TCDD

TOXICOLOGIE

NUMMER 3
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SPECIAL THEME

Water

- BIOREMEDIATION TECHNOLOGY AND ITS POTENTIAL FOR APPLICATION IN GROUNDWATER SYSTEMS
- DOWN THE DRAIN: THE CASE OF PHARMACEUTICAL RESIDUES IN SURFACE WATER
- POLLUTION DUE TO FLOODS AND DROUGHTS
- DRYING LAKES RAISE TOXICITY CONCERNS

Salton Sea, Mecca, United States. Photo by: **Taylor Simpson** on **Unsplash**

NEDERLANDSE VERENIGING VOOR TOXICOLOGIE

Colofon

Toxicologische Communicatie, Data en Documentatie

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TCDD
TOXICOLOGIE

Inhoud

TERUG NAAR INHOUD

Editorial

Let’s start off with a small riddle: what constitutes 75% of your brain, is hardly toxic at all and yet has killed many people, by either being present in excess or by being lacking? Most of you will have guessed it correctly: water. The deadliest types of natural disasters are droughts and floods; water generously gives life, or mercilessly deals out death. The current issue of the TCDD is based on water as a special theme. It is a favorite topic of mine (how Dutch); since I was a child, I’ve had freshwater aquaria and often went fishing to catch new inhabitants. And recently, I’ve set up a pond with a large panoramic window in our garden, filled with native species of flora and fauna. Watching the underwater world is one of the most relaxing experiences I know.

The current issue of the TCDD includes several articles focused on the special theme: Water. Andrea Aldas-Vargas talks about her PhD project in which she explored an environmentally friendly technology to degrade groundwater contamination. There is a piece on surface water pollution due to pharmaceutical residues, a piece on pollution associated with droughts and floods, as well as a piece on drying lakes.

Also in this issue, there is important news on the dissolution of one of the NVT sections, the section Teratology and Reproductive Toxicology. It is unfortunate that such an important topic no longer is represented at the NVT section level. I wish all the best to Manon, Josianne, Sjors and Kirsten and hope that they will remain active in the field of Toxicology.

A report on this year’s NVT Annual Meeting follows. It was a successful event, with an interesting keynote lecture by Matthias Herzler, a regulatory toxicologist from the German Federal Institute for Risk Assessment (BfR). He talked about the Green Deal and the European Chemicals Strategy for Sustainability, the change they are supposed to bring to the field of regulatory toxicology. There were many more interesting lectures and topics; I would recommend checking it out.

Also, there is news from ECHA: in line with their Integrated Regulatory Strategy, risk management has been suggested for 300 out of 1900 screened substances. Then there is the sensitive topic that is Glyphosate: the Risk Assessment Committee (RAC) has stated that the substance is indeed toxic to aquatic life and causes serious eye damage, but in their opinion the available evidence suggests that Glyphosate should not be classified as a carcinogen.

Finally, the NVT section Pharmaceutical Toxicology has provided a piece on the safety of the renewed COVID-19 vaccines that are applied in the autumn vaccination campaign.

I hope you enjoy the current issue; stay safe!

On behalf of the editorial team,

Damiën van Berlo

Photo by Jess Bailey on Unsplash

News from the board

Welcome to the October edition of the TCDD. I now have the honour of acting as the NVT president, taking over from Juliette Legler, who remains as vice president. Since the last TCDD edition we had a very successful NVT annual meeting, in-person at the end of May at the Reehorst in Ede, Netherlands. It was a special meeting as for many of us it was one of the first in-person conferences in over two years. It was good to see people again, listen to talks, view some excellent posters and have some drinks and chats with old and new colleagues. We had another fantastic meeting at the MECC in Maastricht in September. The NVT were happy to facilitate the wider organisation committee of the ICT 2022, combining the EUROTOX and IUTOX in the aptly named “Uniting in Toxicology”. With over 1500 attendees there was something for everyone, great science and great discussions. The pub-up-your poison events and the band at the Gala Dinner, “Cherry and the Sugarstuds” were special highlights.

The NVT is continuing to adapt our sections and educational courses, to keep up-to-date and relevant. I am looking forward to the coming months and years to help facilitate these tweaks and developments.

Sincerely,

Paul Jennings

Ontbinding Sectie Teratologie en Reproductie-toxicologie

De afgelopen jaren heeft de sectie Teratologie en Reproductietoxicologie zich met veel plezier ingezet om het DART vakgebied te vertegenwoordigen. In dit kader hebben we verschillende symposia georganiseerd over bijvoorbeeld het Zika-virus, Obesitas en Reproductie en recentelijk in samenwerking met de sectie Genetische Toxicologie over de toepassing van stamceltechnieken. Ondanks de enthousiaste inbreng van de verschillende sprekers en variëteit in onderwerpen, zien we een afname in het aantal aanmeldingen voor deze bijeenkomsten. We zien dat de behoefte aan een DART specifieke sectie terugloopt en de doelgroep in Nederland erg klein is. Wellicht mede omdat het vakgebied in de verschillende andere secties ook is vertegenwoordigd. Daarom heeft het sectiebestuur besloten om de sectie Teratologie en Reproductietoxicologie te ontbinden. Een van de bestuursleden (Kirsten Hartman-Van Dycke) zal zich aansluiten bij de sectie Geneesmiddelen Toxicologie en hier het DART vakgebied representeren. We willen de bestuursleden en leden van de sectie bedanken voor hun inzet in de afgelopen jaren.

Namens het Sectie bestuur:
- Manon de Raaf – Beekhuijzen (voorzitter)
- Josianne van Vliet (secretaris)
- Sjors Schulpen (algemeen bestuurslid)
- Kirsten Hartman – Van Dycke (algemeen bestuurslid)

TERUG NAAR INHOUD

ARBEIDSTOXICOLOGIE

Verslag symposium "Groepsaanpak van Stoffen"

Voor de hazard- en risicobeoordeling op de werkplek

Symposium georganiseerd door de Sectie Arbeidstoxicologie van de Nederlandse Vereniging voor Toxicologie en de Contactgroep Gezondheid en Chemie, **10 maart 2022**.

Om de blootstelling aan schadelijke stoffen op de werkplek te reguleren kan worden gekozen voor een groepsaanpak. Voorbeelden hiervan zijn te vinden bij de restricties van CMR-stoffen (carcinogene, mutagene en reproductietoxische stoffen) in REACH en CLP, en bij wettelijk vastgestelde grenswaarden voor bijvoorbeeld PAK's en cadmiumverbindingen. Het definiëren van groepen stoffen blijkt echter een uitdaging en zo'n groepsaanpak wordt in de praktijk nog maar weinig toegepast. In dit symposium voor arboprofessionals (toxicologen, arbeidshygiënisten, bedrijfsartsen) zijn de laatste ontwikkelingen op het gebied van groepsaanpak aan bod gekomen. De verschillende sprekers hebben aandacht besteed aan wat onder groepsaanpak wordt verstaan, wat de barrières zijn om het in de praktijk toe te passen, wat de wetenschappelijke en wettelijke mogelijkheden zijn voor het groeperen van stoffen en hebben voorbeelden uit de praktijk gegeven.

Sprekers
- Wat is een groepsaanpak en wat zijn de voor- en nadelen ervan?
  Jolanda Rijnkels, Gezondheidsraad (op persoonlijke titel)
- Wetenschappelijke methoden en ontwikkelingen voor een groepsaanpak
  Dinant Kroese, TNO
- Een grenswaarde voor diisocyanaten als groep
  Remko Houba, NKAL
- Het kiezen van een groepsaanpak t.b.v. de restrictieregelgeving: een paar praktijkvoorbeelden
  Emiel Rorije, RIVM

Presentaties
Te vinden op de website van de Contactgroep Gezondheid en Chemie

Uitgebreid verslag
Aangeboden aan het Tijdschrift voor Toegepaste Arbowetenschap. T.z.t hier te vinden.

Report NVT Annual Meeting 2022

Last spring, the annual NVT meeting was held live and in person again, on May the 24th and 25th at the Reehorst in Ede. A total of almost 200 professionals, PhD candidates and students attended the two-day event. The theme of the annual meeting was: Green Deal, toxicology matter(s). The European Green Deal sets the EU on a course to become a sustainable climate neutral and circular economy by 2050. An important part of the Green Deal is the Chemicals Strategy for Sustainability. It is a first step towards the EU's zero pollution ambition for a "toxic-free" environment.

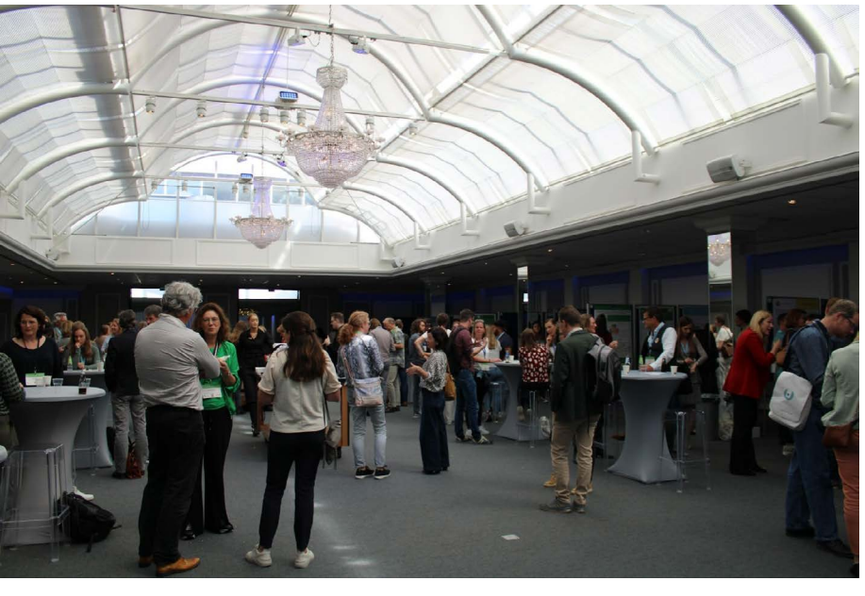
Dr. Matthias Herzler (BfR) kicked-off the meeting with his keynote lecture titled: "The Times, They Are A-Changin' – on the Role and Responsibilities of Regulatory Toxicologists in the Life and Times of the European Green Deal". Matthias discussed his personal perspective on the "European Chemicals Strategy for Sustainability" (CSS) within the "European Green Deal" as an experienced regulatory toxicologist. He raised critical questions regarding both the motivation and the science behind the CSS, such as "What is good regulation?", "What is poor (or good) science?" and "What are their consequences?", which provoked some interesting discussions throughout the whole meeting.

The keynote lecture was followed by a break, which was combined with a poster session. The big salon of the Reehorst was filled with beautiful posters displaying all sorts of interesting and important research. This session gave young scientists the chance to present their latest findings. The posters could be viewed during all breaks and participants were scheduled to present their poster to the jury during their allocated time slots. ⇨

After the break, it was up to three PhD candidates, **Hedwig van Hove** (Radboudumc), **Wenbo Wu** (Maastricht University) and **Tim Somers** (Radboudumc), in their third or final year to present their research during the PhD platform session.

Next, we had the first themed session about 'Non-standard endpoints' (NSE). **Nico van den Brink** (WUR) started off with the NSE in environmental toxicology, followed by **Harm Heusinkveld** (RIVM) addressing neurotoxicity testing and **Raymond Pieters** (IRAS/UU) ended the session with immunotoxicity.

The second themed session covered Next generation risk assessment with **Dinant Kroese** (TNO) discussing hazard and risk assessments based on new approach methodologies (NAM) while **Andrew White** (Unilever) presented industry case studies where NAMs were developed and applied for NGRA. Lastly, **Mark Cronin** (LJMU) finished with his presentation on how to make adverse outcome pathways (AOPs) quantitative, from knowledge and data to safety assessment.



Emma Kasteel was awarded the 2022 Joep van den Bercken PhD award for her dissertation 'Next Generation Risk Assessment of Chemicals: *in vitro* and *in silico* approaches to work towards enough precision to make a decision'. She presented an overview of her complete research project.

The closing session on May 24 was titled '**Future proofing NVT: moving our sections forward**.' The NVT is made up of seven specialty sections which differ in size and scope. Some sections have many participants while others struggle to attract sufficient participants for their activities. A survey was sent to all participants so the board could know more about the opinions of NVT members on the current sections and if they have new ideas for the future of the sections. The results were discussed during this session. Afterwards it was time for a reception with drinks and a walking dinner at the Reehorst. During the evening program a fierce pool competition was held at Q's pool centrum.

The second day, the 'young scientists' day, was opened with a keynote lecture by **Majorie van Duursen** (VU) titled 'Thirty years after "Wingspread" – endocrine disrupting chemicals: past, present and future'. During her lecture, she described the developments behind the discovery and acknowledgment of the concept of endocrine disruption to understand current issues and address future perspectives on endocrine disruption.

The PhD/MSc speed presentation session included short 3-4 minute presentations in which students highlighted their most interesting and remarkable findings. They were given by **Victor Amstutz** (Maastricht University), **Leonie Czernik** (Radboudumc), **Maxime Birza** (UU), **Adele Selma Ferrario** (KWR), **Charlotte Hoogstraten** (Radboudumc), **Yara Minten** (VU), **Laura Samrani** (RIVM), **Damian Roelofsen** (Radboudumc) and **Christy Tulen** (Maastricht University).

In the next session the participants attended one of the three workshops. During the '**Safe-by-design - a Serious Game'** workshop, the implications of Safe-by-Design were explored through a fictitious design process of a novel nano-enabled product. In the '**Theatre skills**' workshop participants unravelled the secrets of theatre performance that can make their presentations inescapable. ⇨

The third workshop was an **'Introduction to Benchmark Dose (BMD) analysis and PROAST'**. After completing this workshop the participants were able to perform a BMD analysis independently, using the PROAST software.

The last session of the meeting was the career session. The career session was moderated by **Lenny Kamelia** who guided an interesting discussion between the audience and the session panellists, i.e. **Peter Theunissen** (CBG-MEB), **Martijn Roosenboom** (Shell) and **Majorie van Duursen** (VU). Each panellist works in a different field, namely in regulatory, at a company or in academia. The attendees were able to ask questions on what choices the panellists had to make to get where they are in their career and if they perhaps regret one of these decisions.

The second and last day ended with an award ceremony. All posters and presentations were thoroughly judged by the NVT jury, which consisted of experts from academia, industry and regulatory agencies. As expected, the competition was high since a lot of valuable and novel research was presented. The people that were awarded for their presentations were: **Hedwig van Hove** (Radboudumc, PhD platform award), **Irene Gosselink** (Maastricht University, PhD poster prize), **Celia Arenas González** (UU, MSc poster prize), **Christy Tulen** (Maastricht University, PhD speed presentation), **Yara Minten** (VU, MSc speed presentation) and **Winnie Henderson** (UU, participation award).

We look back on a great event with lots of great lectures, presentations, posters and social interactions. Once again, we would like to thank everyone who was, directly and indirectly, involved in participating and organizing the annual meeting of 2022. Next year's annual meeting will be organized by the NVT board members Juliette Legler and Peter Theunissen. The PhD organising committee consists of Viënna van de Laarschot, Irene Gosselink, Julia Meerman, Nathalie Dierichs, Kiri Romano Olmedo and Joyce van der Heijden. We're looking forward to seeing you next year!

2022 organising committee - Hans Bouwmeester, Paul Jennings, Martijn Rooseboom, Peter Theunissen, Annemijne van den Berg, Joyce van der Heijden, Merel van der Most, Lennart van Melis, Nienke Ruijter, Fabian Wagenaars

So save the date: June 7-8, 2023, the Reehorst, Ede! Any input or ideas can be emailed to nvtmeeting@gmail.com!

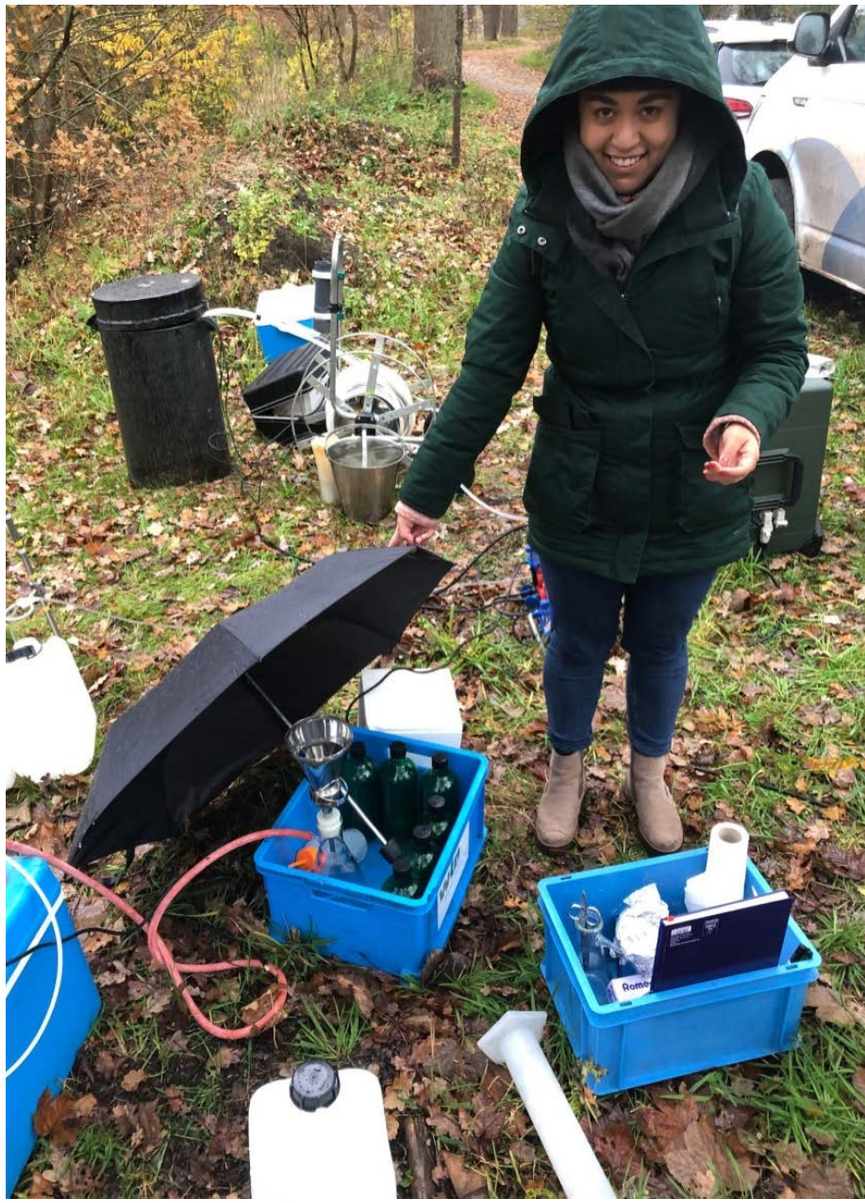
Bioremediation Technology and its Potential for Application in Groundwater Systems

Groundwater, together with glaciers and polar icecaps, are the main reservoirs of freshwater in the world. In the Netherlands, more than half of the drinking water is produced from groundwater. Recent studies have shown that some contaminants such as pesticides, are present in groundwater systems as micropollutants, namely at nanogram to microgram per liter concentrations. These pollutants still enter groundwater systems despite reductions in pesticide use in the last decades.

By *Andrea Aldas-Vargas, Wageningen University Department of Environmental Technology*

Biodegradation is a natural process that contributes to micropollutant removal. Bioremediation is an environmentally friendly technology that relies on living organisms to biodegrade contaminants. In-situ micropollutant remediation represents a very promising sustainable measure. Yet, in-situ remediation is a delicate process because drinking water sources need to be protected from any activity that is a risk for drinking water production. Biodegradation processes in groundwater can be restricted by the depth-dependent redox conditions and the oxygen-limited oligotrophic environment. The main goal of my PhD project was to better understand the biological and environmental factors playing a role in the biodegradation of pesticides at micropollutant concentrations in groundwater systems, with the eventual goal of using this information to better assess and enhance biodegradation processes in drinking water wells.

During my project, microbial communities in real groundwater locations used for drinking water production were explored and the main selective pressure exerted on groundwater microbial communities were identified. The microbial community composition in two monitoring wells was studied using 16S rRNA sequencing technologies together with groundwater geochemical and pesticide composition. The sequencing data revealed that taxonomic classification was limited by the lack of groundwater reference sequences in databases. Geochemical conditions showed to exert selective pressure on microbial communities in the field despite the presence of pesticides. Further, the microbial communities' metabolic potential for pesticides biodegradation in groundwater systems was explored. Using metagenomic data, microbial communities were taxonomically classified and a snapshot of the metabolic capacity of microbial communities for some micropollutants biodegradation is presented. The microbial communities from ten monitoring wells were studied using metagenomics data together with groundwater geochemical and pesticide composition. Field microbial communities showed to still be difficult to classify taxonomically by the use of metagenomics. Although there is still a lack of information about anaerobic ⇨



pesticide biodegradation enzymes, potential biodegradation enzymes for other micropollutants was observed in field microorganisms.

In terms of bioremediation technologies, the microbial pesticides biodegradation capacity of field samples was tested under laboratory conditions. For that, groundwater samples containing field microbial communities were used to set up biostimulation laboratory batch experiments. Groundwater samples were amended by different stimulants such as nitrate, oxygen, and DOC. The results of these experiments revealed that oxygen+DOC was the most effective amendment for 2,4-D removal after 42 days. More importantly, it was demonstrated that there is pesticides biodegradation capacity in the field but not the right conditions for microorganisms to be actively biodegrading. Biostimulation showed to be an effective remediation technology with potential for application in groundwater systems. Additionally, the potential of an exogenous inoculum to enhance pesticide biodegradation in column experiments was studied. Column experiments were set up with real aquifer material resembling different redox conditions present in the field. The existing microbial community was modified by two bioaugmentation inoculations per column. The pesticides biodegradation activity was monitored before and after the addition of an active biodegradation inoculum. The added inoculum had a temporary effect on the pesticide removal efficiency under different redox conditions. For iron-reducing conditions, bioaugmentation resulted in an increase on 2,4-D removal efficiency in both inoculations. For sulphate-reducing conditions, the first inoculation increased 2,4-D removal efficiency and the second one resulted in a decrease in removal efficiency. Thus, bioaugmentation showed to have potential for the removal of 2,4-D under emulated challenging groundwater environmental conditions.

The most interesting finding of my PhD project is that there is 2,4-D biodegradation potential in groundwater microbial communities but environmental conditions need to be improved. Furthermore, traditional remediation technologies showed to have potential for the removal of pesticides in groundwater systems. There is still room for research especially regarding the effect of low concentrations on pesticide removal, the effect of environmental conditions on biodegradation of specific pesticides, and the mineralization processes in the subsurface. Field microbial communities and their metabolic potential and activity need to be further studied as well.

From a technological perspective, more investigation is necessary to better understand the pesticides fate in the environment, to determine the effects of groundwater flow on pesticide fate and microbial communities, to develop effective tools to monitor biodegradation and to understand the potential risks associated to bioremediation technologies.

The research conducted during my PhD project aimed at understanding the environmental factors that exert pressure on field microbial communities, with the eventual goal of using this information to better assess natural attenuation. This project was conducted in close collaboration with drinking water companies that allowed the unique opportunity to access production locations, and learn from historical monitoring data. My research project showcases how academia and companies can benefit from each other to tackle environmental problems that are of societal relevance.

Currently, I work as a Postdoctoral Researcher in the Department of Environmental Technology at Wageningen University. The research project where I collaborate takes place at a former Manufactured Gas Plant (MGP-site) production facility, which is now the Griftpark in Utrecht. In the 100 years of operation, tar residues of this gas production ended in tarpits in the soil. At present, the transport of aromatic compounds to deeper groundwater is controlled by technological measures. The research aims to replace the technical measures by Nature Based Solutions (NBS) to protect the deeper groundwater from contamination. In this project, the municipality Utrecht, Deltares and University Utrecht are also involved. Next to my role as a researcher, I contribute in creating public communication strategies related to the power of microbes and their role in the Griftpark project.

Down the drain: the case of pharmaceutical residues in surface water

By *Carolien Schophuizen*

We are all aware of the beneficial effects of pharmaceuticals on human and animal health, food production and economical welfare in general. However, one area for which we still could use some common understanding, are the effects on pharmaceuticals and their degradation products in the environment. Pharmaceuticals are constantly released, and the quantities used and discharged are increasing through pharmaceutical manufacturing, consumption as well as improper disposal of expired products. This increase is connected to an aging population, increasing lifespans, economic growth as well as engineering of new pharmaceuticals or higher dosing and prolonged use. Some of us may be aware that the presence of pharmaceuticals in the environment has also been adopted as an emerging policy issue, under the UN strategic approach to international chemicals management (www.saicm.org). The OECD, the WHO and the UN environment program have been tasked with assisting countries to address this issue.

In 2019 a report was published by the OECD, which not only focused on the potential consequences of pharmaceutical residues in freshwater, but also addressed the policy responses to prevent and remedy emerging concerns [8]. The report stresses that, because pharmaceuticals are intentionally designed to interact with living organisms at low doses, even low concentrations in the environment can have unintended, negative impacts on freshwater ecosystems. For example: psychoactive compounds may disturb fish behavior making them less vigilant [10, 14]; endocrine disrupting substances may interfere with thyroid-dependent processes that are fundamental for amphibian metamorphosis [9]; and the release of antibiotics into freshwater could exacerbate the advance of antimicrobial resistance [11]. In general, assessing the risk of all possible scenarios (the abundance of pharmaceuticals on the market, mixture combinations, other chemicals, exposure pathways, additive or inhibitory effects, transformation products etc.) is not considered feasible.

The OECD report identified potential vulnerabilities in the current policy responses, and provided recommendations on how they may be improved. Currently, country responses are mostly reactive; the focus is on monitoring, substance by substance, which is very resource intensive. This results in the vast majority of pharmaceuticals remaining unmonitored. Also, wastewater treatment plants cannot remove all pharmaceuticals efficiently, and cleaning all contaminants requires costly, and high-energy technologies. Therefore, a lifecycle approach for pharmaceuticals is recommended. In such an approach, action is taken from the design phase though to the disposal. According to the OECD report, policies can be applied at every stage of this lifecycle, as indicated below.

1. Improve knowledge understanding and reporting of the occurrence, toxicity and impacts of pharmaceuticals in the environment. What is the relative risk of pharmaceuticals in comparison to other contaminants in water? More data sharing is recommended to increase the accessible body of knowledge and reduce unnecessary testing (**see Box 1**).

2. Source directed measures could include the focus on environmental risks in risk-benefit analyses for pharmaceutical authorization, as well as prioritization of substances and water bodies of highest concern. The development of biodegradable pharmaceuticals, was proposed though it is questionable if the stability of such pharmaceuticals would be adequate to certify the quality of the product for the user during its shelf life and in-use period [6].

3. Use oriented measures directed at promoting sustainable use.

4. And lastly, end-of pipe measures were suggested to include upgraded wastewater treatment plants, public take back of unused drugs. ⇨

BOX 1:
For active substances that were marketed after 2006 an environmental risk assessment dossier is provided to the national authorities (nationally authorised products) or the European Medicines Agency (centrally authorised procedures). When a certain trigger value, based on the use of the substance, is met, this dossier contains experimental studies. However, the outcome of this risk assessment and the underlying data are often not publicly available or very hard to find. Dutch water managers have often voiced their need for this data [7]. As this can only be solved in the European context, the Netherlands have been lobbying in the European arena and with industry to increase the availability of this information. Currently, the European Commission has stated in their Strategic Approach that there should be a Union-wide database. The pharmaceutical industry, together with universities and public partners such as the European Medicines Agency and National Institute for Public Health and the Environment (RIVM), is working on developing a database to meet these requirements within the IMI-PREMIER project (www.imi-premier.eu).

Implementation of policies take time. Collaboration between stakeholders is required and needs to be set up; government, pharmaceutical industries, wastewater treatment facilities, NGO's and academia are required to work together on this.

In 2020, Wöhler et al. reported that even though there are no limit values regarding the toxicity of a mixture of pharmaceuticals in water, the contribution of pharmaceutical water pollution is still significant compared to other forms of water pollution [13]. Thousands of papers have been published on pharmaceuticals in water bodies over the world, in the last 30 years. However, according to a review by Sumpter et al. (2022) many of these papers focused on the detection of only a small group of pharmaceuticals, while there is limited to no information on ecotoxicity or human effects of the vast majority of pharmaceutical micropollutants [12]. They argue that, thanks to analytical chemistry, it is known and clear, that many pharmaceuticals are present in the aquatic environment across the entire world (e.g., Wilkinson et al., 2022). Nonetheless, it is robust, reliable (eco)toxicity data that are still lacking.

Of course, work is being performed regarding the (eco) toxicity of pharmaceutical microcontaminants. In a recent published work, Hejna et al. (2022) examined the occurrence and ecotoxicity of pharmaceuticals in water, and summarized the toxicity of NSAIDS on non-target organisms [4]. Here, again it was noted that there is limited insight into the propagation of the effects of pharmaceutical contaminants from the lowest to the highest trophic level, as well as a need for information on their effects at cellular and tissue levels in freshwater species.

The case-by-case and substance-by-substance toxicity evaluation of active substances and their metabolites in water is bound to be a near endless and very time-consuming task. The development of models may give policy makers a slightly better starting point to develop actual mitigation and control strategies. Though models may never be perfect, they could certainly provide us handholds. For example, the development and use of *in silico* tools and QSARs could aid in the prediction of toxicity and assessment of the impact of biologically active contaminants [5]. Also, models have been developed to derive PECs (predicted environmental concentrations) for chemicals [1].

In a study by Duarte et al. (2022), which was part of the MEDUWA project (Medicijnen Uit het Water, https://www.meduwa.uni-osnabrueck.de/en/), the concentrations of pharmaceuticals in the Vecht river in the Netherlands were estimated by making use of a GREAT-ER model (geography-referenced regional exposure assessment tool for European rivers) to derive PECs [2]. In the applied model they also took into account the trans-boundary pharmaceutical consumption patterns, social economical factors, environmental factors and spatiotemporal information. By combining this information with existing ecotoxicological data and PNECs, the ecological risk quotients (RQs) were calculated for this water body under different scenarios. The study revealed the significance of appropriate area-specific models and the use of ecotoxicological information. In another study by the same authors, an exposure model was developed and used to assess the human health risk of oral and dermal exposure under a variety of exposure conditions [3]. In the extreme scenarios (both considering environmental and human factors), API mixture risks were found of potential concern, while the risks of individual APIs were negligible. Showing again that a deterministic exposure model can be used to estimate (health) risks of pharmaceuticals in the water environment. The studies are an example of a collaborative effort towards the use ⇨

of a model to support local authorities in the development of risk-management strategies that are both feasible and locally relevant.

In conclusion, pharmaceuticals are an integral part of our society nowadays. It is clear that their use may also affect our environment. Estimating the impact of this specific category of contaminants in surface water is complicated due to their many forms and presence as a complex mixture among other contaminants. The availability of data regarding the (eco)toxicity, transport, occurrence and fate of pharmaceuticals in the environment, can still be considered a key starting point for thorough risk assessment, and is required as a basis for the development of management strategies at every stage of the lifecycle of a pharmaceutical product.

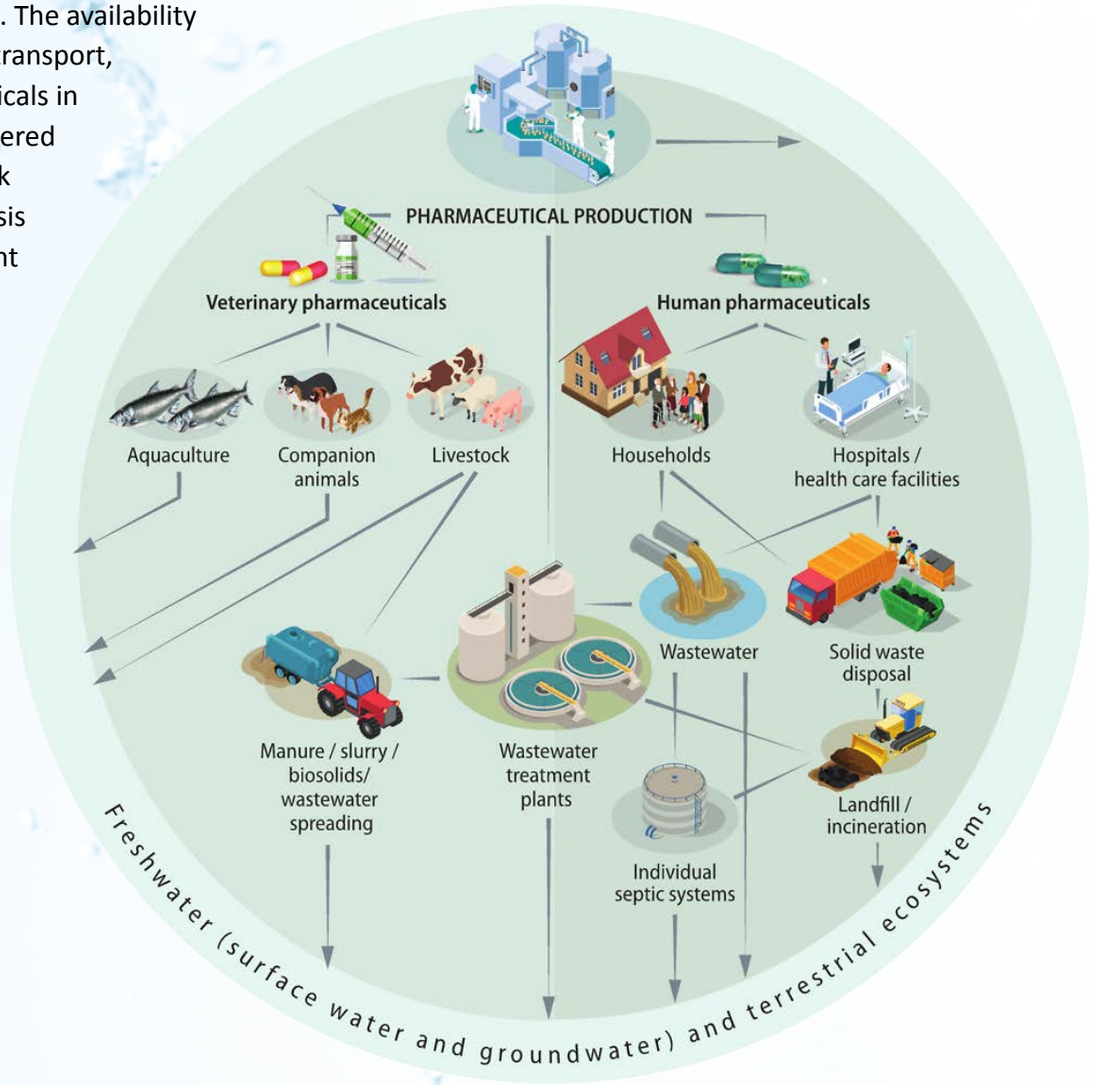


Figure 1: Origins of pharmaceutical residues in freshwater and terrestrial ecosystems, reproduced from OECD report on Pharmaceutical Residues in Freshwater [8]

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TERUG NAAR INHOUD

Pollution due to floods and droughts

By *Damiën van Berlo*

To sustain life on Earth, there are only a few critical necessities. One of those is liquid water. As much as we need it to survive, there is a dark side to water as well. Water in itself is hardly toxic at all; the LD50 is over 150 ml/kg in rats. In very specific conditions (such as marathon running), people have been known to die from water intoxication. The actual cause is hyponatremia, characterized by sodium levels dropping below ca. 135 mmol/L. Even if water poisoning does happen occasionally, but for the most dangerous properties of water we should look elsewhere. Over the last century, the frequency and duration of floods and droughts has increased greatly. The Dutch are all too familiar with the risks associated with water (1953 is still a national trauma), but as a people, we are usually quite well able to manipulate and control it. A lot of our country is below sea level and was turned into land by our ancestors, by building dikes around certain parts of the sea and then draining the area inside of water. For the average Dutch person, serious drought is less common than flooding, although the summer of 2022 was particularly dry. Let's have a look at both phenomena with the eye of a toxicologist.

Too much of a good thing…

Flooding is one of the most commonly occurring natural disasters, and its effects have immense impact. Homes are washed away and people drown in the raging torrents; these are the immediate effects. There are also secondary effects that are less visible and probably less terrifying to behold, but claim even more lives.

In the top 10 of deadliest floods (no, the 1953 North Sea Flood doesn't even come close) in human history we find multiple incidents in China. The Yangtze Kiang and Yellow River are notorious for swelling beyond their banks under conditions of heavy rain. In 1931, the Yangtze Kiang and Huai River had swollen to enormous proportions due to heavy rainfall. According to the official report, 140.000 people drowned, with many more perishing due to lack of food and a cholera epidemic. Estimations of the total death toll vary wildly. A similar event occurred in 1887, with the Yellow River overcoming its dikes, inundating 130.000 km2 of land including agricultural settlements and commercial centers. Two million people lost their homes and a million or more people died either by drowning or by the famine and infectious disease epidemics. In 1975, the Banqiao dam failed due to immense rainfall by typhoon Nina, and a wave of 3 to 7 meters high and 10 km wide brought death and destruction to the Chinese people.

A recent example is the 2022 Pakistan flood, caused by melting glaciers and heavy monsoon rain; almost 2000 people died and 10-12% of the country was submerged. There has been an increased risk of waterborne diseases including diarrhea, cholera, dengue and malaria. Also, most people still remember the Boxing Day tsunami in 2004 very well; around 230.000 people were killed in 14 different affected countries. The video footage of tourists and natives fleeing the beaches, running for their lives, is still chilling today.

In the Western world, floods are less common due to milder/colder climate conditions. A less known effect of floods also commonly occurs in the West however; flood-related pollution. Raw sewage often mixes with flood waters and spreads throughout the inundated region, potentially ⇨

Hankou city hall during the 1931 flood (source: Wikipedia)

contaminating drinking water supplies. Inhabitants are warned to be careful with the flood water, to prevent children from playing in it and to boil water intended for drinking.

Also, runoff due to heavy rainfall is a problem due to the pollution it causes; it is often considered as one of the most significant contributors to water pollution. Stormwater runoff is the water that runs off roofs and driveways and for instance picks up fertilizers, oil, pesticides, dirt, bacteria as it flows towards streams, rivers, lakes and finally the ocean (*Zhang et al., 2020*; *Revitt et al., 2014*).

Too little of that good thing might be even worse

Like floods, droughts have been one of the most deadly type of natural disaster in the last decades. According to a recent report, in the last 50 years droughts have caused 650.000 fatalities (*WMO, 2021*). Most fatalities have been in Africa, with the severe African droughts of 1975, 1983 and 1984 contributing significantly. Worryingly, both the number of droughts *and* their duration has been increasing since 2000; in a United Nations it is estimated that by 2050, 4.8 to 5.8 billion people will live in areas that are water-scarce at least once month each year (*UNCDD, 11 may 2022*).

Copernicus Sentinel-2 satellite images show the stark difference between August 2021 and August 2022 on the Rhine River near Cologne (source: ESA)

Drought also has toxicological significance. When the water flow of rivers and streams is reduced, pollutant concentrations rise. In the summer of 2022 (*WeerOnline website, 18 Aug 2022*), in the Netherlands the Rhine water flow was only 650 m3/sec, which is much lower than the average flow of 2200 m^3/sec. This flow is lower in summer of course compared to the yearly average, roughly around 1500 m^3/sec (https://clintel.nl/hoe-uitzonderlijk-is-die-lage-rijnwaterstand/). If the water flow is reduced to only 50% of the average, the concentration of pollutants could be expected to double if all other factors remain the same. During the most recent summer, there was a mass mortality event in the Oder river which involved fish, beavers, clams, crayfish and other wildlife (*ABC news, 12 Aug 2022*). The cause of this is not yet clear, but it is thought that it might have involved higher nutrient concentrations leading to reduced oxygen levels and increased concentrations of pollutants. Analysis of water samples has led to various potential culprits identified, including salts, golden algae bloom, mercury poisoning and mesitylene (a benzene derivative); the Polish and German governments differ in their opinion on the main responsible factor. It is possible that this mass mortality event is not due to concentration increases related to low water flow, but to a large amount of chemical waste that was dumped into the river (*ABC news, 12 Aug 2022*). A combination of both is very well possible. Whatever the cause, it will take the river years to recover from this ecological disaster.

What might be more surprising, is that drought can also affect air pollution. The ambient air will be more dusty under arid conditions, and thus can contain increased levels of particulate matter. Toxic algal blooms can release airborne toxins (*CDC, Health Implications of Drought*). But also, under dry conditions ozone levels can increase, because plants shrink their stomata to prevent water loss, which reduces their ability to take up ozone (*Demetillo et al., 2019*). This reduction was found to be around 15% during a severe drought in California, USA (*Demetillo et al., 2019*).

As a conclusion to the above, it is safe to say that although pollution is probably not the *main* problem associated with flooding and drought, it does add insult to injury...

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Drying Lakes Raise Toxicity Concerns

Utah's Great Salt Lake and California's Salton Sea have been reported to be releasing "Toxic Dust"

By *Barae Jomaa*

Utah's Great Salt Lake and California's Salton Sea are some of the largest salt lakes and, as they are both drying up[1], heavy metal rich lakebed sediments are becoming exposed to the winds[2,3]. Salt lakes form when the water flowing into the lake cannot escape to the ocean (terminal lake). The source of the heavy metals can be either natural or resulting from human activity.

The weathering of rocks and soil erosion over long periods of time, supply water bodies with heavy metals. Water will normally contain trace amounts of heavy metals and most countries have limits on the levels of heavy metals that are allowed in drinking water[4]. As an example, according to the World Health Organisation, arsenic is naturally present at high levels in the groundwater of Argentina, Bangladesh, Chile, China, India, Mexico, and the USA. Nonetheless, mining exposes water bodies to at least ten times more metals from metal-bearing ores than natural phenomena[5].

While mining and industrial production have taken some of the blame for the Great Salt Lake's heavy metal content, the heavy metals in the Salton Sea are thought to be mostly of natural origin, likely with some contribution from agricultural run-off[2,6].

Arsenic, cadmium and chromium can negatively affect DNA repair and synthesis while lead and mercury are known to affect the central nervous system and can be particularly toxic to the developing brain[7,8]. Epidemiological studies have found a strong link between heavy metal exposure and chronic diseases including cancer, cardiovascular disease, diabetes, degenerative neurological conditions, kidney disease, respiratory diseases and skin ailments[9].

Given the hazard, there is rising concern that dust arising from the drying lakes will represent a potential risk to neighboring towns, especially during fall and spring when winds are the strongest[10]. Joel Ferry, a Republican state lawmaker, has even called the drying of the Great Salt Lake an "environmental nuclear bomb", as reported by the New York Times[11].

An exhaustive study on dust and its heavy metals content in and around the Great Salt Lake was conducted by Kevin Perry, Professor in Atmospheric Sciences at the University of Utah. Dr. Perry and his colleagues found the ten most uniformly-distributed elements were antimony, arsenic, barium, calcium, cobalt, lithium, magnesium, selenium, uranium and zinc. Moreover, arsenic and lithium had average concentrations in excess of both industrial and residential EPA Regional Screening Levels (RSLs). These Regional Screening Levels (RSL) can be described as risk-based concentrations derived from standardized equations combining exposure information assumptions with EPA toxicity data (United States Environmental Protection Agency, 2020). The researchers also found that the low spatial variation of arsenic and lithium might indicate that the high concentrations of these elements could be related to natural occurrence rather than the result of human activity[12].

Ideally, one would want to stop or even reverse the drying of the lakes altogether rather than have to manage the consequences. In a study by Wurtsbaugh et al. entitled "Decline of the World's Saline Lakes", the global scale of the drying of salt lakes is reviewed. The authors conclude that "in many cases" the reduction of lake inflows is related to human consumption rather than climate change[13]. This is somewhat good news as this re-emphasizes our ability change the course of history – in a positive direction. ⇨

Image: Great Salt Lake salt dome. **Image credit:** Farragutful

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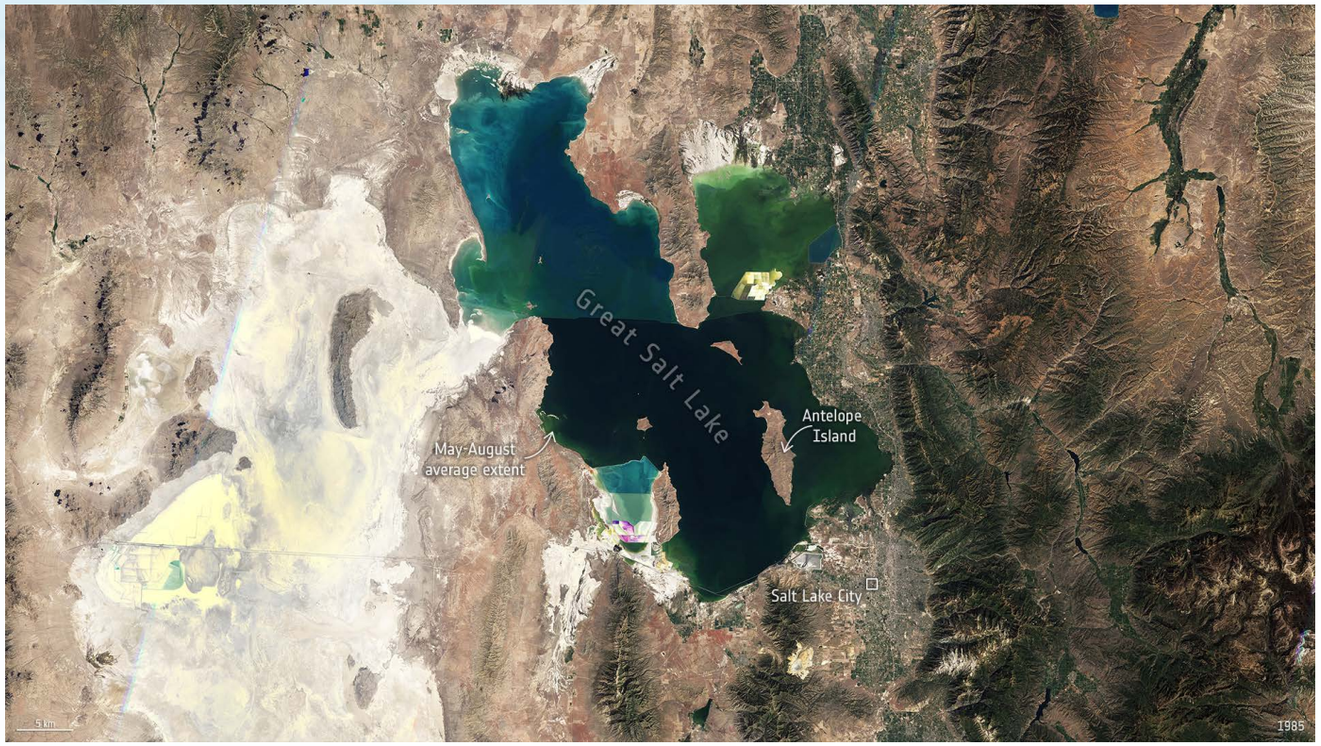

Great Salt Lake in 1985

Great Salt Lake in 2022

USGS/contains modified Copernicus Sentinel data (2022), processed by ESA

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Photo by Mat Napo on Unsplash

SARS-CoV-2 vaccinatie: nieuwe ronde, (ver)nieuw(d)e vaccins

Een bijdrage van de NVT Sectie Geneesmiddelentoxicologie

Door *Damiën van Berlo, Lambert Creuwels, Kirsten Hartman-van Dycke, Sylvia Le Dévédec, Yolanda Ponstein, Ilonka van Hoof, Daan Touw*

Op 6 januari 2021 werd een 39-jarige verpleeghuismedewerkster ingeënt met een COVID-19-vaccin, als eerste in Nederland. Het betrof hier het vaccin dat door BioNTech/Pfizer is ontwikkeld. Sindsdien is een groot deel van de Nederlandse bevolking gevaccineerd: 82.8% van de bevolking van 18 jaar en ouder heeft de basisserie van de coronaprikken gehad; voor de groep van 12 jaar en ouder geldt dit voor 80.8% (bron: Coronadashboard). Bij de ouderen, die zoals bekend erg kwetsbaar zijn voor COVID-19, liggen deze percentages nog duidelijk hoger.

Waar men initieel terughoudend was met het vaccineren van zwangere vrouwen omdat men niet wist hoe zij hier op zouden reageren (klinische studies om het vaccin te testen bevatten geen zwangere vrouwen), weet men inmiddels dat COVID-19 tot ernstige zwangerschapscomplicaties kan leiden. De belangrijkste reden voor het ernstiger ziekteverloop bij zwangere vrouwen is dat hun longcapaciteit afneemt naarmate de zwangerschap verder vordert en de foetus groeit (RIVM website, Zwangerschap en COVID, laatste update 14 oktober 2022). Inmiddels worden zwangere vrouwen dan ook uitgenodigd voor vaccinatie: de vaccins van Pfizer (Comirnaty) of Moderna (Spikevax) kunnen veilig worden gegeven tijdens zwangerschap (RIVM website, Zwangerschap en COVID, laatste update 14 oktober 2022).

Naast het BioNTech/Pfizer vaccin (Comirnaty) dat als eerste werd ingezet in Nederland, is er in ons land gevaccineerd met vaccins ontwikkeld door Moderna (Spikevax), AstraZeneca (Vaxzevria), Janssen (Jcovden) en Novavax (Nuvaxovid). Deze vaccins hebben een zeer grote bijdrage geleverd aan het beschermen van de volksgezondheid en het normaliseren van de maatschappij. Wereldwijd zijn, alleen al in het eerste jaar dat werd gevaccineerd, tientallen miljoenen levens gered door de COVID-19 vaccins (*Watson et al., 2022*).

Sinds eind 2021 is de dominante variant van het SARS-CoV-2 virus de omikronvariant, waarvan de BA.1, BA.2 en BA.5 subvarianten achtereenvolgens de besmettingscijfers domineerden. Inmiddels nadert de herfst, en het is ⇨

bekend dat een respiratoir virus zoals SARS-CoV-2 zich dan makkelijker en sneller verspreidt. Ook weten we dat de immuniteit die (booster)vaccinaties (of infectie) opleveren, geleidelijk afneemt (*Edridge et al., Nature Medicine 2020*). Inderdaad lijkt er een nieuwe besmettingsgolf te zijn ingezet en de verwachting is dat deze zal toenemen in intensiteit; hiertoe is de overheid recent (19 september 2022) gestart met de najaarsronde van de herhaalprik; inmiddels (cijfers eind september, CoronaDashboard) heeft 5% van de bevolking van 60 jaar en ouder een herhaalprik gehad, de verwachting is dat dit percentage snel zal oplopen. ⇨

Als Sectie Geneesmiddelentoxicologie vinden wij het nuttig om ons eerdere stuk in de TCDD over vaccinveiligheid (*How safe are vaccines really?*, TCDD 4, 2020) op te volgen met de huidige stand van zaken. Voor dit stuk richten wij ons op de nieuwe bivalente vaccins van Pfizer/BioNtech (*Comirnaty Original/Omicron BA.1*) en Moderna (*Spikevax bivalent Original/Omicron BA.1*), omdat die conform het advies van het Outbreak Management Team-Vaccinatie (OMT-V) voornamelijk zullen worden toegediend in de najaarscampagne (bron: *GGD/GHOR, 29 juli 2022*).

Beiden zijn vernieuwde varianten van de bestaande Pfizer/BioNtech en Moderna vaccins en zijn dus gebaseerd op mRNA-vaccin technologie. Deze technologie was ten tijde van de eerste COVID-19 vaccinaties heel nieuw en bood voordelen ten opzichte van de 'klassieke' vaccins; met name het voordeel dat deze vaccins veel sneller kunnen worden ontwikkeld. De bijzondere eigenschap van de vernieuwde *bivalente* vaccins is dat zij bescherming bieden tegen zowel de heersende omikron-variant als tegen de oorspronkelijke Wuhan-variant; vandaar "bivalent", tweewaardig. Prof. Ton de Boer (College voor de Beoordeling van Geneesmiddelen, CBG) verwoordt dit als volgt:

> "*De oorspronkelijke coronavaccins blijven effectief tegen ernstige ziekte, ziekenhuisopname en overlijden. Deze nieuwe, aangepaste vaccins zorgen voor een bredere bescherming tegen verschillende varianten. Hiermee verwachten we dat ze helpen om de bescherming tegen ziekte te behouden, ook als het virus verandert.*" **(CBG-MEB, 1 Sep 2022)**

De 'Human Medicines Committee' (CHMP) van het EMA heeft deze vaccins (*Comirnaty Original/Omicron BA.1* en *Spikevax bivalent Original/Omicron BA.1*) goedgekeurd op 1 september 2022 (*EMA nieuwsbericht, 1 Sep 2022*). *Comirnaty Original/Omicron BA.1* is getest in twee klinische studies: één in meer dan 1800 volwassenen van 55 jaar en ouder die voorheen drie doses Comirnaty hadden ontvangen (primaire vaccinatie en booster) en één in 600 personen tussen de 18 en 55 jaar oud die ook in een eerder stadium waren gevaccineerd met drie doses Comirnaty. Voor *Spikevax bivalent Original/Omicron BA.1* is een klinische studie met meer dan 800 proefpersonen van 18 jaar en ouder uitgevoerd. In deze studie wordt een vergelijking gemaakt tussen personen die alleen met het originele Spikevax (primair en booster) zijn gevaccineerd en mensen die Spikevax hebben ontvangen als primaire vaccinatie en *Spikevax bivalent Original/Omicron BA.1* als booster-vaccinatie. De EMA concludeert qua *veiligheid* dat de aangepaste vaccins kunnen leiden tot milde, kortdurende bijwerkingen; het beeld lijkt zeer op dat van de originele vaccins (Comirnaty en Spikevax). Dit is goed nieuws, omdat we van de originele vaccins van BioNtech/Pfizer en Modena weten dat deze relatief weinig bijwerkingen vertoonden.

Overigens zijn de oorspronkelijke vaccins grondiger getest in grotere studies; bij een aanpassing, zoals dat ook plaatsvindt bij de jaarlijkse griepvaccins, zijn dergelijke groot opgezette klinische studies niet nodig. ⇨

Photo by Mat Napo on **Unsplash**

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Behalve door het uitvoeren van klinische studies vóór een vaccin op de markt mag komen, worden de bijwerkingen van vaccins ook *ná* marktintroductie gemonitord door het bijwerkingencentrum *Lareb*. Hier kunnen (of moeten) zowel gevaccineerde burgers (of hun partners, mantelzorgers enz.) als zorgverleners (huisartsen, medisch specialisten etc.) meldingen doen; voor de minder ernstige bijwerkingen wordt aangenomen dat deze worden ondergerapporteerd; ze zullen beduidend vaker optreden dan gemeld. Voor ernstige bijwerkingen is het beeld duidelijk nauwkeuriger: zorgverleners zijn *verplicht* om vermoedens van ernstige bijwerkingen te melden ((Geneesmiddelenwet Art.78 lid 3). Bijwerkingen worden “ernstig” genoemd wanneer zij voldoen aan één of meer van de volgende criteria:

- leidt tot ziekenhuisopname of verlenging ervan;
- leidt tot blijvende invaliditeit of arbeidsongeschiktheid;
- uit zich in een aangeboren afwijking of misvorming;
- leidt tot de dood of levert levensgevaar op;

In deze gevallen is het bovendien waarschijnlijk dat een zorgverlener hier kennis van neemt; deze is zoals gezegd verplicht om er melding van te maken bij Lareb.

Voor de bestaande Comirnaty en Spikevax vaccins, waarvan de nieuwe varianten zijn afgeleid, zijn de ernstige bijwerkingen die incidenteel kunnen optreden een heftige allergische reactie (incidentie onbekend, maar infrequent) en een ontsteking van de hartspier (myocarditis) of het hartzakje (pericarditis) (beiden “very rare”, ofwel <1/10.000 vaccinaties, bron: bijsluiters en *Lareb, 2022*). Deze treden zoals gezegd alleen in zeldzame gevallen op, wat inhoudt in dat de vaccins over het geheel genomen zeer veilig te noemen zijn. In de media is veel aandacht geweest voor het optreden van trombocytopenie, ofwel stolselvorming in combinatie met een verlaagd aantal bloedplaatjes; dit bleek een bijwerking te zijn na toediening van de vaccins van AstraZeneca en Janssen, maar dit zijn niet de vaccins die in de najaarscampagne worden ingezet en die onderwerp zijn van dit stuk.

Aangezien de aangepaste vaccins (*Comirnaty Original/ Omicron BA.1* en *Spikevax bivalent Original/Omicron BA.1*) een overeenkomstig veiligheidsprofiel hebben als de vaccins waarvan zij zijn afgeleid, is een soortgelijk positief beeld in de algehele populatie te verwachten voor deze breder beschermende middelen.

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Reactie Op Het Artikel
‘Concern Over Benzene in Personal Care’

Het artikel ‘Concern Over Benzene in Personal Care’ in mijn optiek om nuancering vraagt. Want zoals het nu in het artikel wordt geponeerd, geeft dit op mij als lezer een stellige indruk dat benzeen een wereldwijde risicokwestie is voor in cosmetica. Een kwestie die tot nu toe onderbelicht is, al was het maar door het afsluitende citaat: ‘Over the past two years, it has become increasingly clear that benzene is present all around us, not only in the air we breathe but also in the personal care products that we use on a daily basis.’

Door *Remco Schade, Veiligheidsbeoordelaar van cosmetische producten & productontwikkelaar, CosTec*

Echter, de auteur refereert in zijn artikel nadrukkelijk naar enkele cosmetica-benzeenincidenten in de Verenigde Staten (VS). Terwijl in vele andere landen & statenverbanden striktere regels gelden voor wat betreft benzeen- en onbedoelde sporen hiervan- in cosmetica. De VS loopt in deze bijvoorbeeld achter op de Europese Unie (EU), waar de autoriteiten het voorzorgsprincipe hanteren. Hierdoor is het gebruik van een CMR-stof als benzeen per definitie verboden, opgenomen in de Annex II van Verboden Stoffen in de Cosmetica Verordening. De auteur stipt dat in zijn inleiding gelukkig ook even aan.

Door het voorzorgprincipe zal een veiligheidsbeoordelaar in de EU geen cosmetica mogen goedkeuren welke een significante hoeveelheid aan benzeen bevat. Zoiets kan in de VS dus wel gebeuren, mede doordat er geen wettelijk verplichting is tot productveiligheidsbeoordeling en de producten daar sowieso aan minder complexe zuiverheidseisen dienen te voldoen.

Een ander benzeenrisico waar de auteur de lezer op wijst, dat is ‘Carbomer’, waarbij benzeen als proceshulpstof bij de vervaardiging van dit polyacrylzuur wordt ingezet. Echter, in tegenstelling tot in de VS, mag zo’n klassieke type carbomeer in de EU (allang) niet meer worden toegepast in cosmetica. Benzeen is daarin namelijk technisch vermijdbaar, kan als proceshulpstof vervangen worden door veiliger alternatieven zoals cyclohexaan. Een veiligheidsbeoordelaar zal geen akkoord geven op een cosmetische formule waarin benzeen-carbomeer is verwerkt, noch mag een fabrikant zo’n eindproduct legaal op de EU-markt brengen.

Laatste opmerking, de UV-filters: de OTC-geneesmiddelenstatus van zonbeschermingsproducten in de VS zorgt voor de nodige beperkingen in hun innovatie. Zodat men vaak nog noodgedwongen met oudere types UV-filters in hoge concentraties formuleert: Avobenzone, Oxybenzone, PABA en dergelijke stoffen. Buiten de VS worden zulke UV-filters tegenwoordig op veel beperkter schaal toegepast. Soms zijn ze zelfs niet meer toegestaan- of nog uitsluitend in lage concentraties, zijn vaak opgevolgd door geavanceerdere types UV-filter. Waardoor de benzeen-kwestie wegvalt.

Resumerend, van benzeen staat vast dat het gezondheidsschadelijke effecten kan veroorzaken, als zodanig in vele landen & statenverbanden onderhevig aan strenge veiligheidscriteria voor in cosmetica. In de VS is er sprake van een andersoortige (risico)situatie & perceptie, wat tot de nodige incidenten heeft geleid.

Immediate risk management suggested for 300 harmful chemicals

Assessing chemicals in groups has sped up authorities' work, with assessments for 1 900 substances finalised in 2021. For around 300 of these, risk management actions could begin immediately.

Helsinki, 17 June 2022 – ECHA's fourth report under its Integrated Regulatory Strategy has been released, showing that considerable progress has been made on accelerating the pace at which regulatory actions are identified for substances of concern.

In 2021, assessments were finalised for more than 1 900 substances, mostly grouped based on their structural similarity. This was 30 % more than in 2020. Around 300 of these substances require risk management measures, while 800 do not currently require further action. The remaining 800 need more data to be generated, and around 350 of these are expected to move to risk management in the future.

Since group assessments became the focus, from 2019 to the end of 2021, a total of about 3 800 substances have been assessed – including 134 phthalate and phthalate-like substances and 148 bisphenols. The first batch of 19 group assessments was published at the end of 2021 and covered more than 450 substances.

Around 25 % of the assessed substances require further risk management. Some need to be restricted and have been included to the European Commission's Restrictions Roadmap. The assessments will continue to feed into the roadmap and directly contribute to the aims of the EU's Chemicals Strategy for Sustainability and the Green Deal.

This leaves 75 % where no further regulatory action is currently needed, because they are low hazard, the potential for exposure is limited or there are already risk management measures in place.

But hazards need to be confirmed before risk management actions can start, and more data is often first needed. Companies need to proactively update their registrations with up-to-date information to avoid regulatory actions being planned based on outdated data.

ECHA's report also highlights a steep increase in substances needing harmonised classification and labelling (CLH), with the number tripling in 2021 compared to 2020. With CLH often a prerequisite for moving ahead with further regulatory measures, authorities must dedicate sufficient resources and start preparing proposals for these substances to avoid creating a regulatory backlog.

The regulatory needs of almost 1 300 high-volume substances (above 100 tonnes per year) remain to be assessed.

Recommendations

- *Member States* need to dedicate resources to work on substances that need further regulatory action without delay – particularly for harmonised classification and labelling.
- *Member States and ECHA* should intensify collaboration so they can discuss and agree on which substances to prioritise. They should also use the Commission's Restrictions Roadmap to identify candidates for restriction.
- *Companies* should proactively review and update data in their registration dossiers, as the information they provide is the basis for the assessment of regulatory needs.

Background

ECHA's Integrated Regulatory Strategy aims to speed up data generation, identification of groups of substances of concern, and regulatory action. It does so by integrating different regulatory processes into one coherent approach to manage chemical risks effectively and efficiently. The strategy also encourages collaboration between ECHA, Member States and the European Commission.

The goal of the strategy is to clarify which registered substances are a high priority for regulatory risk management or data generation, and which are currently a low priority for further regulatory action.

ECHA/NR/22/13

Glyphosate: no change proposed to hazard classification

ECHA/NR/22/10

ECHA's Committee for Risk Assessment (RAC) agrees to keep glyphosate's current classification as causing serious eye damage and being toxic to aquatic life. Based on a wide-ranging review of scientific evidence, the committee again concludes that classifying glyphosate as a carcinogen is not justified.

Helsinki, 30 May 2022 - RAC has concluded that the existing classifications for glyphosate as a substance that causes serious eye damage and is toxic to aquatic life with long lasting effects should be retained. The committee found that the available scientific evidence did not meet the criteria to classify glyphosate for specific target organ toxicity, or as a carcinogenic, mutagenic or reprotoxic substance.

The committee assessed glyphosate's hazardous properties against criteria in the Classification, Labelling and Packaging (CLP) Regulation. They considered an extensive volume of scientific data and many hundreds of comments received during consultations when forming their opinion.

The new RAC opinion is consistent with the proposal of the four Member States currently assessing glyphosate: Sweden, France, Hungary and The Netherlands as well as with RAC's 2017 opinion.

The adopted opinion will be published on ECHA's website and sent to the European Commission and European Food Safety Authority (EFSA) by mid-August. EFSA will carry out its risk assessment of glyphosate, with this expected to be ready in July 2023.

The European Commission will analyse EFSA's conclusions and the renewal assessment report that was prepared by Sweden, France, Hungary and The Netherlands. The Commission will then put forward a renewal report and a draft regulation to Member States on whether the approval of glyphosate can be renewed or not.

Background

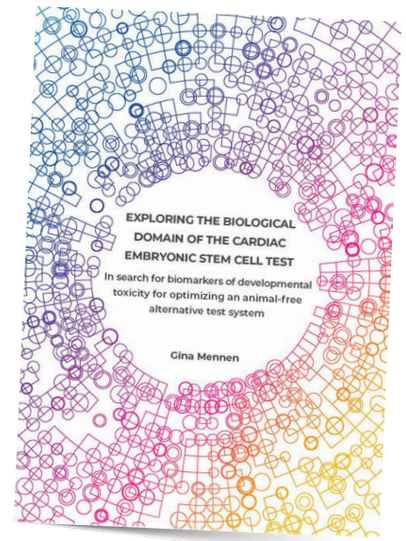
Harmonised classification and labelling
Together with the Commission and the Member States, ECHA implements the harmonised classification and labelling (CLH) process for hazardous substances. The aim is to protect people's health and the environment from those hazards that matter the most.

Harmonised classification and labelling focuses only on the hazardous properties of the substance: its potential to cause harm. It does not assess the exposure of people or the environment to glyphosate. This will be part of the peer review of the risk assessment done by EFSA.

Committee for Risk Assessment (RAC)
The Committee for Risk Assessment is made up of scientists nominated by EU Member States and appointed by ECHA's Management Board in their personal capacity. The committee has observers from different EU organisations representing civil society, academia and industry. Together, they are responsible for making scientific opinions that are then used by the European Commission and EU Member States when deciding how chemical risks need to be controlled.

Exploring the biological domain of the cardiac embryonic stem cell test

In search for biomarkers of developmental toxicity for optimizing an animal-free alternative test system



By *Gina Mennen, PhD*

On Tuesday August 30th, I defended my dissertation entitled: “Exploring the biological domain of the cardiac embryonic stem cell test - In search for biomarkers of developmental toxicity for optimizing an animal-free alternative test system”. My defence was at Utrecht University and I already knew of a few hick-ups before starting as the railway strikes were planned for that day. Fortunately, my promotors, supervisors, the committee, former colleagues, friends, and family were able to make it to the defence anyway.

I performed the research project mainly at the centre for Health Protection of the RIVM under supervision of prof. dr. Aldert Piersma. The project was supported by the French National Association for Research and Technology (ANRT) through a CIFRE PhD grant. In this collaboration also Université Paris-Saclay was involved, represented by prof. dr. Marc Pallardy. My other supervisors were dr. Nina Hallmark, dr. Helen Tinwell, and dr. Rémi Bars. I also stayed in Sophia-Antipolis (Alpes-Maritimes, France) for almost a year to apply for the PhD grant. During that time, I was working in the lab to set up the embryonic stem cell test, which is an *in vitro* model for early developmental toxicity screening.

In comparison to a complete and intact organism, *in vitro* models are relatively simplistic and have limitations such as a reduced number of endpoints or available mechanisms. Additionally, the chemical distribution in the body and chemical breakdown (metabolism and excretion) can’t be assessed *in vitro* and culture conditions may influence the test readout. These limitations including reproducibility, sensitivity, and transferability highlight the need to validate these *in vitro* systems to achieve regulatory acceptance, while maintaining or even improving the ability to support safety assessment requirements.

It is not anticipated that a single *in vitro* assay will replace 1:1 the *in vivo* models. It is more likely that a collection of several assays will be needed, where each one might answer a specific question and together an assessment of developmental and reproductive toxicity can be made. Encouragingly, multiple promising advances in test systems have been made for alternative testing for developmental toxicants, including the cardiac mouse embryonic stem cell test (mESTc). Compared to other test systems, the mESTc benefits from being almost completely animal free.

My dissertation describes investigations on the murine cardiac embryonic stem cell test (mESTc), expanding on the merits of stem cell research as a tool for predicting chemical hazards to early embryo development. The overall aim of my research was to explore the biological domain of the mESTc and to use this knowledge to better discriminate ⇨

between molecules of the same class of structurally related chemicals, by selecting gene-expression based biomarker profiles beyond cardiac differentiation.

Two approaches were used for identifying gene transcripts as potential biomarkers. A hypothesis-driven targeted approach of biomarker selection based on existing mechanistic knowledge, by studying selected gene pathways based on existing literature. A hypothesis-generating data driven approach of biomarker selection was also taken based on genome wide expression screening.

The achievements in my dissertation include the broad characterization of heterogenous cell differentiation in the mESTc, identifying additional non-cardiomyocyte cell types like neural crest cells and neural cells. The results showed that different structurally related chemical families can perturb a different part within that biological domain. Valproic acid analogues and organophosphates affected neural crest cell markers, whereas morpholines and piperidines affected neurogenesis related markers. Within structurally similar chemical families, the use of additional pathways can enhance the sensitivity of the mESTc.

Further insight was gained on the impact of *in vitro* culture conditions and their impact on the discrimination between different chemical compounds within the mESTc. Culture conditions as oxygen level and specific inducers influence the status of the embryonic stem cells or the direction of pluripotent stem cell differentiation. Consequently, the sensitivity to gene transcript biomarkers was affected when exposure chemicals were tested for developmental perturbation within the mESTc. This should be considered when applying the mESTc in a test battery for quantitative hazard assessment of chemicals. Additionally, a review of endoderm- and mesoderm-derived cellular pathways employed in embryonic stem cell differentiation research was performed, exploring additional embryonic stem cell differentiation pathways that might be used in the future in novel EST systems.

My work contributed to our mechanism-based knowledge for hazard assessment of chemicals which in general is of added value as compared to the lacking mechanistic information from the standard developmental toxicity studies conducted in laboratory animals. To improve the robustness of the mESTc, next steps are needed based on obtained results in this dissertation. The culture conditions should be as optimal as possible in terms of sensitivity and should be improved to meet culture conditions which are as realistic as possible to the human situation. Additionally, in terms of moving forward to a complete animal-free method there is the need to step away from animal materials as foetal bovine serum (FBS) and in case of histochemistry the use of antibodies if possible. Replacing FBS has already been proven to be successful and can additionally improve standardisation of the test since FBS contains variable components.

When knowing the optimal culture conditions and the complete biology of the mESTc, the test should be combined with other test methods by integrating it in test strategies for hazard assessment and prioritisation including modelling of kinetics. To gain awareness and trust in animal alternative test methods it is key to make a change to eventually be able to apply alternatives to animals to the actual practice for risk assessment in the future.

https://www.publicatie-online.nl/publications/gina-mennen/ to unlock use: 160481

Working at a biotech company

By Amer Jamalpoor, *PhDStudy Director Developmental Toxicology, Toxys*

I have been informed that the section "what's next" is intended to expose Ph.D. candidates, that are getting registered as toxicologists, to the types of work they can expect upon completion of their Ph.D. track.

In general, toxicologists are concerned with the detection and effects of toxins, and they are involved in designing and conducting studies to determine the potential toxicity of substances to humans but also to animals and plants. Toxicologists provide information on the hazards of these chemicals to the federal government, the public, and private businesses. This means, as a toxicologist graduate, you have a wide variety of opportunities that allow you to constantly evolve in your career path, while expanding the knowledge and learning from the past.

Start of my career as a Toxicologist

My basic academic and research interests lie in drug safety and efficacy with particular emphasis on using animal-free technologies to resolve a human-relevant question. The birth of this passion began during my days as a Bachelor of Pharmacy student (2007), where I performed my very first animal testing to assess genotoxic effects of compounds. There, I realized that animal testing poses not just ethical issues but scientific ones too, and since then I have dedicated my career to its replacement with scientifically advanced animal-free approaches.

"Helping people in the best possible way to decide on their future career, is what I love to do"

I have obtained my master and Ph.D. degrees in the field of Human Toxicology and Pharmacology. My research focused on the development of human-relevant *in vitro* screening platforms for predictive toxicology that utilize human stem/primary cells combined with omics-based biomarker identification. I developed and modelled human kidney proximal epithelial cells and kidney organoids to identify and test the toxicity profile of potential therapeutic agents for kidney disorders. Using these models, we have identified a combination therapy that showed a great potential and encouraging results in reversing the cystinotic (monogenetic kidney disorder) phenotype *in vitro*.

In 2020, I joined Toxys to lead the developmental toxicology department, utilizing my expertise in molecular and cellular biology. Toxys is a Dutch biotech company that offers expertise in the fields of genotoxicity, developmental toxicology, and mechanistic toxicity. We develop and offer unique *in vitro* cell assays with the focus on understanding the mode-of-action of toxic compounds. At Toxys we ⇨

strongly believe in new approach methods to replace or reduce animal-based toxicity testing.

My main responsibilities at Toxys include implementing and extending the applicability domain of the ReproTracker assay. ReproTracker is a state-of-the-art human stem cell-based *in vitro* assay that rapidly and reliably identifies developmental toxicity hazards of new drugs and chemicals.

Responsibilities as a Developmental Toxicologist
Being the study Director-Developmental toxicology, I am engaged with a wide variety of activities, ranging from managing a team, designing toxicological studies, developing new assays, customer interactions, grant writing, partnership and scientific collaboration, and the list goes on and on.

I work together with a growing number of customers from different industries ranging from pharmaceutical companies to chemical and consumer-goods companies. The aim is to help them determine the potential developmental toxicity of their substances at an early phase of their drug development process.

"I love my job at Toxys as everyone shares the same vision and is dedicated to the mission"

Me in a nutshell:

- Group leader of a multi-disciplinary team with a track record in scientific data evaluation, integrated safety assessment, and scientific writing.
- Study director of *in vitro* developmental toxicity studies in support of pre-clinical late discovery/early development projects.
- Lead toxicologist responsible for the design, coordination, and supervision of the R&D Projects.
- Design of early toxicological studies in compliance with ICH guidance, integrated scientific data interpretation, and close collaboration with (pre)clinical representatives.
- Provide scientific input with regard to the potential mechanism of developmental toxicity in molecular pathways and propose appropriate follow-up.
- Provide up-to-date knowledge regarding innovative approaches in predictive toxicological research.
- Involved in gaining the confidence of stakeholders by demonstrating the importance and applications of the animal-free approaches in the field of teratology.

I hope this small piece of text can give you a better understanding of what your future career might look like as a toxicologist.

AIO toxafette - Sabbir Ahmed

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 pass the baton to a fellow PhD-student. This time Sabbir Ahmed from Utrecht University opens up about his project.

Can you introduce yourself?
I am Sabbir Ahmed, from Bangladesh, currently pursuing my Ph.D. in regenerative medicine at Utrecht University. My research focuses on the development of biomarkers for kidney disease progression.

How would you explain the subject of your research to a layperson?
We all know that we have two kidneys, which sometimes do not work well. There are many reasons for that, including injury at different parts. Once kidneys are damaged, they could progress to many severe conditions. Therefore, it would be wise to identify the injury at earlier stages. However, there aren't enough biomarkers available that could identify the disease at earlier stages. My research focuses on developing biomarkers to identify kidney diseases before progressing to later/ untreatable conditions.

What was your motivation for starting a PhD. program?
I am passionate about research and like to do experiments that could generate new knowledge and ideas, which could be helpful for humankind.

Why did you choose a subject in toxicology?
We expose to many toxic substances every day. Currently, available literature has taught us the pattern of harmful effects of such substances. However, many of the toxic compounds are not well characterized yet, and require more extensive studies on their mechanism, poisonous dose, and sources. In addition, during my master's, I studied toxicology courses and was exposed to different research works in this field.

How do you see the future of your research topic? What do you hope for?
Currently available plasma/urine biomarkers for kidney disease are neither sufficient nor sensitive. Even the gold standards have been demonstrated as insensitive in many studies. However, those biomarkers are still being used in clinics as no (or very limited) better alternatives have been identified yet. Therefore, there is an urgent need to develop biomarkers that could detect kidney diseases at early stages and prevent the damage from progressing to later stages that require dialysis or kidney transplant. I think, in the near future we will be able to find some promising biomarkers, and able to provide early intervention to the disease.

How do you expect society will benefit from your PhD-research?
The findings from my research will contribute to the understanding and validation of novel biomarkers that can help reduce treatment costs of kidney diseases, the suffering of patients, and stressful conditions for patients' families.

If you could start over your studies/research project, what would you do differently?
I would follow additional courses to strengthen my biostatistics skills.

Do you keep up-to-date regarding developments in your field? How?
Yes, I try to keep myself updated. I participate in symposiums, conferences and workshops. Moreover, we have regular group meetings where all researchers present their work on rotation, 2-days every week. We can discuss findings and troubleshoot. ⇨

Does the project meet your expectations, why or why not?
Yes, the project met my expectation. However, I believe there is always room for betterment. If I had opportunities, I would like to validate the biomarkers, I am currently validating in animals, in clinical cohorts of kidney patients with multiple etiology.

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 finishing my Ph.D., I would like to continue my career in research, preferably in academia. I think academia provides more opportunities, such as being involved with teaching and training. Moreover, I would perhaps get more flexibility to explore this field instead of focusing on specific goals. Currently, I am not planning on going abroad.

Please answer the question from the last toxafette PhD-candidate: "If everything is possible, what do you want to do with the knowledge you have from your PhD?"
I would like to utilize my knowledge for my future research career.

Could you suggest a question to the next PhD-candidate for the Toxafette?
Question: Why do you think a Ph.D. degree was necessary for you?

Inschrijving Register

Voorletters	Achternaam	Datum inschrijving	Datum afloop registratie
S.	Zhao	12-07-2022	12-07-2027
L.C.	Jager	12-07-2022	12-07-2027
M.	Shi	12-07-2022	12-07-2027
D.	Wang	12-07-2022	12-07-2027
M.J.W.	Elders - Meijerink	12-07-2022	12-07-2027
M.G.G.	Sturkenboom	21-07-2022	21-07-2027
F.	Akuoma	04-10-2022	04-10-2027
E.G.E.	Hurkmans	04-10-2022	04-10-2027
A.P.	Nagelkerke	04-10-2022	04-10-2027
S.M.	Shaikh	04-10-2022	04-10-2027

Inschrijving TiO

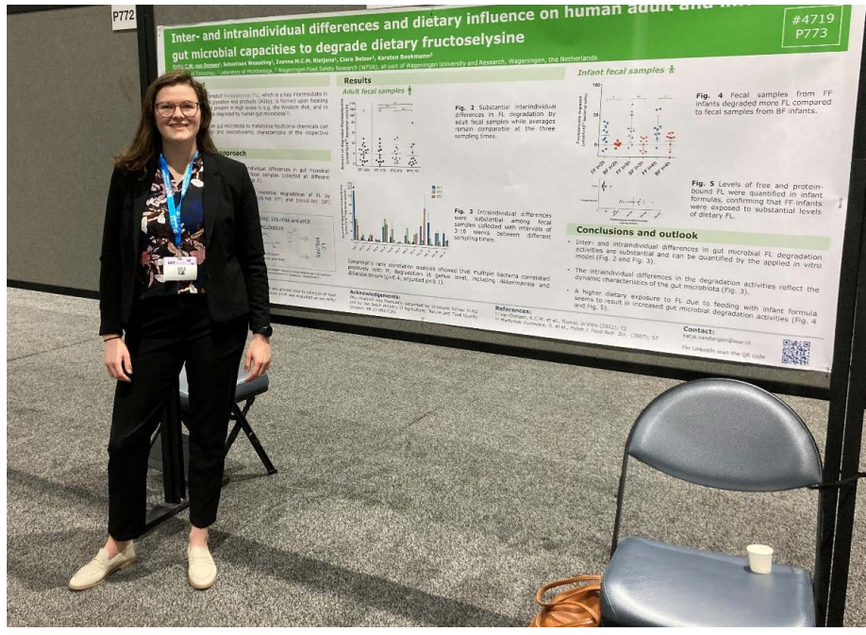
Voorletters	Achternaam	Opleider	Datum inschrijving
S.M.	Shaikh	Prof.dr. M. van den Berg	05-05-2022
G.A.	Aalderink	Prof.dr.ir. I.M.C.M. Rietjens	12-07-2022

61st Annual Meeting Society of Toxicology (SOT)

San Diego, USA – 27th-31st of March 2022

By Katja van Dongen

Division of Toxicology, Wageningen University and Research



1. During SOT I had the opportunity to present my work on inter- and intra-individual differences in human gut microbial degradation activities. The gut microbiota is able to metabolize certain foodborne chemicals when entering the gut, thus making it a relevant organ to study as well for toxicokinetics. In this research, we quantified inter- and intraindividual differences in gut microbial degradation of the dietary glycation products fructoselysine and carboxymethyllysine. To do this, an *in vitro* model was developed, where in short we incubated individual collected human fecal samples with the substrate of interest under anaerobic conditions and quantified the fate of the chemical over time by LC-MS/MS. Large interindividual differences, but also intraindividual differences were observed which is relevant to consider when assessing the metabolic activity of the gut microbiota. Dietary exposure was hypothesized to be one major responsible factor for these differences in degradation activities, and we further explored this by comparing gut microbial fructoselysine degradation activities of fecal samples from exclusively breast-fed and formula-fed infants, the latter being exposed to high fructoselysine levels via the infant formula. There we showed that fecal samples from formula-fed infants indeed had significantly higher fructoselysine degradation activities compared to fecal samples from breast-fed infants, showing the adaptation ability of the human gut microbiota to dietary exposures. In general, it shows that the gut microbiota can be an important organ to consider for toxicokinetics which can be evaluated by the applied *in vitro* model.

2. There were many interesting sessions – smaller symposia, plenary sessions and poster presentations. One session that stood out to me was the 'let's talk about sex – through the lenses of a toxicologist', chaired by Jamie Young. There were several very interesting and lively presentations and discussions on the differences between sex and gender, sex differences in disease development and sex differences in toxicological evaluation, to provide a general view. It was useful and insightful to have emphasize on this and I think the session did a great job to stress the need to consider sex differences and think about these as well in toxicological sciences.

In addition, there was a session on the gut microbiota and toxicity entitled 'the microbiome in toxicity and disease: a yin and yang duality for the host throughout the life span'. I found this a very interesting session because of the topic and because not only toxicologists but also microbiologists were invited as speakers. This multidisciplinarity provided an overview of the diversity of functions of the gut microbiota and how important it is to consider for host health, where not only immediate effects need to be considered but long-term effects as well. Examples were provided of links between the gut microbiota development and cognition and mental health, but also effects on offspring, on female reproduction and the relation with gut health. In the presentation a major focus was on the toxicodynamic effects on the gut microbiota, while toxicokinetic and metabolic function is of importance as well.

This links to a third learning I got at SOT which was from posters on the gut microbiota. Few posters considered the gut microbiota in some way, and most of them mainly investigated gut microbiota composition. However, a few posters also included a functional output of a toxicodynamic effect. By use of metabolomics they linked effects on the gut microbiota to functional effects, which is I think an important step in how to evaluate toxicodynamic effects on the gut microbiota in toxicity testing.

3. Choosing the right model to study your research question is of high importance to reach valuable answers.

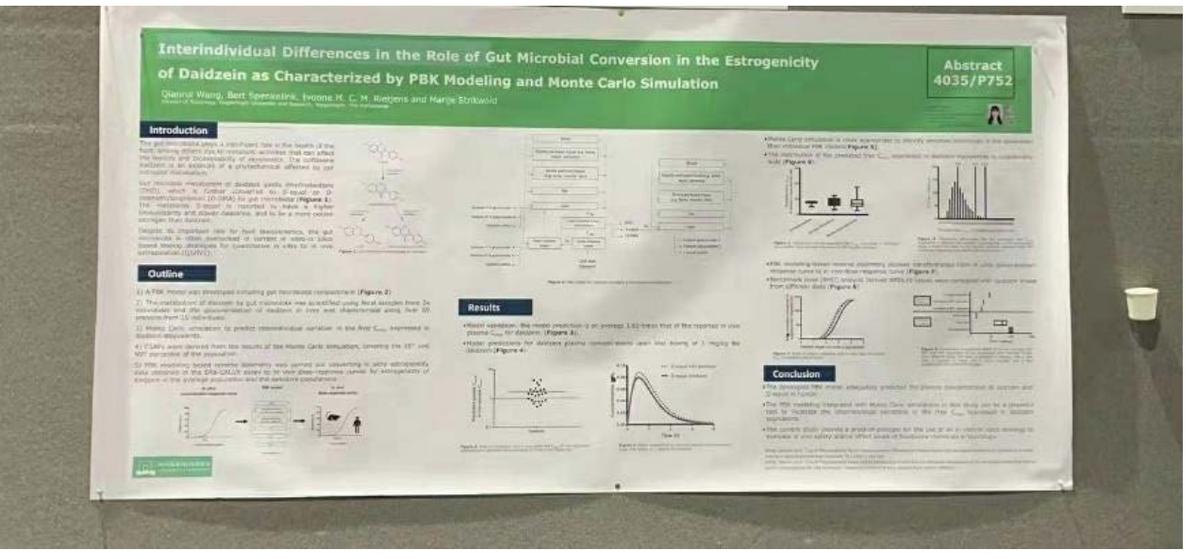
4. The conference organizers developed an App with the program instead of hard copy program booklets and also supported to join the conference online, which both help to make the event less harmful for the climate.

The SOT 61st Annual Meeting and ToxExpo

From 27-31 March 2022, The SOT 61st Annual Meeting and ToxExpo was held in San Diego, US. There were over 6000 attendees, 70 scientific sessions, 250 exhibitors and 60 social events. As the most important annual conference in toxicological field, SOT gathered toxicologists world-wide and offered a unique opportunity to meet colleagues and network professionally with scientists.

By Qianrui Wang
Wageningen University and Research, Sub-department of Toxicology

During the conference, my poster was presented in the session of Biological Modeling, entitled “Interspecies and Interindividual Differences in the Role of Gut Microbial Conversion in the Estrogenicity of Daidzein as Characterized by PBPK Modeling and Monte Carlo Simulation”, where the isoflavone daidzein was used as model compound for building a PBPK model, and the plasma concentrations of its intestinal microbial metabolite S-equol were predicted. Subsequently, the PBPK model was coupled with Monte Carlo simulations taking into account variability in metabolism related kinetic parameters, providing the distribution of the daidzein and S-equol plasma concentrations in a large population. Altogether, the described in vitro-in silico strategy provides a proof-of-principle for assessing gut microbial metabolism and including it in PBPK modelling as part of the development of New Assessment Methods (NAMs) in safety testing.



Besides my own poster, I also explored some other fields via listening to parallel presentations and watching posters. For example, it was impressive to join the session “Optimizing the design of repeated-dose animal studies to inform human health risk assessment by integrating exposure, in vitro and in silico data”, where I noticed that many scientists are developing and optimizing approaches as I am doing in my PhD studies, to apply them in PBK models to predict the concentrations of chemicals in plasma and target organs. This provides information about chemical hazard and enables risk assessment with the aim of reducing animal use. It was impressive to talk with Qian Zhang, associate professor from Emory University, which made me realize that in future toxicological research, computational technologies such as machine learning and artificial intelligence may play very important roles. In other parallel sessions, keynote lectures and debates also discussed important issues such as PBPK modeling for non-pharmaceutical compounds, safety risk assessment under data-rich and data-poor conditions and new testing strategies.

In summary, it was my pleasure to attend the SOT 61st Annual Meeting and ToxExpo and present my poster. I learned a lot from the impressive presentations, posters and also the talks with scientists. Finally, I would like to acknowledge NVT for the travel bursary and I wish more young scientists could also have this opportunity to attend conferences.

TERUG NAAR INHOUD