TCDD

TOXICOLOGIE

NUMMER 38
DECEMBER 2023

SPECIAL THEME

Baby steps

NEDERLANDSE VERENIGING VOOR TOXICOLOGIE

Colofon

Toxicologische Communicatie, Data en Documentatie

Bestuur
Voorzitter
Paul Jennings, *Vrije Universiteit Amsterdam*
Vice-Voorzitter
Juliette Legler, *Institute for Risk Assessment Sciences (IRAS), Universiteit Utrecht*

Secretaris
Hester Hendriks, *Rijksinstituut voor Volksgezondheid en Milieu*
Yvonne Staal, *Rijksinstituut voor Volksgezondheid en Milieu*
Penningmeester
Laura Hondebrink*, NVIC, UMC Utrecht*

Lid
Hans Bouwmeester, *WUR*
Anne Kienhuis, *Rijksinstituut voor Volksgezondheid en Milieu*
Joanne Salverda, *Nouryon*

Secretariaat
Secretariaat Hester Hendriks,
Rijksinstituut voor Volksgezondheid en Milieu
Postvak 1, Postbus 1, 3720 BA Bilthoven
E-mail: secretaris@toxicologie.nl

Redactie
Héloïse Proquin, *National Institute for Public Health and the Environment (RIVM)* Damiën van Berlo, *National Institute for Public Health and the Environment (RIVM)* Carolien Schophuizen, *Synthon BV*
Marcha Verheijen, *Maastricht University*
Barae Jomaa, *Colonial Chemical*

Webredactie
webmaster@toxicologie.nl

Lidmaatschap en Adreswijzigingen
Ledenadministratie NVT, p/a KNCV
Postadres: Loire 150, 2471 AK, Den Haag
tel. 070 - 337 87 97
Via NVT website na inloggen
http://www.toxicologie.nl
E-mail: administratie@toxicologie.nl

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
(extra kosten EEMS: 10,= euro)

Indien u ervoor kiest zelf uw contributie over te maken, dan worden € 3,- administratiekosten in rekening gebracht.

Sluitingsdata kopij 2023
24 november

Kopijbus
redactie@toxicologie.nl

Website NVT
http://www.toxicologie.nl

Vormgeving
Marleen Mulder
Green Bean Design
www.greenbeandesign.nl

TCDD
TOXICOLOGIE

Inhoud

TERUG NAAR INHOUD

Editorial

As the year comes to a close, it is time for the last edition of the TCDD. However, it is a first for me! I recently joined the editorial team of the TCDD so a short introduction is warranted. As a third year PhD student at the department of Toxicogenomics at Maastricht University, I study transcriptomic changes in the human heart in response to anthracycline exposure in different settings.

In my projects I combine bioinformatics with hands-on wet-lab experiments to better understand what is going on with one of our most important organs once toxicity arises. Whenever I'm not behind my computer or the bench you can find me in my vegetable garden, fixing up my home or walking the dog in the beautiful hilly south of Limburg.

In the concluding issue of this year's TCDD we are taking (baby) steps into the influence of endocrine disruptors on us humans. What is the current stance of REACH on endocrine disruptors and is an update in this field warranted? What about pesticides, biocides and CMRs? Screening of potential endocrine disruptors is a continuous process, what are the European regulations and recent developments in a regulatory context? Toxic chemicals can be found in and around children's toys and in the kitchen, what are regulations, implications and perspectives? Furthermore, we highlight two young scientists working in context of endocrine disruptors.

On behalf of the editorial team, I wish you warm and happy holidays and an interesting read.

Sincerely,

Jelmer

Photo by Jess Bailey on Unsplash

SECTION RISK ASSESSMENT AUTUMN SYMPOSIUM

REACH revision & endocrine disruption: Are we up for the challenge?

10 October 2023 (13.30 – 17.00 h) – NVWA, Utrecht

Welcome and introduction
The meeting had an unexpectedly exciting start with a fire drill at the NVWA building. After everyone was back and seated, the chair welcomed everyone to the symposium and introduced the first speaker.

Assessment of endocrine disruption in a regulatory context and revisions of CLP and REACH legislations by Wieneke Bil (RIVM)
This presentation introduces the history, definition, and current regulatory measures of endocrine-disrupting substances (ED). The current definition includes that the substance causes ED-mediated adverse health effects in an intact organism or its progeny or (sub)populations. Relevant effects include those on reproductive organs and their function. There also has to be a biologically plausible link between this effect and exposure to the substance.

OECD recognizes five levels of information density on ED substances, ranging from low to high-level studies for either human health or the environment. ED features prominently in the EU chemicals strategy for sustainability. The new CLP criteria are based on WHO definition and PPP/BP criteria. They have a Cat 1 and Cat 2 which are quite similar to those for CMRs in that they differ on strength of evidence rather than potency. There are separate criteria for human health and the environment. There is a transition period till November 2026 for existing substances. There is a draft guidance on the ECHA website, the final version is still being worked on.

A REACH update should be coming later this year (Note: latest information: postponed; not this year). In this update, it is anticipated that new NAMs will be included in Annex VII for ED related *in vitro* mechanistic studies. At higher tonnage levels, additional mechanistic *in vivo* studies are foreseen. It is the intention to include ED under the definition of SVHC and extend the generic restriction for CMR substances to ED substances.
A few relevant research projects are mentioned: EURL Ecvam did a large project on validation of *in vitro* methods to detect thyroid disruptors. The PEPPER platform was initiated by France for pre-validation of ED characterization methods. The ORION cluster is now taken up under PARC.

Lessons learned in biocide and pesticide ED assessments – an authority perspective by Suzanne van den Berg and Jessica Broeders (CTGB)
This presentation focusses on ED assessments already performed in the regulation of pesticides and biocides (PPP and BP). Between PPP and BP the ED criteria are the same, but there are few differences in derogations. The criteria for BP and PPP were adopted in 2017 and the guidance in 2018. So far, no CLP evaluation has been needed, but this will change with the update on the CLP regulation and the templates for active substance dossiers will be amended accordingly.

Specifically for biocides, there are not yet that many ED evaluations finalized as for PPP. There are still some old (backlog) dossiers that are not yet finalized, for which a limited ED assessment can be done. Moreover, there are discussions ongoing on e.g. in situ formed substances, how to test highly reactive substances, use of non-guideline studies from public literature, when to accept waivers based on a history of safe use, and how to use information from other legislations. For specific questions, there is an ED Expert Group that can be consulted. Propiconazole is given as an example of an ED substance that was authorized due to the lack of available alternatives for wood preservation. It was noted that there is no agreed methodology to assess ED risks under BPR.

The definition of an active substance under the BPR includes impurities. Therefore, the presence of impurities considered as having ED properties, will trigger the identification of the active substance as an endocrine disruptor. However, impurities

are generally included in the studies with the active substance and then there would be no need to determine whether each impurity may have ED properties. Disinfection By-Products are not part of the active substance but have to be part of the risk assessment. Some substances can have an impurity and/or a DBP, thus, how to deal with the ED assessment should be determined on a case-by-case basis. ED assessment is also required for co-formulants when biocidal products are concerned.

PPP focuses mainly on the active substances, where experience has been gained over the last years. The first expert meeting for ED was in January 2019. ED assessments were conducted by EFSA during the transition period, afterwards by the Member States. Member States use the same levels as given by OECD; most dossiers needed additional information to complete the dataset according to the EFSA/ECHA ED guidance.

Examples: an ED substance for the Thyroid-modality (name not given). It was positive in Derek Nexus, and there were *in vitro* and *in vivo* adverse effect studies in rats and dogs, but not *in vivo* mechanistic studies. As there were adverse effects and a plausible link it was considered ED. A second example is a substance with EAS (Estrogen Androgen Steroid)-modality. Adverse effects were seen in the testis and epididymis. There was an increase in serum LH and FSH levels in the rats amongst others.

Within the field of PPP, in some cases the ED assessment can be waived. This is mainly done for natural substances that have a high background exposure and for which no adversity is known. It is uncertain whether this will be possible when PPP has to be classified for ED under the CLP Regulation.

For both BP and PPP, the regulations will have to be updated to differentiate between Cat 1 and 2.

Stakeholder perspective: Chemicals industry by Nina Hallmark (BAYER on behalf of CEFIC)

The scope of the presentation is the broad chemicals industry, with a focus on REACH. CEFIC is the European Chemical Industry Council, representing the chemicals industry, excluding pharmaceuticals. One of their key principles is that chemicals should be safe as proven by risk assessments. The attention for ED has been ongoing for decades, resulting in the new criteria today. The question is raised whether the 2018 criteria are applicable to all legislations. CEFIC started in 1996 the Long-range Research Initiative (LRI) to advance scientific assessment of chemical safety. They also contribute to regulatory guidance development. The scientific assessment can be well harmonized, even though the consequences may differ between legislations. This requires overarching criteria.

Many elements from the PPP requirements are also relevant for the new criteria. For applicants there is a large Excel form that should contain all available data, which is very time-consuming, but also comprehensive and helpful. All information is pulled together, and a conclusion is drawn. This tool may also be useful for other legislation. However, data gaps are an issue, in particular on ecotox aquatic species and mechanistic information. The ECHA EFSA ED assessment has a streamlined assessment process. If there is a data gap, the clock is stopped for 30 months to generate this data.

REACH is different from pesticides as you do not perform all studies for all substances. An important change is the inclusion of mechanistic information rather than only on adversity, as the current information requirements are insufficient in most cases to fulfill the criteria. When gathering data, don't forget to include also non-standard studies, including publications. The most important consideration is which data are needed to fulfill the criteria, but also solubility, applicability domain of NAMs, non-EATS substances are relevant for the assessment.

Practical considerations: lab capacity is at a peak already. There is a shortage of qualified personnel. There is a need for a tiered prioritization approach, putting animal testing as a last resort. Harmonization of the criteria and guidance is very important to gain consistent evaluations.

For industry a big question is prioritization; there are too many substances to evaluate all at the same time. Tonnage may be used as surrogate of exposure, in line with the work in US. NAMs may be used to predict adversity.

On CLP industry has some concerns, in particular the communication of Cat 1 and 2 and what they mean. The challenge for industry is to move more to safe and sustainable chemicals through innovation.

In conclusion ED identification is not new and is possible, the REACH challenge is data sufficiency. There is already a clear tiered approach that can be followed to reach a conclusion. As there is an unprecedented quantity of new safety data generation, reporting, assessment, and decision making needed, we need to work together as stakeholders to best achieve this protection goal.

We are looking for a new board member who wants to contribute to the exciting field of toxicological risk evaluation. If you are interested to join the board of the NVT section Risk Assessment we invite you to contact Anette Wilschut (Annette.Wilschut@dsm-firmenich.com) before February 1st, 2024.

CMR Substances found in Childcare Articles. So what?

By *Carolien Schophuizen*

Recently a news article was published on the ECHA website titled “ECHA’s investigation finds toxic chemicals present in childcare products.” The short article informs the public about the findings of an investigation report that revealed the presence of substances causing cancer, genetic mutations, or harm to reproduction in everyday items like car seats, bibs, and baby changing mats. Naturally, various media outlets picked up the story, as it directly alarms concerned parents, grandparents, and caretakers. However, it prompts the question: how concerned should we actually be?

While the actual investigation report explicitly outlines assumptions and uncertainties, offering clarity on the basis for risk assessments, these nuances don’t seem to be effectively communicated in the news article. The release by ECHA might raise concerns, especially among parents, due to sentences like “presence of substances causing cancer and genetic mutations or harming reproduction,” which imply a direct link between detected hazardous substances in childcare items and potential adverse effects in infants, including childhood cancer.

Children are considered more vulnerable to chemical hazards than adults, owing to physiological differences and unique behaviors. Therefore, using risk assessment methodologies tailored for children is crucial to comprehensively address potential risks. However, it’s important to note that merely detecting a hazardous substance in a childcare product doesn’t automatically imply an associated risk. In today’s context, advanced detection technologies can identify chemicals at remarkably low levels. While some level of exposure may be deemed acceptable, the absence of a quantitative exposure assessment makes it challenging to accurately estimate the risk associated with hazardous substances. Therefore, determining which levels of exposure can be considered acceptable becomes crucial.

In the case of ECHA’s report, it was written to support the European Commission in preparing for a potential future restriction. The document emphasizes that the likelihood of exposure is not quantitatively presented but rather in terms of available evidence indicating potential exposure under normal conditions. This includes both the release and emission of substances from childcare articles and subsequent uptake by children through oral, dermal, or inhalation routes. Factors like high vapor pressure and the leaching of non-covalently bound substances contribute to the risk but also add complexity, making precise risk estimation challenging. The lack of a quantitative assessment and reliance on available evidence suggests a major uncertainty in actual exposure levels.

While catchy, the news item published on the ECHA website lacked the nuance provided in the report, potentially amplifying concerns without offering a clear understanding of the toxicological aspects involved. To me, this highlights the importance of maintaining a balanced perspective in any news article aimed at the general public, avoiding sensationalism, and providing nuanced information, especially when it concerns childcare product safety.

Identification of Endocrine Disruptors in a Regulatory Context

An Overview of EU Regulations and Recent Developments

This article has been reviewed by Wieneke Bil, Toxicologist and Risk Assessor at the National Institute for Public Health and the Environment (RIVM), and is based on the overview of policy on endocrine disruptors originally written in Dutch by the RIVM

Substances that interfere with the hormone system, known as endocrine disruptors (EDs), pose a potential threat to human health and the environment. Policy within the European Union (EU) aims to prevent or minimize exposure to these substances, recognizing their adverse effects. A 'fitness check' conducted by the European Commission in 2020 revealed gaps related to EDs in legislative frameworks, notably in the Cosmetics Regulation, the Food Contact Materials Regulation, the Toys Directive, and the Medical Devices Regulation.

EU LEGAL FRAMEWORKS AND CRITERIA

REACH Legislation

Under the REACH Regulation (EC) 1907/2006, Article 57 outlines criteria for substances classified as Substances of Very High Concern (SVHCs). Endocrine disrupting substances fall under Article 57 f), enabling their identification as substances having an equal level of concern as those that are Persistent, Bioaccumulative and Toxic (PBT) and Carcinogenic, Mutagenic, and Reprotoxic (CMR) substances. Identification of EDs under the REACH Regulation is based on the definition of EDs specified by the World Health Organization.

Screening and Evaluation Processes under REACH

Member states and the European Chemicals Agency (ECHA) screen REACH-registered substances for endocrine-disrupting properties, placing relevant substances on the CORAP list for evaluation. The ECHA's expert group on endocrine disruptors then assesses substances for their (potential) endocrine disruptive properties. The chemicals that have been discussed by this group are on the "Endocrine disruptor assessment" list. Subsequently, the REACH Member State committee determines whether a substance qualifies as an endocrine disruptor, impacting its usage when included on the SVHC list.

Plant Protection Products and Biocidal Products

Since 2018, scientific criteria have been in place that govern the assessment of endocrine disrupting properties of active substances in plant protection products and biocidal products. Member states assess these substances following published guidance, with ECHA's Endocrine Disruptors Expert Group providing advice for biocides, and EFSA's Endocrine Disruptors Expert Group providing advice for PPPs. If deemed an endocrine disruptor under these regulations, these chemicals face exclusion from the European market (in principle).

Pharmaceuticals and Cosmetics

The effects pharmaceuticals have on the environment, including endocrine disruption, are evaluated in the approval of veterinary or human medicinal products. Unlike veterinary medicines, an environmental assessment with a negative outcome does not affect the approval of https://rvs.rivm.nl/onderwerpen/stoffen-en-producten/Geneesmiddelen human pharmaceuticals. It can, however, lead to risk-mitigative measures to be taken to minimize the adverse effects to the environment.

In 2018, the European Commission adopted a review on the Cosmetics Regulation, in which was noted this regulation does not have explicit provisions on endocrine disruptors. In the review, the European Commission established a priority list of 28 potential EDs in cosmetics not already covered by bans or restrictions in the Cosmetics Regulation. The Scientific Committee on Consumer Safety (SCCS) was specifically asked to evaluate the risks of the use of these chemicals in cosmetic products with regard to their potential endocrine disruptive effects.

Legislation in the Netherlands

The Netherlands enforces stringent requirements for SVHC-listed substances with endocrine disrupting properties, integrating them into the ZZS list. Substances on the "Endocrine disruptor

assessment" list of ECHA are included on the list of potential ZZS and in this way receive specific attention in the process of granting permits for the emission of chemicals.

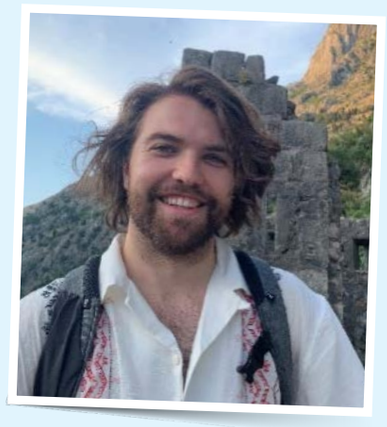
Recent EU Developments

The European Commission's Chemicals Strategy for Sustainability aims to minimise overall exposure of humans and the environment to endocrine disruptors, strengthening information requirements across legislation (including that of REACH, cosmetics, and food contact materials), as well as accelerating the development and uptake of methods to generate information on endocrine disruptors though screening and testing of substances. One of the recent successes of the European Commission is the introduction of new hazard classes for endocrine disruptors in CLP. Introduction of these new hazard classes allows for identification of chemicals as known or presumed endocrine disruptors (category 1) or suspected endocrine disruptors (category 2) for human health and the environment. The CLP revision ensures horizontal legislation on EDs, increases protection of human health and the environment to chemicals with these hazardous properties, and strengthens communication of hazards of chemicals among manufacturers, importers and downstream users.

Towards a virtual embryo

Computational modeling of neural tube closure defects

We all share a universal dream: that every newborn arrives in this world healthy and thriving. However, this dream often clashes with reality. With birth defects affecting an estimated 3% of infants globally each year, the prevalence of these conditions is alarmingly high. These defects can be caused by exposure to harmful chemicals. In our rapidly evolving world, with hundreds of new chemicals introduced annually, ensuring their safety is more crucial than ever. Hence, we extensively test these chemicals in pregnant animals.



By *Job Berkhout;*
Revisions *Aldert Piersma*

But there's a hitch in our current approach. The methods we use, though well-intentioned, are fraught with ethical concerns, high costs, and time-consuming processes. More importantly, they often fall short in predicting human health outcomes, raising a fundamental question: Isn't there a better way?

In response, we propose a paradigm shift, turning our focus to human biology, physiology, and toxicology. Our approach is demonstrated through a single case study: the neural tube closure. This process, an essential step in the development of the brain and spinal cord, is highly susceptible to chemical interference. Any misstep in this intricate closure can lead to severe birth defects, underscoring its importance in chemical safety assessment.

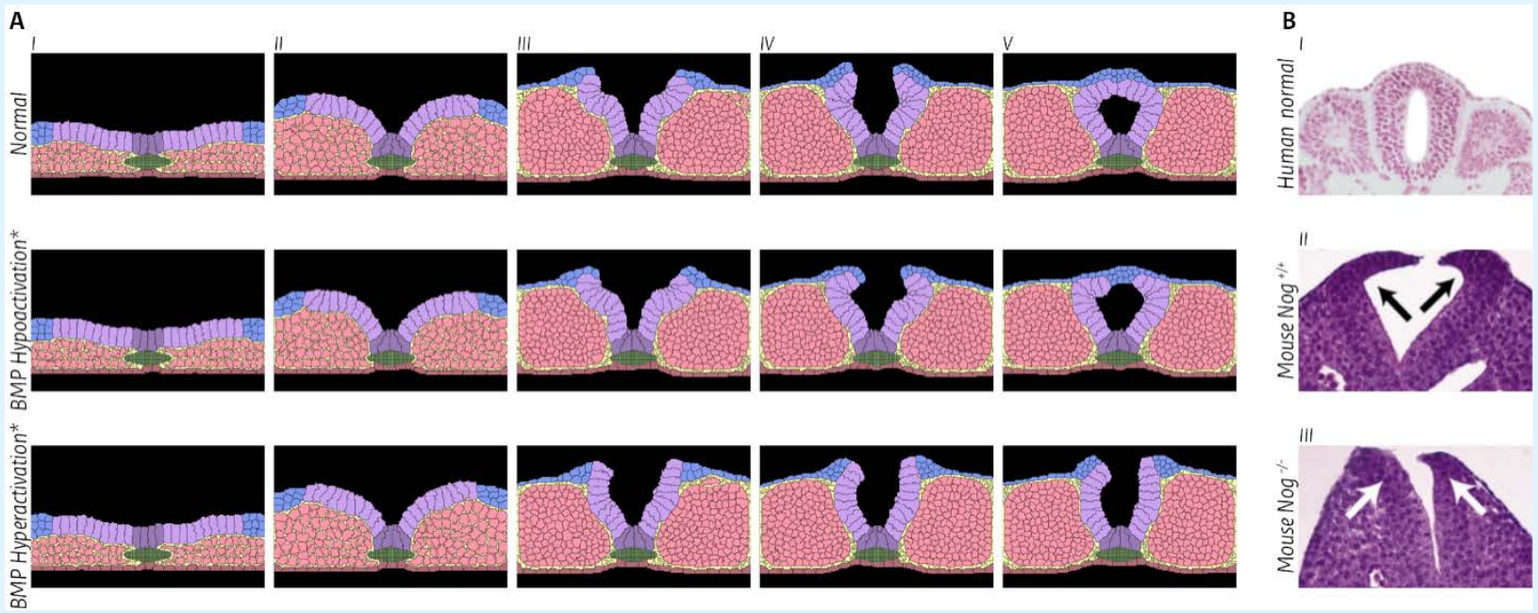
To deepen our understanding, we developed a physiological map of human neural tube closure, detailed in Heusinkveld et al. (2021). This map revolves around the crucial all-trans-retinoic acid (ATRA)-related molecular pathways and their potential disruption during neural tube closure. Building upon this foundation, we developed a computational multicellular agent-based model (ABM). ABM is a computational method in which individual entities, or agents – in this case cells – are simulated to mimic and study complex behaviors. This approach can be used to predict whether chemicals impact the development of the neural tube in a probabilistic manner, which offers insights into the neural tube closure and chemical disruption of this process. ▶

Our ABM is a powerful tool that aligns with known biological patterns. It has the capability to simulate a range of 'what-if' scenarios. For example, we want to understand the impact of a chemical on neural tube closure. We start by assessing this chemical in dedicated cell culture systems, observing changes in gene expression. These changes in gene expression are then replicated as adjusted parameters in our model. This step enables us to directly observe how the chemical might affect neural tube closure. Essentially, this method translates molecular-level effects, measured in *in vitro* studies, into understandable predictions about their impact on neural tube closure.

Additionally, this approach offers mechanistic insights that are often obscured in animal models. In animal studies, we know the input (the chemical exposure) and the output (the presence or absence of a defect), but the intricate interplay of biological processes in between remains unclear. Our ABM helps clarify these processes, providing a clearer understanding of how chemicals might disrupt development at a cellular and molecular level. This is crucial, as it bridges the gap between a molecular alteration and a developmental outcome, something that animal models, due to their black box nature, often struggle to do.

Agent-based modeling opens the door to understanding complex biological processes like neural tube closure and shows the potential to improve chemical safety assessment. Applying this approach in a toxicological context marks a significant stride towards reducing reliance on animal testing, aligning more closely with ethical standards and human health outcomes.

Looking ahead, our model is just the beginning of a journey toward a more ethical and effective approach to chemical safety assessment. Future improvements to the model will focus on enhancing its accuracy and allowing it to predict the effect of chemical exposure on biological processes. With this model, we aim to make another step towards a future in which chemical safety assessments are not only more ethical but also more aligned with human biological responses, paving the way for safer chemicals and healthier lives.



Computational model of neural tube closure built in CompuCell3D, modeling three different scenario's. Top; neural tube closure (NTC) without perturbation, Middle; NTC with a reduction in the morphoregulatory signal BMP, Bottom; NTC with an increase in the morphoregulatory signal BMP. Asterisk indicates a NTC defect. The NTC starts with a flat ectoderm (I) in which the notochord (green) will trigger formation of the median hinge point (MHP) (dark purple) (II), causing the first invagination of the neuroectoderm (light purple). The paraxial mesoderm (light red) will proliferate, further increasing the invagination, and form compact cell structures known as somites (III). Then the bending of the tube will occur following formation of the dorsolateral hinge points (DLHP) (IV). Subsequently, the neuroectoderm and the surface ectoderm (blue) will fuse, closing the neural tube (V). The neural crest cells will detach and move away. (B) Transverse sections of neural tube closure. (I) Human carnie stage 11, 11th somite [Cork and Grazzer, 2012]. (II) Mouse E9.5, Nog +/+ , stained with H&E. The black arrows indicate exaggerated formation of dorsolateral hingepoints (DLHPs) at the top of the tube [Ybot-Gonzales, 2007]. (III) Mouse E9.5, Nog -/- , stained with H&E [Ybot-Gonzales, 2007]. The white arrows indicate lack of DLHPs formation.

Toxic Toys

The New York Toxic Chemicals in Children's Products (TCCP) rule: Necessity, Scope, and Limitations

By *Barae Jomaa*

The New York Toxic Chemicals in Children's Products (TCCP) law, established under the Environmental Conservation Law (ECL), is aimed at safeguarding the well-being of children. Addressing the presence of toxic chemicals in consumer products intended for children aged twelve and under, including cosmetics and toys, the law mandates the disclosure of specific chemicals while prohibiting others[1].

A vulnerable group: Object-to-mouth behavior has the potential to expose children orally to chemicals found in toys. *Image courtesy of Jolenepienaar. Creative Commons Attribution 4.0 International license.*

The law's inception stems from concern over the detection of harmful substances, such as lead, cadmium, cobalt, arsenic and antimony, being detected in children's toys and products[2,3]. Children are more vulnerable to toxic chemicals than adults due to various reasons including their higher surface area to volume, higher inhalation rate per unit of body weight, and higher ingestion of food and water per unit of body weight[4]. Moreover, frequent object-to-mouth, hand-to-surface and hand-to-mouth behavior that is typical of children means that chemicals found in toys can enter the body with greater ease. To make things worse, given that children are in a key phase of growth and development, exposure to harmful substances can have unique and lasting implications.

Despite historical incidents, regulatory gaps have persisted. The lack of stringent guidelines and comprehensive enforcement mechanisms created a public perception that manufacturers weren't being held accountable for the presence of harmful chemicals in children's products. The TCCP law aims to bridge these gaps by establishing clear guidelines for chemical reporting, defining prohibited substances, and instituting reporting thresholds.

Considering that only benzene, asbestos, and tris(1,3-dichloro-2-propyl) phosphate are banned from being intentionally added to children's products, the law is mostly based on the so-called right-to-know principle. This type of approach is meant to encourage manufacturers to try to eliminate chemicals of concern so that they alleviate themselves from the burden of reporting and avoid any associated reputational damage.

The TCCP law categorizes chemicals into Chemicals of Concern (COC) and High Priority Chemicals (HPC). COCs encompass substances identified by government entities or credible scientific evidence as carcinogens, reproductive or developmental toxicants, neurotoxicants, asthmagens, endocrine

disruptors, or those exhibiting persistence and bioaccumulation. HPCs are COCs that are present in children's products and have been found in 1) humans 2) household dust, indoor air, drinking water or elsewhere in the home environment 3) fish, wildlife or the natural environment; or 4) the sale or use of the chemical or a children's product containing the chemical has been banded in another state.

The law mandates the Department of Environmental Conservation (DEC) to identify COCs based on widely recognized, authoritative, and scientifically credible lists of toxic chemicals. DEC considers lists from various entities, including the World Health Organization, U.S. Environmental Protection Agency, and the European Chemicals Agency. The DEC also reviews lists from other states' children's product programs. There are currently 600 chemicals or groups of chemicals that are deemed to be of concern.

During the third virtual public meeting on TCCP, Alan Kaufman, a children's products industry veteran with experience in product safety and regulatory compliance, criticized the broad net cast by the authorities for selecting the chemicals of concern. Reflecting some of the concerns of his peers, he stated that "the criteria that are used for identifying the chemicals are overly inclusive. Some of the sources are questionable, like IARC and (California) Prop. 65."

The TCCP law imposes reporting obligations on manufacturers, importers, or first domestic distributors of children's products containing COCs or HPCs. These entities must disclose the presence of these chemicals at or above practical quantification limits (PQLs).

The determination of PQLs is a crucial aspect of the reporting process. The law outlines the lowest level that can be reliably achieved within specified limits of precision and accuracy during routine laboratory operating conditions. DEC uses a comprehensive approach to establish PQLs, drawing from other state children's product programs, Restricted Substances Lists (RSLs) by corporations, commercial laboratory product test reports, and scientific studies.

As the TCCP program is an ongoing effort, some of the chemicals of concern are still without a PQL. The establishment of reporting thresholds poses challenges for both regulators and industry stakeholders. The ability of the industry to comply will be impacted by the clarity and reasonableness of reporting thresholds. For example, some PQLs were read-across from similar substances which is a practical approach that may have limitations once theory is put to practice. Measuring substances in certain matrices (e.g. plastic) can also be challenging.

Moreover, difficulty in distinguishing between different complex substances (e.g. quaternary ammonium compounds differing only in alkyl chain lengths) and/or isomers has already been highlighted as a hurdle that needs to be overcome.

Besides the three substances banned when intentionally added, there is no distinction between intentionally added chemicals, byproducts or contaminants. Washington, Oregon and Vermont have similar laws in place but provide higher reporting thresholds of 100ppm for contaminants. Part of the reasoning is that 1,4 dioxane, a byproduct of ethoxylated ingredients, will be restricted to 1ppm in household cleaning and personal care products sold in New York by the end of 2023. This means that setting 100ppm for contaminants would not align well with the restriction on 1,4 dioxane. As there may be other similar situations, the regulator finds it more appropriate not to have a distinction between the requirements for intentionally added chemicals and those that may be present as contaminants.

Kaufman underlined the "tremendous cost of testing for 600+ substances" and suspects that "a lot of manufacturers will simply report something that probably isn't there," adding that "it's going to be a critical error here, not to put that contaminant reporting limit in place. I think what's going to happen is you're going to get a number of people simply reporting all 600 substances and I don't know that the department is ready for that. I also don't think that's going to be useful either to the department, or to the consumer."

Also taking part in the third virtual public meeting on TCCP, Timothy Sullivan, children's products industry veteran with experience in product safety and regulatory compliance, expressed his concern with the PQLs for PFAS. He stated that emerging regulations around the world that relate to PFAS "are coming up as intentionally added" and this is an important distinction as it relates to the low thresholds for PFAS that the EPA is looking at (e.g. in wastewater) because it's in parts per

trillion. “It’s easy for our industry to trace back and restrict intentionally added substances at the thresholds that might be hazardous to children’s health. It is nearly impossible to be able to prove that all of these 600 chemicals are not unintentionally present in our products. To be able to prove it, we have to test all of them at these low levels,” he said. The cost for the industry is clearly very significant. Another issue raised by Sullivan is that for PFAS, companies may be regulated below ambient levels in air and water.

While industry might lament the billions of dollars in added cost for complying with regulations aimed at consumer safety, the regulators will point to the billions of dollars that may be saved in health costs[5]. Ultimately the question should be whether a law based on disclosure provides information that may be useful to the consumer and the regulators. Detractors will point to the lack of exposure information and hence the lack of clarity as to whether or not a chemical of concern may present a risk to the consumer. What is the amount of the chemical of concern that is leaching out of a plastic toy? Is a volatile substance still present by the time it reaches the consumer? Proponents of such right-to-know measures will emphasize the importance of transparency. What could we potentially be exposed to without our knowledge? At the moment these are questions that remain unanswered. Ultimately, the continued open dialogue between the various stakeholders will ensure that the end goal of protecting consumer health can be achieved successfully and without undue burdens to the industry.

References:

1. Toxic Chemicals In Children’s Products - NYDEC. https://www.dec.ny.gov/environmental-protection/help-for-businesses/toxic-chemicals-in-childrens-products.
2. Motavvef, A. Toxic Chemicals Found in NYC Toys and Children’s Products. *WE ACT for Environmental Justice* https://www.weact.org/2015/12/toxic-chemicals-found-in-nyc-toys-and-childrens-products/ (2015).
3. Becker, M., Edwards, S. & Massey, R. I. Toxic Chemicals in Toys and Children’s Products: Limitations of Current Responses and Recommendations for Government and Industry. *Environ. Sci. Technol.* **44**, 7986–7991 (2010).
4. US EPA NATIONAL CENTER FOR ENVIRONMENTAL ASSESSMENT, W. D. Child-Specific Exposure Factors Handbook (2008, Final Report). https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=199243.
5. Trasande, L. *et al.* Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union. *J. Clin. Endocrinol. Metab.* **100**, 1245–1255 (2015).

Advancing *In Vitro* Endocrine Disruption Testing: Insights from the SCREENED Project

Unraveling the Impact of Environmental Chemicals on Thyroid Function through Innovative *In Vitro* Models and Omics Technologies

By *Marta Nazzari*

Endocrine disrupting chemicals (EDCs) are a big group of manmade compounds that pollute the environment. They interfere with the normal functioning of the endocrine system, including the thyroid, and constitute an important environmental concern. They are found in many everyday products, and daily exposure of the general population occurs via the diet, air, skin, and water. My PhD project is funded by SCREENED, a European cluster of eight projects aimed at developing new test and screening methods to identify EDCs. In particular, SCREENED focused on the thyroid, an essential endocrine organ understudied within the field of toxicology.

The tests currently approved by the OECD (Organisation for Economic Co-operation and Development) to identify EDCs with a thyroid-disrupting activity are only *in vivo*. These tests determine whether compounds are toxic for the thyroid by detecting alteration in the serum levels of thyroid hormone (TH), produced by the thyroid, and used as an indicator of thyroid dysfunction. However, there is no way of knowing if these compounds are toxic in other ways for the thyroid that do not cause alterations of the TH production. Additionally, a recent retrospective review of 124 reproductive screening studies on mice performed using some of the OECD-approved tests that also measure TH levels have concluded that including TH measurements does not provide specific information needed to assess endocrine disruption, as TH alterations are recorded but conclusions on the underlying causes cannot be drawn. Instead of adding additional endpoints to the *in vivo* studies, the authors recommend investing on the development and validation of *in vitro* assays, as they can be more functional in elucidating the mode of action in humans.

SCREENED aimed at answering the following questions: can we develop 3 dimensional *in vitro* models of thyroid for studying the effects of EDCs? And are these compounds having a deleterious effect directly on the thyroid?

To this end, our partners at the Université Libre De Bruxelles in Belgium developed a protocol for differentiating thyroid organoids from human and mouse embryonic stem cells which we used for our experiments together with thyroid cell lines. We focused on four EDCs classes named organophosphate flame retardants (OPFRs), phthalates, polycyclic aromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs) and performed several screenings during the project using a biologically relevant dose range, testing the difference between static and organ-on-a-chip culture conditions, as well as evaluating the response over a short- or long-term exposure. We used several omics technologies (bulk and single cell RNA-Seq, ATAC-Seq and liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS)) to study how EDCs can affect the transcriptome, proteome and epigenetic status of cells.

To provide some examples, we observed that our *in vitro* thyroid model can respond to aryl hydrocarbon receptor (AHR) agonists such as PAHs or some PCBs. This response includes the induction of the CYP450 genes *CYP1A1* and *CYP1B1*, a phenomenon to our knowledge to date only described in a handful of thyroid cancer cell lines. We also observed that phthalates can induce fatty acid metabolism and downregulate signal transduction of known signaling proteins like GTPases, tyrosine kinases and TGFB family members and extracellular matrix organization. Combining gene, miRNA and protein expression data, we built a machine learning classification model that could help us identify if an unknown sample was exposed to one of the EDCs classes we studied.
To summarize, we showcased how omics technologies can be used in toxicology experiments to elucidate the cell response to toxic chemicals and provided hypotheses to be further tested with targeted experiments. SCREENED started developing a model and tested it, laying the basis to eventually lead to the use of *in vitro* models for endocrine disruption testing.

PFAS in food and food contact materials

Per- and polyfluoroalkyl substances (PFAS) are a group of human-made chemicals widely used in various industrial and consumer products due to their unique properties, such as water and grease repellence. These chemicals have gained attention due to their persistence in the environment and adverse effects on human health. The special theme of TCDD (2023 – nr 2) was on PFAS. While reading this issue with great interest, we noticed that there was little attention for the occurrence of PFAS in food, feed and food contact materials (FCM) and the related risks for human health. PFAS may enter the food chain via various routes, for example when vegetables are grown on contaminated soil. PFAS can also transfer from feed to products of animal origin such as meat, milk and eggs. In the contribution below we substantiate this topic from our perspective.

By Jacqueline Steenbergen – Biesterbos, Michiel den Braver and Krista Bouma

Office for Risk Assessment & Research (BuRO), Netherlands Food and Consumer Product Safety Authority (NVWA)

PFAS can transfer from feed to products of animal origin such as meat, milk and eggs.

Health based guidance value

In 2020 the European Food Safety Authority (EFSA) published a scientific opinion regarding PFAS in food (EFSA CONTAM Panel, 2020). In this opinion a tolerable weekly intake (TWI) of 4.4 ng/kg body weight per week was derived, based on a sum of four PFAS, also referred to as the EFSA-4 (PFOA (perfluorooctanoic acid), PFNA (perfluorononanoic acid), PFHxS (perfluorohexane sulfonic acid) and PFOS (perfluorooctane sulfonate)). Health risks cannot be excluded if exposure exceeds this value.

EFSA concluded that negative effects on the immune system are the most sensitive toxicological endpoint. These findings were considered robust since immune effects were consistently observed for PFOA and PFOS in rodents and in humans (EFSA CONTAM Panel, 2020). In humans a decreased immune response upon vaccination of children was linked to EFSA-4 serum levels. Immune effects are also observed for several other PFAS. The TWI consists of the sum of the EFSA-4 because these substances were detected in most blood samples of the children included in the key studies (EFSA CONTAM Panel, 2020). In humans, the EFSA-4 share toxicokinetic properties and show similar accumulation and long half-lives. Also, for other toxicological effects observed in laboratory animals these compounds share similarity, such as effects on the liver and serum thyroid hormone levels. EFSA concluded that the available data do not allow the derivation of potency factors of the individual congeners for the critical effect. As a pragmatic approach, EFSA assumed equal potencies for effects of these four PFAS on the immune system (EFSA CONTAM Panel, 2020).

Application of the health-based guidance value in risk assessment

Since the TWI is based on the sum of four PFAS, some questions are raised by the application of this value in risk assessment. The EFSA-4 are not the only PFAS which are present in food, drinking water and soil. PFAS consist of many congeners that occur in various combinations and, as such may exhibit mixture toxicity. EFSA indicates that other PFAS are likely to cause similar effects to the immune system, however the EFSA TWI can only be applied to this limited selection of four PFAS. In addition, in cases where only the level of one PFAS is analyzed, application of the TWI to this single PFAS may underestimate the total risk of all present,

but not detected PFAS. There are currently two possibilities for the application of the EFSA TWI in risk assessment.

Equipotency

As explained, the EFSA TWI can only be used in a risk assessment dealing with one or more of the EFSA-4 and assumes equipotency of these four PFAS congeners. According to EFSA, this is currently the most accurate method for PFAS risk assessment due to limited data on immunotoxicity for most PFAS. If concentrations of other PFAS are known (for example GenX) the EFSA TWI cannot be applied for risk assessment. Consequently, other PFAS have to be assessed according to substance-specific health-based guidance values, which are not available for most PFAS. In addition, substance specific health-based guidance values are (in absence of information on the immune effects) based on effects that occur at much higher doses, which may result in an underestimation of the actual risk. For this it is assumed that all other PFAS have an immunotoxic effect and that this effect occurs at lower concentration than other toxic effects.

An unexplored alternative could be the use of Toxic Units, i.e. using the sum of the ratio exposure / health based guidance value of the individual PFAS for risk assessment. Since a congener-specific health-based guidance value is lacking for most PFAS, the applicability of this method will be limited.

Relative potency factors

RIVM addresses the question on how the EFSA TWI should be used in risk assessment (RIVM, 2021a) and how to deal with PFAS other than the EFSA-4. RIVM proposes to use relative potency factors (RPFs) derived from a different toxicological endpoint (Bil et al., 2022; Bil et al., 2023). The RPFs which are currently derived by RIVM present the toxic potency of the individual PFAS against the index substance PFOA. By means of RPFs it is possible to incorporate other PFAS than the EFSA-4 in a risk assessment.

RPFs are currently available for 23 PFAS, including GenX, and are extrapolated from the potency of the individual PFAS to exert hepatotoxicity (Bil et al., 2021). For example, according to this method the RPF for GenX is 0.06, meaning that this substance is 17 times less toxic than PFOA (RIVM, 2021b). The sum of the weighed concentrations of PFAS is expressed as a PFOA-Equivalent (PEQ). For example, a milk sample contains a combination of three PFAS (A, B and C). PFAS A is PFOA and has a RPF of 1, which is multiplied by the concentration of A that is present. PFAS congeners B and C have a RPF of 0.1 (B) and 0.01 (C) (both less potent than PFOA), respectively, which are multiplied by the concentration of B and C that is present. The weighed levels of A, B and C are then summed and expressed in PEQ units to allow evaluation of the toxicity as if it contains solely PFOA and subsequently compared to the health-based guidance value (i.e. EFSA TWI).

Since at present there is no scientific consensus on the best approach to calculate PFAS concentrations, BuRO uses both methods simultaneously when calculating the exposure in a risk assessment.

Legislation

In European legislation, policy-based implementation of chemical food safety is based on the principle that food shall not be placed on the market if it is unsafe. Policy enforcement therefore relies on legal limits that define the maximum permissible levels of substances in food. For this purpose, product standards have been established at the European level, i.e. the MRL (Maximum Residue Limit) and ML (Maximum Limit). MRL relates to substances that can be found as residues in food, such as plant protection products. A MRL is based on good agricultural practices and the fact that exposure to residues does not exceed health-based guidance values. An ML relates to substances that can be unintentionally introduced into food, such as environmental contaminants and are set based on the ALARA (As Low As Reasonably Achievable) principle. For additives (E numbers), the product standard is defined in terms of maximum use levels. All three are legal limits that have been established for a specific substance-food combination. The Specific Migration Limit (SML) is the maximum permitted amount of a given substance released from a material or article into food or food simulants. This is expressed in mg of substance per kg of food. Exceedance of a legal limit does not necessarily imply that there is an acute health risk.

As the risk assessment by EFSA showed that PFAS exposure of the consumers exceeds the health-based guidance value, MLs for PFAS were established by the European Commission. In this way, food business operators are forced to ensure that their products contain as little contaminants as possible. Regulation (EU) 2023/915[1] describes MLs for four individual PFAS (PFOS, PFOA, PFNA and PFHxS) and the sum of these four, present in meat and edible offal, fishery products and bivalve mollusks and eggs. The European Commission also issued a recommendation[2] on the monitoring of perfluoroalkyl substances in food. In time this monitoring will provide new data that can be used for future establishment of additional MLs for PFAS.

Food contact materials (FCM) are regulated by material category. Only starting substances and additives included in the list of authorized substances may be used for the manufacture of the food contact materials. Often a restriction is set for authorized substances, such as a Specific Migration Limit (SML). An overview of all the authorized PFAS for food contact materials can be found in a RIVM report (Bokkers et al., 2018). Some material categories are regulated at the European level and others at the national level. There is a specific regulation for plastic food contact materials, i.e. Regulation (EC) No 10/2011[3]. At the national level, material categories are regulated in Appendix A of the

1 Commission Regulation (EU) 2023/915 on maximum levels for certain contaminants in food and repealing Regulation (EC) No 1881/2006.

2 Commission Recommendation (EU) 2022/1431 on the monitoring of perfluoroalkyl substances in food.

3 Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food.

Commodities Act Regulation on Food Contact Materials[4]: Chapter II - Paper and paperboard, Chapter III - Rubber and rubber products and Chapter X - Coatings.

For paper and paperboard FCM only a polymeric PFAS is authorized as starting substance, namely diphosphoric acid, polymers with ethoxylated reduced methyl esters of reduced polymerized and oxidized tetrafluoroethylene. PFAS can be present as NIAS (non-intentionally added substance), as recycled paper and paperboard may be used as raw material for producing paper and paperboard intended for food contact. This may be a source of unintentionally added PFAS due to possible contamination of these recycled materials. For NIAS the general requirement applies; article 3 of Regulation (EC) No. 1935/2004[5] states that food contact materials, under normal or foreseeable conditions of use, do not transfer their constituents to food in quantities which could endanger human health.

Due to its environmentally persistent properties, PFOS is restricted to a concentration of 0.1% by weight in articles (Regulation (EU) No 2019/1021)[6]. For coatings, a restriction of 1 µg/m^2 applies. In this Regulation PFOA is also restricted in articles to a maximum content of 0.025 mg/kg.

Risk assessment of PFAS in food

In 2022 BuRO published an advice on the health risks of environmental contaminants in wilderness meat from floodplains (BuRO, 2022). Wilderness meat originates from specific breeds of cattle that are kept year-round in floodplains for natural grazing. Surplus animals that cannot be rehomed to other areas are slaughtered and their meat is sold to a specific group of consumers. Due to the potential high chemical contamination of floodplains BuRO investigated the health risks related to environmental contaminants in this meat. The advice describes the assessment of the consumers' health risks in relation to dioxins and dioxin-like PCBs, heavy metals and PFAS. Measurements were performed by Wageningen Food Safety Research (WFSR). On PFAS BuRO concluded that consumption of wilderness meat by adults can lead to an exposure equal to 50% of the TWI. This finding was based on the consumption of 300 grams of wilderness meat per week and application of RPFs for the exposure calculation. When equipotency is assumed, the calculated exposure is equal to 20% of the TWI. Therefore, the PFAS exposure due to the consumption of wilderness meat alone does not lead to a health risk for adult consumers. The intake of PFAS from other sources (which is considerable) is not included in this risk assessment. Lower detection limits are needed to definitively assess the risks since some PFAS may be present around the detection limit; if the concentrations of non-detects are set equal to the detection limit a health risk cannot be excluded.

Based on the data currently available, the consumption of reasonable quantities of wilderness meat appears to exceed the tolerable upper intake level for children, only if RIVM's RPF method for exposure calculations is used. This means that the consumption of wilderness meat may increase health risks for children consuming wilderness meat on a regular basis. The assessments for both adults and children show the effect of the method, which is used for the exposure calculations; the assumption on relative potencies of PFAS may strongly affect the conclusion on risk.

Recently RIVM calculated the quantity of PFAS that people ingest through food and drinking water and concluded that the ingested quantity of PFAS exceeds the health-based guidance value (Schepens et al., 2023). Consumption of fish is an important source of PFAS, but also the consumption of tea, coffee, cereal products, milk products, meat, eggs, fruit and vegetables attribute to PFAS exposure. The PFAS concentration in drinking water depends on the type of water used as a source, as surface water contains more PFAS than ground water. RIVM points out the importance of eating a varied diet in order to avoid ingesting a large amount of PFAS. By doing so, people will not eat foods with a high PFAS concentration too often (Schepens et al., 2023).

The Netherlands Nutrition Centre (Stichting Voedingscentrum Nederland) promotes the Wheel of Five, a practical information tool used to guide eating habits of Dutch consumers in order to stay healthy. The Nutrition Centre advises eating fish once a week because it is beneficial for the heart and blood vessels. Although high concentrations of PFAS were found in fish, this advice has not been changed[7], as the health benefits are considered greater than the health risks (based on the currently available knowledge).

Risk assessment of PFAS in FCM

In 2021 WFSR, commissioned by the NVWA, studied the migration of PFAS from paper and paperboard into food. The study included easy and fast food that was packaged directly in paper and paperboard, such as pizzas, hamburgers, fries, sandwiches, wraps, muffins, donuts and drinks such as coffee and milkshakes. In this study, 50 different foods from the above categories were examined for the presence of PFAS. The analytical method included 23 different PFAS, such as PFOA, PFOS, GenX, perfluorocarboxylic acids and perfluoro sulphonic acids. In only 1 sample (minced-meat sausage, frikandel) a trace of PFHxA and PFOS was detected, this was however below the limit of detection (LOD). The LOD in meat was 0.025 µg/kg for both PFHxA and PFOS. Based on daily consumption of 1 minced-meat sausage (85 g) and the LOD of 0.025 µg/kg, the exposure to PFOS and PFHxA from the minced-meat sausage will not exceed 0.005 ng/kg bodyweight per week. PFOS is included in the EFSA-4 and the estimated exposure can be directly compared to the EFSA TWI. For PFHxA RIVM reported an RPF value of 0.01 (Bil et

4 wetten.nl - Regeling - Warenwetbesluit verpakkingen en gebruiksartikelen - BWBR0018370 (overheid.nl)

5 Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC.

6 Regulation (EU) 2019/1021 on persistent organic pollutants.

7 Voedingscentrum duidt: kun je vis eten vanwege PFAS? | Voedingscentrum, accessed on 7th of July 2023.

al., 2021), resulting in a worst-case exposure of 0.00005 ng PEQ/kg bodyweight per week. The estimated exposure of PFOS and PFHxA from this minced-meat sausage is well below the TWI, therefore, no health risk is assumed.

In 2022 WFSR expanded its analytical method to include more PFAS, such as fluorotelomer alcohols, sulfonamides, fluorotelomer sulphonates, mono- and diPAPs and perfluoroalkylphosphinates. The packaging materials of the 2021 study on easy- and fast food were analyzed using this method. PFOS and PFOA were detected in most samples. In addition, small amounts of the perfluorocarboxylic acids PFHxA, PFHpA, PFNA, PFDA, PFUnDA, and PFDoDA, were detected in some of the packaging. Comparing the results of both studies, it can be concluded that PFOA and PFOS were detected in most packaging materials, detectable amounts of perfluorocarboxylic acids were present in some of the packaging materials. However, no detectable migration of these PFAS into the food occurred.

Other PFAS were also detected, such as PAPs, diPAPs and diSAmPAP. The sulfonamides were not detected in any of the packages. Of the FTOHs, 6:2 FTOH in particular was found; the highest amount of 6:2 FTOH (1400 µg/kg) was found in the packaging of a frikandel. Worst-case calculation leads to a migration of 17 ug/kg food, corresponding to an exposure of 3 ng 6:2 FTOH/kg bodyweight per week (based on daily consumption of one minced-meat sausage). When applying the RPF RIVM (0.02), this is converted to an exposure of 0.06 ng PEQ/kg bodyweight per week (Bil et al., 2021). The estimated exposure is well below the EFSA TWI, therefore no health risk is assumed.

In addition, small amounts of PFHxS, PFHpS (qualitative) and 8:2FTOH were found. FTOH's, fluorotelomer sulphonates, mono- and diPAPs were not analyzed in the food itself. Therefore, no conclusion can be drawn on the migration of these PFAS into food. Migration data into food (simulants) are needed to make a more accurate exposure and risk assessment.

About BuRO

The Office for Risk Assessment & Research[8] (bureau Risicobeoordeling & onderzoek; BuRO) is an independent division of the Netherlands Food and Product Safety Authority (NVWA). BuRO provides independent advice to the Inspector-General of the NVWA, to the Dutch Ministry of Health, Welfare and Sport, and the Ministry of Agriculture, Nature and Food Quality. The scientific substantiated risk assessments encompass subjects related to food safety, consumer product safety, animal health, animal welfare, plant health and nature. Advice can be provided upon request or upon initiative of BuRO.

8 https://english.nvwa.nl/about-us/office-for-risk-assessment--research

References

Bil W, Ehrlich V, Chen G, Vandebriel R, Zeilmaker M, Luijten M, Uhl M, Marx-Stoelting P, Halldorsson TI & Bokkers B, 2023. Internal relative potency factors based on immunotoxicity for the risk assessment of mixtures of per- and polyfluoroalkyl substances (PFAS) in human biomonitoring. Environ Int, 171, 107727. Available online: https://doi.org/https://doi.org/10.1016/j.envint.2022.107727

Bil W, Zeilmaker M, Fragki S, Lijzen J, Verbruggen E & Bokkers B, 2021. Risk Assessment of Per- and Polyfluoroalkyl Substance Mixtures: A Relative Potency Factor Approach. Environmental Toxicology and Chemistry, 40 (3), 859-870. Available online: https://doi.org/https://doi.org/10.1002/etc.4835

Bil W, Zeilmaker MJ & Bokkers BGH, 2022. Internal Relative Potency Factors for the Risk Assessment of Mixtures of Per-and Polyfluoroalkyl Substances (PFAS) in Human Biomonitoring. Environmental Health Perspectives, 130 (7). Available online: https://doi.org/10.1289/EHP10009

Bokkers B, van de Ven B, Janssen P, Bil W, van Broekhuizen F, Zeilmaker MJ & Oomen A, 2018. Per- and polyfluoralkyl substances (PFASs) in food contact material. RIMV, Bilthoven. Available online: https://www.rivm.nl/bibliotheek/rapporten/2018-0181.pdf

BuRO, 2022. The health risks of environmental contaminants in wilderness meat from floodplains. Office for Risk Assessment & Research, the Netherlands Food and Consumer Product Safety Authority (NVWA), Utrecht. Available online: https://english.nvwa.nl/about-us/documents/consumers/food/safety/documents/advice-from-buro-on-the-health-risks-of-environmental-contaminants-in-wilderness-meat-from-floodplains

EFSA CONTAM Panel, 2020. Risk to human health related to the presence of perfluoroalkyl substances in food. EFSA Journal, 18 (9), e06223. Available online: https://doi.org/https://doi.org/10.2903/j.efsa.2020.6223

RIVM, 2021a. Notitie implementatie van de EFSA som-TWI PFAS. Rijksinstituut voor Volksgezondheid en Milieu, Bilthoven. Available online: https://www.rivm.nl/documenten/notitie-implementatie-van-efsa-som-twi-pfas

RIVM, 2021b. Revised risk assessment of GenX and PFOA in food. Part 1: Toxicity of GenX and PFOA and intake through contaminated dairy products, eggs and fish. National Institute for Public Health and the Environment, Bilthoven. Available online: https://www.rivm.nl/voedsel-en-voeding/veilig-voedsel/frontoffice-voedsel-en-productveiligheid/beoordelingen-front-office-voedsel-en-productveiligheid

Schepens MAA, te Biesebeek JD, Hartmann J, van der Aa NGFM, Zijlstra R & Boon PE, 2023. Risk assessment of exposure to PFAS through food and drinking water in the Netherlands. Risicobeoordeling van blootstelling aan PFAS via voedsel en drinkwater in Nederland. Rijksinstituut voor Volksgezondheid en Milieu RIVM. Available online: http://hdl.handle.net/10029/626814

Piecing together the genetic puzzle of anthracycline cardiotoxicity

Amidst the many scientific exchanges at EUROTOX 2023 in Ljubljana this past September, I had the opportunity to present some of my latest scientific work: “unraveling novel gene networks in anthracycline-induced cardiotoxicity.” Guided by Dr. Twan van den Beucken and Dr. Florian Caiment, our research takes on the effort of dissecting the complex transcriptomic responses of cardiomyocytes to anthracycline exposure. By combining bioinformatics with hands-on wet-lab approaches, we are peeling back layers of this intricate puzzle.

By *Jelmer Faber*

Though Anthracyclines are known to cause many side effects, they remain to play a prominent role in the field of cancer treatment since their discovery in the 1960s. The shadow of their use is a dose-dependent and cumulative cardiotoxicity, culminating in heart failure – a condition known as anthracycline-induced cardiotoxicity (AIC). This paradox of efficacy and risk has resulted in limited clinical use. The current AIC therapeutic landscape is sparse, with no approved biomarkers for patient stratification and just a single drug specific to the alleviation of this cardiotoxicity (1). This gap highlights the need for a deeper understanding of the biological underpinnings of AIC, aiding the development for more effective patient interventions to mitigate these serious side effects.

Since these mechanisms are partly driven by changes in gene expression, we began identifying critical transcription factors (TFs) that control anthracycline (AC)-induced gene expression changes in human iPSC-derived cardiomyocytes (iPSC-CMs). Two TF prediction algorithms, ChEA3 and LISA, were used to identify key TFs from RNA-sequencing data generated with ACs exposed iPSC-CMs. From our analyses, we successfully identified TFs not yet linked to cardiotoxicity, including GATA2, FOSL1, TCF21, and RUNX2. Additionally, our analysis reaffirmed the involvement of well-documented TFs in AIC, such as TP53, ATF3, FOXO1, and GATA4 (2-4), thereby validating our investigative approach. In total, we selected 27 TFs for further investigation.

We shifted our focus to a more direct, experimental approach. Utilizing lentiviral small hairpin RNAs (shRNAs), we focused on the importance of the selected TFs for the cellular response to the anthracycline doxorubicin. This revealed intriguing dual roles of these TFs: some enhanced the vulnerability of cardiomyocytes to the anthracycline doxorubicin, indicating a potential protective mechanism at work. Conversely, the knockdown of other transcription factors (TFs) led to increased cell survivability, hinting at their role in exacerbating the toxic effects of doxorubicin exposure highlighting the intricate transcriptomic dynamics at play.

We selected four TFs for a more detailed exploration of their roles in AIC. We investigated their influence on mitochondrial activity, the involvement in the DNA damage response, induction of apoptosis, and if these TFs affect the cardiomyocytes’ susceptibility to the uptake of doxorubicin. So far, the preliminary results are promising as we are finishing our experiments.

This research is only a small piece of the puzzle that is AIC, but every discovery brings us closer to a more effective cancer therapy that no longer comes at the expense of cardiac well-being.

Bibliography

1. Henriksen PA. Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. Heart. 2018 Jun;104(12):971-977. doi: 10.1136/heartjnl-2017-312103. Epub 2017 Dec 7. PMID: 29217634.
2. Park EJ, Kwon HK, Choi YM, Shin HJ, Choi S. Doxorubicin induces cytotoxicity through upregulation of pERK-dependent ATF3. PLoS One. 2012;7(9):e44990. doi: 10.1371/journal.pone.0044990. Epub 2012 Sep 13. PMID: 23028726; PMCID: PMC3441731.
3. Yan F, Liu R, Zhuang X, Li R, Shi H, Gao X. Salidroside Attenuates Doxorubicin-Induced Cardiac Dysfunction Partially Through Activation of QKI/FoxO1 Pathway. J Cardiovasc Transl Res. 2021 Apr;14(2):355-364. doi: 10.1007/s12265-020-10056-x. Epub 2020 Jul 16. PMID: 32671648.
4. Karhu ST, Kinnunen SM, Tölli M, Välimäki MJ, Szabó Z, Talman V, Ruskoaho H. GATA4-targeted compound exhibits cardioprotective actions against doxorubicin-induced toxicity *in vitro* and *in vivo*: establishment of a chronic cardiotoxicity model using human iPSC-derived cardiomyocytes. Arch Toxicol. 2020 Jun;94(6):2113-2130. doi: 10.1007/s00204-020-02711-8. Epub 2020 Mar 17. PMID: 32185414; PMCID: PMC7303099.

Radar 4 dec 2023:

Cooking riskier than you might think

In a recent segment on the television show Radar (aired on Monday, December 4th), the TNO report addressing a healthy indoor environment was featured. Piet Jacobs, Senior Scientist at TNO, and Prof. Dr. Philomena M. Bluyssen, Professor of Indoor Environment at the Faculty of Architecture and the Built Environment, Delft University of Technology, discuss the often-underestimated concern of indoor air quality, emphasizing its potential to lead to health issues.

The TNO report emphasizes the health risks associated with cooking, especially with gas, due to the release of harmful substances such as ultrafine particles, nitrogen dioxide, and carbon monoxide. Field research reveals increased indoor particulate matter levels after cooking, particularly in energy-efficient homes. The report recommends revising building regulations to enhance kitchen ventilation, stressing the significance of effective solutions like electric cooking, robust range hoods, and natural ventilation. Exposure to ultrafine particles indoors, especially during cooking, significantly contributes to overall exposure and impacts respiratory health. The findings highlight the necessity for measures to reduce indoor air pollution, particularly in energy-efficient homes, to protect public health. In the Radar fragment, household situations are examined, offering insights on maintaining low levels of nitrogen and particulate matter.

The Radar news topic (in Dutch) can be watched here: https://radar.avrotros.nl/artikel/fragment-koken-gevaarlijker-dan-je-misschien-denkt-55093

AIO toxafette - Noor Verhagen

In each edition of Toxafette, PhD students specializing in toxicology have the opportunity to discuss their research experiences. Every publication highlights a different candidate, who responds to a set of questions before passing the baton to another fellow PhD student. On this occasion, Noor Verhagen, from the Division of Pharmacology and Toxicology at Radboudumc in Nijmegen, shares insights into her project.

Can you introduce yourself?

Hi! My name is Noor Verhagen. Originally, I am from Brabant, but I moved to the beautiful city of Nijmegen 6 years ago to pursue my bachelor's degree in (medical) biology at Radboud University. Afterward, I did my master's in molecular mechanisms of disease, also at Radboud University. During my master's, I had the opportunity to do my internship in the Division of Pharmacology and Toxicology at Radboudumc. I enjoyed this internship a lot, and in collaboration with the division, I wrote a project proposal to continue as a PhD student. This worked out, and currently, I am almost in the second year of my project. When I am not working in the lab, I like to hang out with my friends and family, or you can find me on the hockey field!

How would you explain the subject of your research to a layperson?

Chronic myeloid leukemia is a disease that can be treated quite successfully with a certain type of drugs called tyrosine kinase inhibitors. Unfortunately, sometimes patients become resistant to treatment. There can be multiple explanations for this resistance. I look at a certain mechanism where cancerous cells protect themselves by pumping out the drugs from the cell or accumulate those drugs in places within the cell where they lose their function. This is possibly done by certain proteins, which might be extra active or present in larger numbers in cancerous cells compared to normal cells. If too little of the drug is left in the cancerous cell, this cell will remain in the bone marrow and possibly grow out again. This means that the patient might become resistant to therapy or might even have a disease relapse.
To study this process, I need to recreate the disease situation as it is in patients in the laboratory. This can be done in a petri dish, but this doesn't properly resemble the situation in patients. It can also be done in laboratory animals, but again, this doesn't really resemble the patient's situation and the usage of these animals should be reduced as much as possible. Therefore, I am developing a model called a 'bone marrow on chip' model. It is called this way as it looks a bit like a computer chip. In this chip, there are multiple channels in which cells can be seeded in 3D. The advantage of this model is that different types of cells can be incorporated, which can grow in a 3D environment, the flow of nutrients can be controlled, and the model can easily be put underneath a microscope to see what is going on.

How is your research related to the field of toxicology, and why did you choose this subject?

Cancer studies are one big toxicological puzzle. You want to eliminate the cancerous cells through drug administration, but you want to limit the damage done to the actual individual. It is thus a very delicate balance where you have to look for the little differences between cancerous and non-cancerous tissue. Besides this exciting puzzle, I am very much interested in pharmaceutical research. I am intrigued by the fact that many patients rely on pharmaceutical therapy but that every patient responds differently to treatment. Therefore, I think it is exciting that the model that I am developing can be used as a personalized medicine tool.

What was your motivation for starting a Ph.D. program?

Although I have always liked studying, I found out during my internships how much I actually liked 'creating' my own knowledge by doing experiments. Textbooks and lectures are good fun, but to actually elucidate a mechanism yourself was more up my alley. Also, the management of your very own project seemed exciting. And as said before, I got the chance to write a PhD proposal during my master's. This was a great experience, as you get all the freedom you would like to think about a topic, techniques, questions you want to answer etc. Luckily, I was granted the funds to actually perform this project!

How do you see the future of your research topic (follow-up research / social impact)? What do you hope for?

The ultimate goal of my project is to elucidate the role of drug-transporting proteins in chronic myeloid leukemia. If this is accomplished, we could think about ways to counter this resistance mechanism. This would greatly benefit the quality of life of patients. Besides, I believe that the future of disease treatment and diagnostics is headed towards personalized medicine. The model that I am developing could contribute to this personalized approach.

What is the biggest challenge for you in doing PhD research?
The biggest challenge for me is finishing up different research lines. If you are doing an internship, the end of the project is clearly marked. When doing a PhD, you have quite some time to dwell on details
Sometimes you have to draw hard conclusions and stick with them. But as you always find new interesting things along the way, it is very tempting to continue the research line for too long. This could mean that you drift too far from your original research question.

If everything is possible, what do you want to do with the knowledge you have from your PhD?
As I still have 3 years to go in my project, I am keeping my options open for now. I could imagine myself working as a scientist in a company, but I am also considering a future job that has to do with science communication. I appreciate that within your PhD you have the freedom to explore these options, so therefore I am participating in courses that have to do with, for example, science journalism.

If you could start over your studies/research project, what would you do differently?
Apart from an internship abroad, I have done my entire studies at Radboud University. I do see the advantage in the sense that I know the campus and the people who work here, and thus I know who to consult if I run into problems. Despite this, I would advise switching universities at least once to get a broader perspective on how things are handled elsewhere.

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 finalization of my project, I will probably leave academia, mainly because I want to explore what the field outside of academics has to offer. I do aspire to a function that is related to toxicology and biomedical sciences. To be honest, I do not worry about future plans too much, as I still have some time left in my project. Going abroad is an option that I am seriously considering. I think this is beneficial for your career, as you gain work experience in a different working climate. But for me, a big reason is also personal development, as you learn a lot from moving abroad and integrating into a culture that you are not used to.

Please answer the question from the last Toxafette PhD candidate: How has your PhD journey changed your perspective on Academia?
Previously, I thought everything was very strictly regulated in academia. You only worked with other scientists in your research group, your supervisor knew everything better, and the culture was constantly very formal. Now, I have realized that it is way looser than that. Work with people from other disciplines if you can learn something from them, come up with creative solutions for problems together with your supervisor, and have fun with your colleagues outside of work-related stuff. Having informal chats with your colleagues even helps to create an open environment, which is very beneficial for your research.

Could you propose a question for the next PhD candidate for the Toxafette?
What qualities do you think are important to have as a PhD candidate?

TERUG NAAR INHOUD

Proefschrift promopraatje

Dear PhD Students and Promotors,

We would like to invite you to share your insights with your fellow toxicologists regarding your almost or recently completed **PhD-research project**.

The TCDD always reserves a spot for thesis promo talks. This section where gives PhD students the opportunity to present their recently completed theses, whether they are scheduled for defence, or have been defended recently.

To participate, we kindly ask the following from you:

- A Word document containing a clear and readable summary of your thesis (approximately 750-1000 words).
- A photograph of yourself, for example during the thesis defense.
- An image of your thesis cover.
- A URL to your thesis if it's available online.

Sharing your insights not only provides an opportunity to celebrate your achievements but also contributes to enriching knowledge within the NVT. We sincerely hope that you are interested in presenting and sharing your research with your fellow toxicologists.

If you would like to participate in our thesis promo talk or need further information, please let us know via redactie@toxicologie.nl

We look forward to celebrating your hard work and welcoming your insights!

Prestatie van de ICU-noodzakelijkheid score (INS) bij het voorspellen van de noodzaak voor ICU-opname van geïntoxiceerde volwassen patiënten: het INTOXICATE-onderzoek

EAPCCT, 23-26 may 2023, Palma de Mallorca

Photo by Eugene Zhyvchikon unsplash

Mijn presentatie op het European Association of Poisons Centers and Clinical Toxicologists (EAPCCT) congres ging over het extern valideren van een in 2017 ontwikkeld model wat de noodzaak voor IC-opname inschat van patiënten die zich met een acute intoxicatie op de Spoedeisende Hulp presenteerden. Het model is in 2 eerdere onderzoeken ook extern gevalideerd en nuttig gebleken bij het uit selecteren van patiënten die geen IC-opname nodig hadden, maar in deze onderzoeken werd geen kalibratieanalyse uitgevoerd. Bovendien waren het studies die de ICU Noodzakelijkheid Score (INS) slechts hadden getest in enkele ziekenhuizen.

In mijn onderzoek heb ik de prestatie van het model getest door middel van een multicenter onderzoek waarvoor data is verzameld van meer dan 100 ICUs binnen Europa, en een paar ICUs van andere continenten. Aanvullend, heb ik de prestatie van het model gerapporteerd met behulp van een kalibratieplot. De conclusie van mijn onderzoek is dat het model opnieuw gekalibreerd moet worden door het intercept van de kalibratiecurve aan te passen. Het intercept lag hoger dan 0 in de internationale patiëntenpopulatie, wat aangeeft dat het algehele basisrisico voor de noodzaak van een IC-opname bij vergiftigde patiënten hoger ligt in de internationale populatie dan dat op basis van het model, wat ontwikkeld was met een Nederlandse nationale patiëntendatabase, kan worden verwacht.

De eerste presentatie die gegeven werd op het EAPCCT-congres, en die indruk op mij maakte, was een presentatie over organofosfaat intoxicaties en hoe er nog steeds geen effectieve behandeling bestaat voor wanneer de toxische effecten al hun intrede hebben gedaan. Ze hebben wel gekeken naar het effect van immunosuppressiva, maar het effect was niet significant. Ook hebben ze de mogelijke effectiviteit van maagspoeling onderzocht en het effect daarvan was eveneens niet aantoonbaar. Tot op heden zijn er dus nog steeds beperkte mogelijkheden om iemand met een organofosfaat intoxicatie effectief te behandelen wanneer symptomen al zijn opgetreden. Deze conclusie vond ik ontmoedigend maar interessant. ►

Voor mij is de wetenschappelijke “take home message”: dat het EAPCCT een goed platform is om te netwerken, en dat het netwerken mooie projecten kan voortbrengen. Er waren veel internationale samenwerkingen die via het EAPCCT tot stand waren gebracht en zo mooi onderzoek hebben mogelijk gemaakt.

Voor mij betekent klimaatneutraal dat ik zo min mogelijk per vliegtuig moet reizen. Dit zou kunnen betekenen dat de conferenties gehouden moeten worden op locaties waar de meeste leden wonen. In dit geval zou dat in Europa moeten zijn. Het zou kunnen helpen om het congres niet op een eiland te organiseren, maar op het vasteland, zodat mensen met de auto of trein kunnen reizen. Het verder ontwikkelen van virtuele mogelijkheden zou het ook aantrekkelijker kunnen maken om het congres online te volgen, hoewel ik moet toegeven dat niets te vergelijken is met het daadwerkelijk aanwezig zijn om mensen in het echt te kunnen spreken.

De tweede presentatie die indruk op mij heeft gemaakt, ging over het gebruik van kunstmatige intelligentie voor het diagnosticeren van intoxicaties op zo’n gedetailleerd niveau dat ze proberen te herkennen met welk middel de intoxicatie was veroorzaakt. De data die deze onderzoekers hadden gebruikt, waren gerapporteerd bij de landelijke poisons call center in Duitsland, aan de hand van klinische gegevens. Van een paar middelen wisten ze vrij zeker te voorspellen dat ze waren ingenomen, maar er is nog een lange weg te gaan. Dit interesseert mij omdat ik met mijn eigen onderzoek heb ervaren dat het lastig is het type blootstelling zodanig te categoriseren dat je ze betrouwbaar kunt scheiden van elkaar aan de hand van het klinische beeld. Ook ben ik geïnteresseerd in de positieve en negatieve kanten van het gebruik van kunstmatige intelligentie bij onderzoek op het niveau van klinische data en niet op moleculair niveau of het niveau van DNA sequencing.

De derde presentatie op het EAPCCT betrof een poster waarin ze de chemische overlap hadden bestudeerd tussen psychoactieve stoffen die door de farmaceutische pijplijn waren gefabriceerd en dezelfde psychoactieve stoffen die op de zwarte markt werden geproduceerd, en of de effecten van deze stoffen aan de hand hiervan voorspeld konden worden, en dat was in zekere mate ook zo.

Photo by Eugene Zhyvchikon unsplash

NVT annual meeting June 18 & 19, 2024

We are happy to invite you to NVT annual meeting in 2024 at "Congrescentrum de Reehorst," Ede on June 18 and 19, 2024 to celebrate 45 years of NVT! This meeting is a Lustrum edition which means there will be two "NVT-member" days.

The theme of this year will be Toxicology then and now: Back to the Future.

Since its inception, the field of toxicology has aimed to improve (the protection of) human and environmental health. The way we do this has changed drastically over the years. Scientific innovations, the influx of new and unknown substances onto markets, shifts in public perception, and changes in research populations have warranted the use of new methodologies. Some established practices have been replaced, whereas others were adapted to keep up with the changing times and others still remain virtually the same. Experimental models have evolved from simple two-dimensional systems to complex three-dimensional organoids and organ-on-a-chip models; increased computational power has sparked the use of computational modeling for even the most complex biological phenomena. The use of *in vivo* animal experiments in toxicology and their possible replacement by *in vitro* New Approach Methodologies (NAMs) is extensively debated in society. Artificial intelligence has become widely available, opening the door for new applications in science and helping with processing the immense amount of data generated by both industry and academia. As a consequence, these new developments also highlight the need for regulation and the relevance of regulatory toxicology. An overarching question we may ask ourselves is: Do we need an entirely new framework for toxicology, or do we need to adapt and incorporate these new developments into the current framework? For this year's anniversary edition of the annual Nederlandse Vereniging voor Toxicology (NVT) meeting, we will look back at the history of the field of toxicology; what can we learn from the past, whether every change is an improvement, and what can we expect in the (near) future. In summary: Do we need to go back to the future?

More information will follow soon. Looking forward to seeing you there!

Best regards,

NVT organizing committee

Heleen van der Hout, Maria Kloukinioti, Julia Meerman, Tanne Meuwissen, Damian Roelofsen, Kirsten Veltman, Jiayi Yang, Laura Hondebrink, Anne Kienhuis, Joanne Salverda, Frederik-Jan van Schooten, Yvonne Staal

Inschrijving TiO

Voorletters	Achternaam	Opleider	Datum inschrijving
N.C.	Wieland	Prof.dr. F.G.M. Russel	27-11-2023
K.G.J.	Romano Olmedo	Prof.dr.ir. I.M.C.M. Rietjens	07-12-2023

VOORAANKONDIGING

Op donderdag 28 maart 2024 organiseren de Nederlandse Vereniging voor Toxicologie, sectie Arbeidstoxicologie en sectie Risicobeoordeling, in samenwerking met de Contactgroep Gezondheid en Chemie, een bijeenkomst onder de titel: “Omgaan met Reproductietoxische en Hormoonverstorende Stoffen: Navigeren tussen Theorie, Nieuwe Regelgeving en Praktijk”.

De regelgeving voor blootstelling aan reproductietoxische stoffen op de werkplek gaat binnenkort ingrijpend veranderen. Reproductietoxische stoffen zijn sinds kort opgenomen in de Europese Carcinogens & Mutagens Directive (CMD 2022/431), en de Nederlandse overheid moet de nieuwe regels uiterlijk in april 2024 in het Arbeidsomstandighedenbesluit hebben opgenomen. Voor een deel van de reproductieschadelijke stoffen betekent dit, dat dezelfde verplichtingen gaan gelden als nu al voor kankerverwekkende en mutagene stoffen gelden: een zware inspanningsplicht om deze te vervangen indien dat technisch uitvoerbaar is, en zo niet, een zware inspanningsplicht om de blootstelling te minimaliseren. Dit gaat gelden voor stoffen die zijn geclassificeerd als klasse-1 reproductietoxisch, waarbij wel onderscheid wordt gemaakt tussen reprotoxische agentia zonder en met een veilige drempelwaarde.

We hebben het hierbij over stoffen die schadelijk kunnen zijn voor de vruchtbaarheid (via zowel man als vrouw), die kunnen leiden tot aangeboren afwijkingen bij het kind, of schadelijk voor het kind kunnen zijn via de borstvoeding. Daarnaast is recent ook steeds meer aandacht ontstaan voor zgn. hormoonverstorende stoffen, en worden in het kader van de Europese stoffenwetgeving REACH testmethoden en criteria voor de classificatie ontwikkeld. De aandacht voor reproductietoxische en hormoonverstorende stoffen is verder aangewakkerd door onder meer de problematiek rond PFAS/PFOA, en door een casus in de lycrafabriek van Du Pont (15 ex-werkneemsters die het bedrijf hebben aangeklaagd, nadat zij allen een of meer miskramen hadden gehad).
Voldoende reden om eens aandacht te besteden aan deze categorieën stoffen. In dit middagsymposium zullen de komende wijzigingen in de regelgeving aan bod komen, en verder de toxicologie van reproductietoxische en hormoonverstorende stoffen (incl. testmethoden), hoe bedrijven in de praktijk met de beheersing van blootstelling kunnen omgaan, en een aantal ethische vraagstukken die hierbij naar voren komen.

Conceptprogramma:

- *Europese en nationale wetgeving voor reproductietoxische stoffen en hormoonverstorende stoffen, en de komende wijzigingen daarin*
- *De toxicologie van reproductietoxische en hormoonverstorende stoffen; kenmerken/ eigenschappen, testmethoden en verschillen tussen deze twee categorieën stoffen.*
- *De praktijk in een bedrijf: omgaan met de wetgeving voor reproductietoxische stoffen; informatiebronnen; onderscheid wel/geen drempelwaarde stoffen; schadelijkheid voor mannen resp. vrouwen.*
- *De medisch / ethische invalshoek: casuïstiek en ethische aandachtspunten.*

Nadere informatie volgt op de website van de NVT.

Christmas Puzzle

Maak kans op een mooie prijs én eeuwige roem. Stuur je oplossing naar de redactie van de TCDD via redactie@toxicologie.nl onder vermelding van “uitslag kerstpuzzel 2023”.

Have a chance to win a great prize and eternal fame. Send your solution to the editors of the TCDD via redactie@toxicologie.nl, stating “result Christmas puzzle 2023”.

P	M	O	L	E	C	U	L	A	R	E	P	L	A	C	E	M	E	N	T
M	E	U	L	E	T	G	N	I	T	A	P	I	C	I	T	R	A	P	S
T	E	R	T	S	U	B	S	T	A	N	C	E	S	O	O	T	A	S	T
T	T	A	F	A	O	Y	E	S	T	E	N	T	X	R	D	P	C	A	Y
S	A	O	S	L	G	C	T	H	I	I	N	I	R	I	E	H	D	D	V
E	M	D	X	U	U	E	E	V	F	A	C	C	E	N	W	A	A	N	D
L	C	O	M	I	R	O	N	A	N	O	O	S	M	N	A	R	T	E	T
A	A	X	E	S	C	E	R	I	L	N	L	A	O	O	S	M	A	N	D
B	L	O	T	N	D	T	M	O	C	A	C	I	L	V	T	A	N	V	E
O	C	R	H	T	L	A	G	E	C	O	T	O	E	A	E	C	O	I	T
R	U	U	O	U	T	I	R	I	N	A	M	O	T	T	W	E	I	R	A
A	L	B	D	N	C	N	M	S	N	T	R	R	O	I	A	U	T	O	L
T	A	I	O	A	R	E	U	I	O	W	S	B	R	O	T	T	A	N	Y
O	T	C	L	S	H	M	M	S	L	L	E	C	O	N	E	I	L	M	X
R	I	I	O	C	P	R	O	T	E	O	M	E	U	X	R	C	A	E	O
Y	O	N	G	T	E	X	P	O	S	U	R	E	L	B	Y	A	H	N	H
S	N	O	I	T	A	L	U	G	E	R	R	I	F	G	H	L	N	T	T
T	F	O	E	U	B	I	O	A	C	C	U	M	U	L	A	T	I	V	E
T	N	D	S	U	R	L	A	N	O	I	T	A	T	U	P	M	O	C	E
O	R	G	A	N	I	S	M	Y	C	N	E	R	A	P	S	N	A	R	T

BIOACCUMULATIVE
CALCULATION
CELLS
CHEMICALS
COMPUTATIONAL
CONCERN
CONSUMPTION
CONTAMINANTS
DATA
DETERMINATION
DOXORUBICIN
ENVIRONMENT
ETHOXYLATED
EXPOSURE
FLUOROTELOMER
INHALATION
INNOVATION
LABORATORY
MEASUREMENTS
METHODOLOGIES
MOLECULAR
MUTAGENIC
NVT
ORGANISM
PARTICIPATING
PERFLUOROCARBOXYLIC
PHARMACEUTICAL
PROTEOME
REGULATIONS
REPLACEMENT
SUBSTANCES
TCDD
TOXIC
TOXICOLOGICAL
TRANSPARENCY
ULTRAFINE
WASTEWATER

Oplossing

TERUG NAAR INHOUD