that is present on the EU market, all producers and importers have the obligation to disclose information on this classified hazard via the label and to mention the classification on the safety data sheet (SDS). Formulators need to appropriately classify mixtures containing the substance. For downstream users (professional or industrial parties that use the substance or a mixture containing the substance), it is obligatory to adopt the classification on the label/SDS and to apply suitable risk management measures to protect workers (e.g., ventilation, personal protection equipment). A harmonized classification in CLP can also trigger legal restrictions laid down in other community legislation such as REACH, cosmetics, food safety and worker protection legislation.

One of the classification cases that has sparked discussion in recent years, is titanium dioxide (TiO_2), which is widely used in coatings, food products and pharmaceuticals. For instance, its presence is the reason many pills, sunscreen products, and latex wall paints are white and/or shiny.

Since 2016, the matter of the safety of TiO_2 (especially particles related to possible carcinogenicity) has been the subject of increased regulatory attention, with France submitting a proposal for harmonized classification as an inhalation carcinogen to the European Chemicals Agency. The Risk Assessment Committee (RAC), providing advice to ECHA on matters such as classification, in 2017 supported the proposal for carcinogenicity (but with a lower category) in an opinion. Subsequently, in October 2019, the European Commission adopted Delegated Regulation (EU) 2020/217, formally listing "powdered titanium dioxide (containing ≥ 1% particles ≤ 10 micrometres)" as a *Category 2 carcinogen*.

Titanium dioxide. By The original uploader was Walkerma at English Wikipedia. - Transferred from en.wikipedia to Commons., Public Domain, https://commons.wikimedia.org/w/index.php?curid=2443859

This mandated the addition of the “H351: Suspected of causing cancer when inhaled” warning label to products containing this substance. This classification was effective from 1st October 2021. It should be noted that it *only* applied to mixtures in powder form containing 1% or more TiO_2 in particles with an aerodynamic diameter of < 10 µm.

Soon after the classification was implemented and effective, a number of manufacturers, importers and downstream users appealed the EU decision at the EU General Court. After investigating the case, the General Court annulled the decision on the 23rd of November 2022 and judged that the European Commission “made a manifest error in its assessment of the reliability and acceptability of the study on which the classification was based”. The court also concluded that the properties that caused the observed carcinogenic effects in rats are extrinsic to the substance itself and are not covered by the CLP regulation.

The European Commission and dossier submitter France appealed to the European Court of Justice (ECJ) on 8 and 14 February 2023. The ECJ is the highest court in the European Union and is one tier above the EU General Court. An (unofficial and non-binding) opinion of the Advocate General of the ECJ was published in February 2025, in which it was argued that the court made an erroneous decision and overstepped its authority by questioning the scientific argumentation for the classification: “the court are not scientists”.

On 1st August 2025 the ECJ’s ruling was made public: the ECJ judged that “*even though the General Court exceeded the limits of its judicial review, the annulment of the contested classification and labelling is nevertheless justified. The General Court was fully entitled to hold that the RAC had failed to take into account all the relevant factors for the purposes of assessing the scientific study in question*.” This ruling may be considered as confusing, as it states that 1) the General Court had “exceeded the scope of judicial review”, which is on judicial errors rather than scientific argumentation (which is not the expertise of the EU General Court or the ECJ) and 2) that the General Court was entitled to judge that RAC did not take all relevant factors into account, which would still be a scientific argument.

This means that the classification is now definitely annulled, and it is uncertain whether the classification case for carcinogenicity will be re-evaluated, which could lead to a new CLH proposal. For producers, importers and downstream users this means that the H351 warning label no longer needs to be applied to products containing “powdered titanium dioxide (containing ≥ 1% particles ≤ 10 micrometres)”.

Reflections by the RIVM on the annulment can be found in the coming newsletter (which is due at the end of October 2025) of the “Knowledge and information centre on Risks of nanotechnology” (KIR-nano) via the following link: Newsletter RIVM on Advanced Materials | RIVM

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https://product.enhesa.com/1445005

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:62023CJ0071

Whiteout - Validating new approach methodologies against human data to reassess the safety of E171

By *Nicolaj S. Bischoff*

This thesis integrates advanced in vitro systems, dynamic GI digestion models, and a controlled human dietary intervention to evaluate food-grade titanium dioxide (E171). Across models, E171 increased reactive oxygen species (ROS), modulated colon transcriptomes along pathways related to carcinogenesis, and influenced microbiome metabolism. Critically, in vitro findings were validated against concurrently generated human data from a first-of-its-kind dietary intervention, strengthening the case for human-relevant new approach methodologies (NAMs) in food safety assessment.

Titanium dioxide (E171) served for decades as a whitening/opacifying agent in foods and pharmaceuticals. Following EFSA's 2021 re-evaluation and the subsequent EU ban, international positions remain split, mainly due to uncertainties about human relevance and the role of digestion and food matrices. This work addresses those uncertainties with a tiered, human-centred testing strategy and validates it against human data. The work employs a coherent suite of NAMs, including induced pluripotent stem cell (iPSC)-derived human colon organoids and TNO's TIM-1/TIM-2 gastrointestinal models, followed by a crossover human dietary intervention at a realistic exposure level (2 mg/kg bw/day) to assess concordance across systems. Standardised pipelines (e.g., R-ODAF for transcriptomics) were used to maximise reproducibility and regulatory utility.

Key mechanistic findings across models

Short-term E171 exposure in iPSC-derived colon organoids increased ROS, induced DNA damage (including FPG-sensitive lesions), and altered gene expression in pathways linked to oxidative stress, proliferation, inflammation, and carcinogenesis without showing cytotoxicity. These data provide early mechanistic understanding consistent with a genotoxic and oxidative stress-driven mode of action (MoA). In an APC-mutant colorectal cancer-prone (CRC) model, E171 exposure increased tumor size and modulated pathways involved in cell cycle, nuclear receptor signaling, circadian rhythm, and cancer signaling—changes observable before spontaneous tumor formation. These findings identify pre-neoplastic biological activity consistent with human organoid signals. A systematic review and meta-analysis estimates the lifelong mean dietary exposure at ~1.49 mg/kg bw/day, with higher exposures in children, contextualizing dose selection for experimental and human studies and aligning with EFSA's refined assessments. The impact of a food matrix on dynamic digestion was assessed in the TIM-1 (upper GI tract) and TIM-2 (lower GI tract) models. E171 exhibited an innate ROS-forming capacity in aqueous media, which was attenuated after digestion, consistent with protein corona formation. Additionally, a yogurt matrix also reduced ROS levels in cell-free electron spin resonance (ESR) spectroscopy using the TIM-1 model. Prolonged fermentation had a limited impact on particle size but significantly altered microbiome metabolism, notably increasing butyrate, indicating that E171 modulates the microbiome functionally in the TIM-2 model. Together, these results refine realistic exposure scenarios (particle behaviours along the GI tract; matrix effects) and generate testable hypotheses for human validation.

The decisive step: validation against human data

In a crossover design human dietary intervention study, where each participant served as their own control, exposure to E171 increased systemic ROS in whole blood. It altered the colon transcriptome towards pathways implicated in chemical carcinogenesis via ROS, CRC, PPAR signalling, and a metabolic shift consistent with the

Warburg effect. These molecular fingerprints mirror the organoid and mouse findings, establishing cross-model concordance. Interestingly, neither the food matrix nor GI digestion abrogated these effects in humans, despite attenuation of ROS levels in cell-free environment, underscoring the importance of human physiology and cell-particle interactions that are invisible to acellular assays. To our knowledge, this is the first human dietary intervention to assess the adverse effects of E171 on the colon using molecular endpoints.

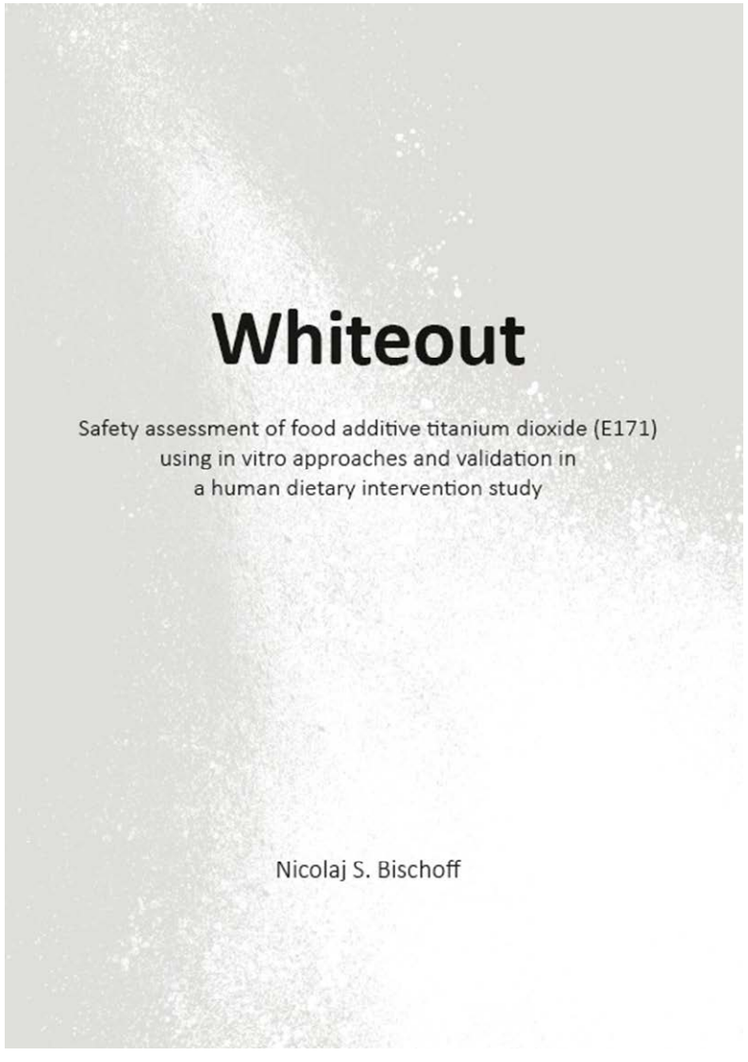
What is the novelty of this work?

- Methodological innovation with regulatory traction. The thesis validates NAMs against concurrent human data, directly addressing the long-standing translational gap in nanotoxicology and the evaluation of food additive safety. This tiered approach provides a human-relevant, reproducible framework for next-generation risk assessment (NGRA)
- Human evidence at realistic exposure. By operating at 2 mg/kg bw/day and capturing biomarkers and transcriptomic endpoints in colon tissue, the study provides human-centred evidence consistent with early carcinogenic processes, bridging in vitro/in vivo mechanistic hypotheses with in-human biology.
- Clarifying the digestion/food-matrix debate. The work demonstrates that protein coronas and matrices modulate acellular ROS, yet do not eliminate human molecular responses, a nuance essential for risk assessment and for interpreting divergent literature findings.

The totality of evidence suggests that ingested E171 can induce oxidative stress, DNA damage, and transcriptional programs related to carcinogenesis in human-relevant systems and in humans under realistic dietary conditions.

These novel data support the precautionary stance adopted in the EU and provide a template for integrating NAMs into regulatory decision-making for orally exposed particulates and other additives.

The case of E171 shows how connecting NAMs with human data can transform food toxicology from speculative assessment to evidence-based, human-relevant evaluation.



AIO toxafette - Jaimy de Schepper

In the toxafette, PhD-students working in the toxicology field get the chance to open up about their experiences in performing research. Every issue a new candidate answers a series of questions, and then passes the baton to a fellow PhD-student. This time Jaimy de Schepper tells us about his project.

Can you introduce yourself?
My name is Jaimy de Schepper, I am an external PhD student at the Amsterdam Institute for Life and Environment (A-LIFE) and I work as a chemical advisor at Het Waterlaboratorium (Haarlem). I have a background in analytical chemistry and am currently developing myself in the field of toxicology through the Postgraduate Education in Toxicology (PET) program to become a registered toxicologist (ERT).

How would you explain the subject of your research to a layperson?
Humans and the environment come into contact with many chemicals substances through air, soil, food and water. Traditionally, scientists assess the safety of the substances in these media one by one. In reality, we are exposed to mixtures of chemical substances at the same time.
My research focuses on water quality, mainly that of the water that is used for the production of drinking water. Herein, I investigate the effects caused by mixtures of chemical substances that may be present in water. While there are many possible effects that are of interest to study, I focus on the disruption of the transport of thyroid hormones in the (human) body.
The challenge is that we do not yet fully understand which chemical substances can disrupt the transport of thyroid hormones in the human body. Therefore, we use a combination of methods to try and identify the chemical substances. Ultimately, we wish to assess if there is a potential risk when exposed to mixtures of these chemical substances to protect human health and the environment.

How is your research related to the field of toxicology, and why did you choose this subject?
My research focuses on mixture assessment and the identification of hazards posed by mixtures of chemicals in water, predominantly water used for the production of drinking water. Using a combination of chemical analytical methods (chemical target analysis, nontarget screening, …) and *in vitro* methods (referred to as bioassays), we aim to identify compounds that can disrupt transport of thyroid hormones in the (human) body. We accomplish this by quantifying cumulative effects caused by mixtures of chemicals, known and unknown, in water using a bioassay. Next, when the toxicity drivers are known, a risk assessment will be performed for human health (i.e. lifelong consumption of drinking water) and the environment (i.e. lifelong exposure of organisms in surface water).

What was your motivation for starting a PhD program?
During my Master's, I wrote my thesis on a subject that falls within my current research area at Het Waterlaboratorium. When presenting and defending my research, my current (co-) promotors offered me an external PhD position in this research area. Het Waterlaboratorium is my main employer, and I am affiliated with Vrije Universiteit Amsterdam.
I certainly also considered pursuing a PhD position at a university, however, the offer to continue my line of research certainly made the difference.

How do you see the future of your research topic (follow-up research / social impact)? What do you hope for?
Within the context of my research, I envision that the identification of bioactive chemical substances during my research will allow performing a risk assessment for the disruption of the transport of thyroid hormones to protect human health and environment.

In the broader context, I envision that bioassays will obtain a more prominent role in monitoring chemical water quality in the future. Currently, bioassays in this context are used widely in research for hazard identification, assessing trends and water treatment processes. In the Netherlands, bioassays are already included in the routine monitoring of four drinking water companies. Outside of the Netherlands, however, it appears

to be used mostly as a research tool.
Related to the latter, I envision that effect-based trigger (EBT) values will receive a higher status in the international scientific community and perhaps later even be adopted in national regulations. Effect-based trigger (EBT) values are used as thresholds to assess bioassay response: if the EBT is exceeded, a potential risk cannot be excluded. There are different methods to derive EBTs, one such method relies on existing limits such as environmental quality standards (EQSs) to protect the environment, or health-based guidance values (HBGVs) to protect human health. Refinement, agreement and adoption of EBTs is needed to provide guidance to drinking water companies and water boards on the operational response required based on bioassay response.

If everything is possible, what do you want to do with the knowledge you have from your PhD? (Future aspirations)
In the future, I wish to play a role in providing the scientific community, drinking water companies, water boards and other relevant authorities with guidance on the applications of bioassays in monitoring chemical water quality. I believe that the knowledge that I obtained from PET courses (e.g. legal and regulatory toxicology, risk communication and perception), as well as the projects during my PhD help in achieving this goal.

Could you describe any experiences collaborating with people or organizations outside of academia to support your research? (Collaborative efforts)
In my research area, many bioassays are available that cover a wide range of endpoints, and in several cases several bioassays may be available for a given endpoint. In one of my studies, we performed a comparison between bioassays that measure similar endpoints, but that were each developed for different applications, such as hazard identification in food and feed. We assessed the suitability of these bioassays for monitoring chemical water quality, with respect to their sensitivity and specificity. The bioassays in this study were each performed by different laboratories, which required alignment in the protocols (i.e. reference standards, reporting, …) and the experimental setup between the laboratories. Given time and budget constraints, full alignment can sometimes be challenging, however the collaborating laboratories were very open to make small modifications for this study.

What are your thoughts on using new technologies like artificial intelligence in toxicology research? Are you using any of these technologies in your work? (Research methodology)
While I am not involved in the development of such technologies, my work certainly does rely on their output. When a bioassay response exceeds the EBT, follow-up research may be warranted to identify the drivers of toxicity. The latter, however, is challenging given that the current coverage of the chemical space in water is not yet fully mapped out. In other words, we do not yet fully understand how many of the chemicals that we may be exposed to can currently be analyzed by chemical analysis. New technologies such as AI can play an important role in 1. assessing the chemical space of the exposome and 2. modelling the contribution of mixtures of known (and unknown) chemicals to bioassay response to identify toxicity drivers.

Do you consider research communication as an important aspect of your PhD and why so? If yes, to what kind of audience? (Communication strategy)
I believe that research communication is essential in any PhD position, whether it relates to communicating to the stakeholders of your project, other scientists during a conference, to your friends and family or to a complete stranger. Every audience requires a different communication strategy. Therefore, it is important to develop communication skills and to continue practicing communication to different audiences throughout your career. I find it interesting how a given audience perceives the relevance of my research area, and the questions they ask related to their knowledge domain or their world view.

What goals do you have regarding your career after finalization of your PhD? Would this be inside or outside academia, and why? Would you consider going abroad?
After finalizing my PhD, my goal is to stay in (semi-)public institutes. The reason for this is that I enjoy working on research that is focused on putting bioassays and other alternative methods into practice. However, in practice this does not mean that this research will not involve collaborations with academia. Such collaborations are key to ensuring that newly developed techniques can be implemented to be used in practice.

Please answer the question from the last toxafette PhD-candidate: How do you integrate input from different disciplines into your research?
My research area uses many chemical analytical methods for the detection, identification and quantification of chemical substances in water. This step is essential to identify the toxicity drivers that cause bioassay response. However, in many cases we do not possess test data of these chemical substances for a given bioassay. Ideally, one would test all identified chemical substances from a water sample in the bioassay, but this is often not feasible. Therefore, literature from other disciplines such as omics are needed to understand biological response upon chemical exposure, which can be used to prioritize chemical substances to be tested in the bioassay to confirm their biological response. Last, developments from the field of data science play an important role to translate high-dimensional data into meaningful results, particularly those obtained from high-resolution mass spectrometry (HRMS).

2025 (8th) International Conference on Toxicology Testing Alternatives and Translational Toxicology

Chengdu, China, July 2nd – July 5th

TRAVELER:
Qiuhui Ren, Division of Toxicology, Wageningen University & Research

My presentation

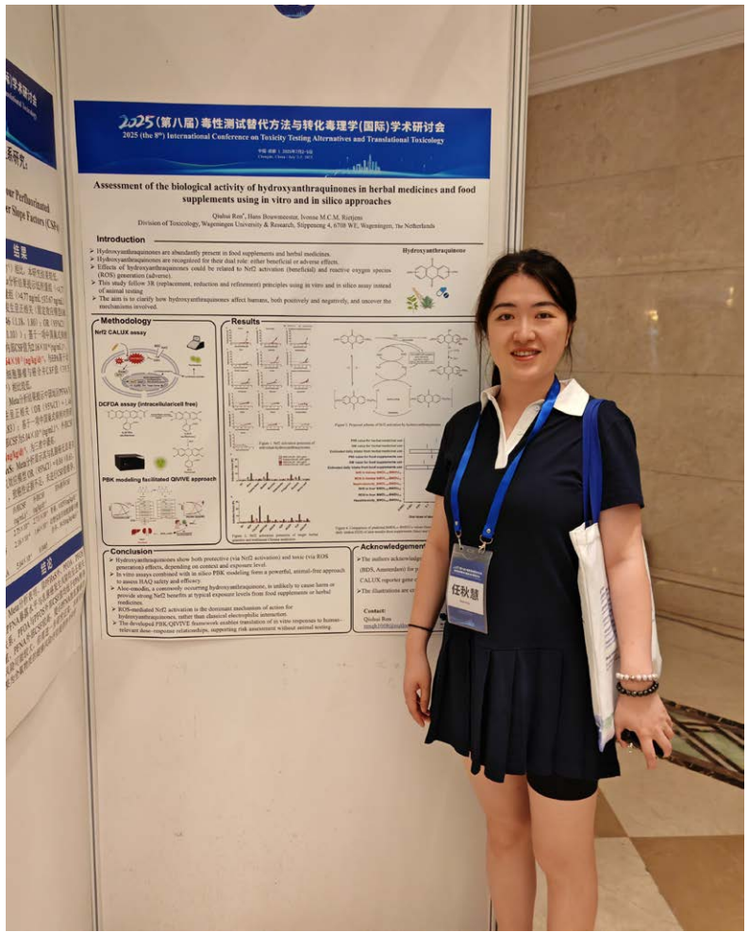
At the 2025 International Conference on Toxicity Testing Alternatives & Translational Toxicology, I presented my PhD research study entitled “Assessment of the Biological Activity of Hydroxyanthraquinones in Herbal Medicines and Food Supplements Using In Vitro and In Silico Approaches.” This research focused on hydroxyanthraquinones (HAQs), a group of natural compounds abundantly present in medicinal herbs. These compounds can produce both beneficial and adverse effects, largely depending on their ability to activate the Nrf2 pathway or generate reactive oxygen species (ROS). To reduce animal testing and enhance human relevance, I employed a fully animal-free testing strategy including high-throughput in vitro assays and in silico assay – physiologically based kinetic (PBK) modeling. This allowed for quantitative in vitro-to-in vivo extrapolation (QIVIVE) of dose-response relationships. Our findings showed that Nrf2 activation by HAQs results primarily from ROS generation via deprotonation and electron transfer, rather than quinone electrophilicity. Notably, at current human exposure levels, aloe-emodin is unlikely to induce either significant protective or harmful effects. This integrated approach not only aligns with the 3Rs (Replacement, Reduction and Refinement) principle but also provides a robust framework for evaluating bioactive compounds in food and herbal products.

Most interesting insights from the conference

There are three presentations have been deeply impressed me.

First, Prof. Chunying Chen (National Center for Nanoscience and Technology) delivered a plenary talk on “Nano-Bio Interface Mechanism-Based Strategy for Nanomaterial Safety Evaluation.” She presented cutting-edge tools such as single-cell mass spectrometry and synchrotron radiation techniques to demonstrate how nanomaterials interact with intestinal microbiota and epithelium. Her work revealed that gut microbes can metabolize engineered nanomaterials, influencing both local and systemic toxicity. This presentation broadened my view on how gut-related processes could modulate compound activity which is also important to be considered for metabolism of hydroxyanthraquinones in future.

Second, Dr Annelies Noorlander introduced how to use PBK modelling to support feed and food related hazard and risk assessment. In one case study, she used PBK models to derive chemical-specific adjustment factors (CSAFs) for alkenylbenzenes used in animal feed, accounting for species differences in metabolism. In a second case, she addressed a real- life PFOS contamination incident in sheep, modeling internal exposure levels in tissues to guide regulatory decisions. Her work demonstrated the regulatory applicability and flexibility of PBK models, especially when rapid, non-animal assessments are needed. This was both technically insightful and highly relevant to my own QIVIVE approach.



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Third, Dr Haixia Sui (China National Center for Food Safety Risk Assessment) presented a case study on using the Weight of Evidence (WoE) approach to evaluate safety of Bisphenol A (BPA). By systematically integrating in vivo, in vitro, epidemiological, and in silico data—including NAMs such as QSAR and PBK—she illustrated how WoE provides a transparent and reproducible risk assessment strategy. This approach could help us to make a wise decision even facing conflicting data, emphasizing the importance of frameworks that can incorporate diverse NAM evidence. This is quite relevant to my current position as a regulatory toxicologist.

Overall, these presentations emphasize that integrating mechanistic data, in silico models and evidence synthesis methods is not only scientifically robust but increasingly accepted in regulatory science, which means a promising direction for modern toxicology.

Take home message

Modern toxicology aims to be human-relevant and animal-free. Combining advanced in vitro testing, modeling, and WoE is important to building a reliable and ethical safety assessment system.

Climate neutral efforts

The organizers supported sustainability by offering digital conference materials, which I also preferred and used throughout the conference.

Society of Environmental toxicology and Chemistry (SETAC) Europe 35th annual meeting

Vienna Austria, 11 – 15 May 2025

TRAVELER:
Martien H.F. Graumans
Department of Environmental Science, Radboud Institute for Biological and Environmental Sciences, Radboud University.

My presentation topic

Within scientific SETAC track ‘Ecological and Human Health Risk Assessment of Chemicals, Mixtures and Stressors and Risk Mitigation Strategies’, I had the opportunity to present my PhD- research about the chemical and toxicological evaluation of advanced oxidation treated pharmaceutical residues in wastewater. This presentation focussed on the mitigation of pharmaceuticals from hospital sewage water using plasma technology for the formation of oxidative species. During my talk I demonstrated the effectiveness of on-site oxidative treatment using a laboratory-scale plasma activated water generator. With the application of oxidative chemistry, pharmaceuticals are degraded into transformation products before reaching complete mineralisation. The effectiveness of the advanced oxidation processes (AOPs) on untreated and oxidatively treated aqueous matrices were evaluated using a HeLa cytotoxicity assay and an *in silico* environmental risk assessment model. It has been presented that advanced oxidation processes

Fig. 1: The Austria Center Vienna

Fig. 2: Inside at the venue

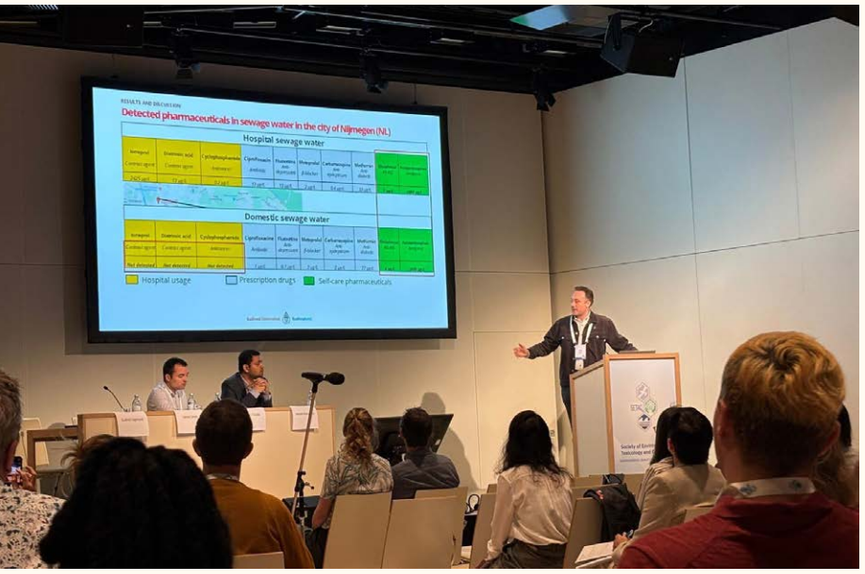

Fig. 3: Presenting my PhD work on Monday 12 May 2025

are very powerful techniques to pre-treat sewage water for the removal of pharmaceuticals and to lowering (eco) toxicity. Based on the laboratory data I explained that there is an opportunity for scale enlargement and deployment of on-site oxidative treatment prior to conventional wastewater treatment.

SETAC Vienna at a glance

The 35th annual SETAC meeting in Vienna offers the possibility to share, learn and discover the latest scientific research within the field of environmental chemistry and toxicology. The scientific programme was entitled “Innovation for Tomorrow: progress in safe and sustainable concepts”. With this theme it was aimed to promote interdisciplinary innovations for safe and sustainable opportunities beyond the development of new substances or products. The theme supported various topics implementing 7 different tracks for parallel sessions to link the multiple disciplines working in the field of environmental toxicology and chemistry. Throughout 5 conference days (11 – 15 May) the participants were inspired, fed with new knowledge and tools to ensure and contribute in a safer and more sustainable future.
With diverse daily keynote speakers we were all stimulated and equipped with a mindset to contribute in safe and sustainable challenges. On Sunday, John Elkington opened the conference with his reflection on possible directions for the chemistry of the future. With relatable examples on polypharmacy or other chemical cocktails pollution he demonstrated that innovative thinking can lead towards solutions for the future. On Monday Katrin Vorkamp demonstrated that scientific results on chemicals in vulnerable ecosystems such as the artic can impact policy. Next to that, careful monitoring of chemicals of emerging concern (CECs) is of great importance and provides knowledge on how climate change influences the persistence and (re)distribution of legacy substances. The Tuesday speaker Marco Baity-Jesi provided an eye-opening talk on how machine learning/Artificial Intelligence can help in the development of SSbD chemicals but also support in *in silico* chemical risk assessment.

On a personal level I was really inspired by the latest research performed in the field of non-target analytical screening. Not particular inspired by a single person, but motivated by the multiple presentations within the track: “Environmental Chemistry and Exposure Assessment: Analysis, Monitoring, Fate and Modelling” presented the possibilities for the characterisation and identification of a high number of different chemicals. New approaches in the field of analytical chemistry, such as (semi-) automisation, bulk sample preparation (e.g. µSPE in 96 well plate format) showed that during one single measurement neutral and acidic compounds could be rapidly analysed or with the use of a hydrophilic interaction liquid chromatography columns (HILIC) both positive and negative ionised molecules are easily separated. Subsequently are computational tools used for the substance characterisation and preliminary hazard assessment.

SETAC take home message

To contribute in chemical safety and anthropogenic pollution mitigation, the multidisciplinary collaboration between experts in the field of environmental chemistry and toxicology is needed to ensure innovation and sustainable progress.

Fig. 4: Group picture with the colleagues from the Environmental Science department, Radboud University

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Sustainability at SETAC Vienna
Sustainability practices were in accordance with the Guideline of the Austrian Ecolabel for Green Meetings and Green Events. The venue was easy accessible with public transport (metro), the catering was full vegetarian and cooked with seasonal available and local food. Delegate material were ecofriendly produced and printed and lanyards were reused for future meetings. In a personal level, I travelled as much I could with public transport towards and from the airport. During the conference meeting I used a 7 day Vienna public transport ticket (Unlimited travel with tram, bus, metro and train).

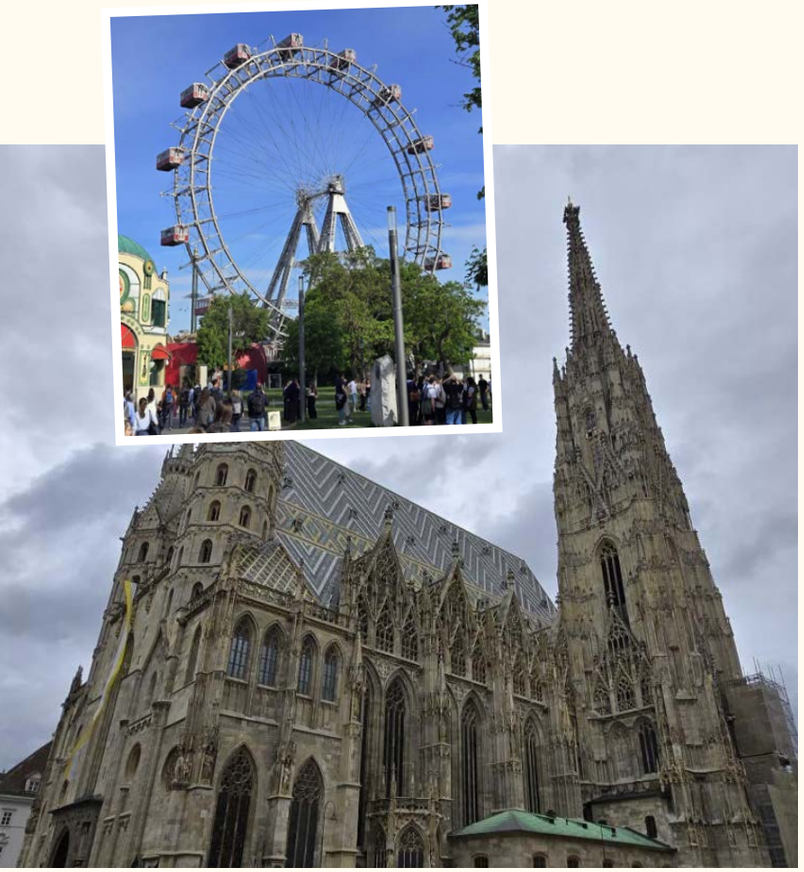

Fig. 5: Quick Vienna sightseeing at the Prater park and the Stephansdom

65th annual meeting of the Society of Birth Defects Research and Prevention

Denver, The United States, June 28–July 2, 2025

TRAVELER:
Danlei Wang, PhD, ERT;
Wageningen University

My presentation was a part of *Opportunities and Applications of NAMs for DART Testing from Hazard to Risk Assessment Symposium.* It was my great honor to be invited by BDRP to present our team research at WUR entitled *PBK Modelling to Link Human Biomonitoring Data for Marker PAHs to Critical Concentrations in a Battery of In Vitro Test Systems Predictive for Prenatal Developmental Toxicity.* Our team research provided a hazard classification approach using an in vitro battery including embryonic stem cell test, zebrafish embryotoxicity test, AhR CALUX assays that adequately predicted in vivo prenatal toxicity of petroleum substances. This allows selection of the worst case for further testing under REACH. Main scientific findings suggested 1) The prenatal developmental toxicity of petroleum substances is mainly associated with 3-7 ring polycyclic aromatic hydrocarbons (PAHs), 2) Developmental toxicity of methylated PAHs depends on the site of methyl substitution, 3) Metabolism of alkyl substituted PAHs depends on the site of substitution, length of alkylation and species. To facilitate human risk assessment,PBK modeling can convert data for marker PAHs in a battery of in vitro test systems to predict prenatal developmental toxicity.

In the symposium session, three other 3 speakers were from ExxonMobil Biomedical Sciences, Inc. , National Institute of Environmental Health Sciences and Merck &Co., Inc. The

presentation dived into the innovative application of New Approach Methodologies (NAMs) in Developmental and Reproductive Toxicology (DART), addressing the growing need for advanced methods to enhance regulatory decision-making and human risk assessment in developmental toxicology. First, the issues, needs, and decision frameworks of regulatory authorities for developmental toxicology were discussed, highlighting opportunities for NAMs to streamline and improve assessments. Insight was provided on recent guidance for validation and application, specifically regarding state-of-the-art tests for DART and how to define the applicability domain. One of the crucial issues is how in vitro test results can be translated to human biology to facilitate more informed, relevant assessments, often requiring advanced computational approaches. New developments in PBPK modeling can support the translation of concentrations that trigger responses in in vitro systems to predicted and measured human exposures. Practical examples for in silico models that allow quantitative in vitro-in vivo extrapolation were presented and discussed, as well as curated high-throughput screening data mapped to mechanistic target groupings and developmental toxicity modes of action. I gained valuable insights into the latest advancements in NAMs and their practical applications in regulatory contexts, fostering novel approaches to DART testing. They all inspired me to develop NAMs and identify the gaps in the regulatory context in the future research.

A presentation titled “BOOST-HP DrugScan: Identifying Medications Associated with Pregnancy Loss Using Data-Mining Techniques” showcased how advanced analytics can uncover potential drug-related risks during pregnancy. A data-mining framework was designed to identify medications potentially associated with pregnancy loss. It uses large healthcare databases to detect statistical signals through methods like TreeScan, which scans for associations without predefining outcomes. These signals are then triaged by experts for biological plausibility and clinical relevance. High-priority findings undergo formal pharmacoepidemiologic evaluation using advanced causal inference techniques. This three-stage process—data scan, expert review, and validation—enables scalable, ethical, and efficient identification of drug safety concerns in pregnancy, especially for medications lacking robust clinical trial data.

BOOST-HP enhances pharmacovigilance by integrating real-world data with expert-driven analysis.

Take home message: Integrating mechanistic science and emerging technologies enhances our ability to predict, prevent, and understand birth defects, advancing maternal-fetal health through interdisciplinary collaboration.

The conference minimized environmental impact through digital materials, sustainable catering, and hybrid access, while participants supported climate goals via eco-travel, reusables, and carbon offsets.

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EVENTS AND ANNOUNCEMENTS

From Lab 2 Law Meeting Summary and NVT Annual Meeting 2026 Announcement!

By *Damian Roelofsen*

The NVT 2025 meeting, themed *“From Lab 2 Law”*, was a great success and we saw a lot of participants from academia, regulatory bodies and industry. There was a lot of interest from a broad audience, from students to experienced toxicologists and related experts. Highlights included two excellent keynote lectures—one on new approach methodologies and their role in advancing risk assessment, and another on chemical stressors and their impact on biodiversity. Engaging sessions on environmental exposure to chemicals, case studies that bridged risk and regulation were given by experts from the field. A series of inspiring workshops on networking, science communication, and the use of computational tools in toxicology provided interesting new insights.

We thank everyone who contributed to making the meeting such as success, and we are looking forward meeting you all at the next year’s NVT meeting, which will take place on **23 and 24 June 2026** (add to your online calender: **NVT Annual Meeting 2026**) **at Congrescentrum Eenhoorn in Amersfoort.**

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TCDD is de nieuwsbrief van de Nederlandse Vereniging voor Toxicologie (NVT).
De Vereniging beoogt de belangen van het vakgebied Toxicologie in de ruimste zin te behartigen; de Vereniging heeft uitdrukkelijk niet de bedoeling de rechts-positionele belangen te behartigen van de individuele leden, tenzij deze belangen direct gerelateerd zijn aan de beoefening van het vakgebied. Gehele of gedeeltelijke overname van de inhoud van TCDD is alleen mogelijk met schriftelijke toestemming van de redactie.

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