TCDD

TOXICOLOGIE

NUMMER 39
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SPECIAL THEME

From Farm to Fork:
The Safety of What is on Our Plate

- IS ORGANIC FOOD FREE OF PESTICIDES OR PESTICIDE RESIDUES?
- GENETICALLY MODIFIED VEGETABLES: SCARY OR NOT
- FROM PROTEST TO PROGRESS: HOW CRISPR CAN IMPACT AGRICULTURAL CHALLENGES
- SOIL POLLUTION IN RELATION TO AGRICULTURE AND FOOD SAFETY
- THE BIG BEEF - WHY HORMONES GET INTO MEAT AND WHAT THAT MEANS TO CONSUMERS

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TCDD
TOXICOLOGIE

Inhoud

TERUG NAAR INHOUD

Editorial

In this edition of the TCDD, we explore the field of agro-toxicology. It's a topic that remains ever relevant, since farming is an essential part of our society. Moreover, it is a persistently current topic, especially in light of the ongoing farmers' protests. While we will steer clear of political discussions, we would like to shed light on some interesting toxicological aspects within agriculture.

We delve into the challenges and solutions within this dynamic yet steadfast field of work. From examining organic food and pesticides to evaluating the impact of genetic modification and the application of new gene technologies, we also explore how agricultural practices influence our environment, ecosystems, and health.

Of course, we haven't forgotten our classics. In the section "What's Next?", Barae Jomaa opens up about his career within toxicology, Marvin Martens makes Adverse Outcome Pathways come to life in the section "Proefschriftpromopraatje", and in the "Toxafette" Marjolein van Borselen shares her experiences in performing PhD-research that integrates elements of both pharmacology and toxicology.

We hope you find this edition both engaging and enlightening.

Happy reading!

Carolien Schophuizen

Photo by Jess Bailey on Unsplash

SECTIONS PHARMACEUTICAL TOXICOLOGY AND GENETIC TOXICOLOGY

INVITATION: Spring symposium - April 24, 2024
Genotoxic impurities in pharmaceutical products

The manufacturing process of pharmaceuticals is often based on a number of chemical reactions. During this process, byproducts called impurities may be formed that might still be present at low levels in the end-product. Strict ICH guidelines are in place to control these levels at acceptable amounts. The lowest acceptable levels are applied to potential genotoxic impurities. An example of such impurities that have had a lot of attention the last few years are the "*N*-nitrosamine" impurities. For example, since 2018, numerous lots of valsartan were found to contain higher than acceptable levels of *N*-nitrosodimethylamine (NDMA). *N*-nitrosamines are often genotoxic and potent human mutagens. In this spring symposium, the invited speakers will give an overview of the challenges related to genotoxic impurities in pharmaceutical products, from a regulatory, academic, industry and patient communication point of view.

During the symposium there will be sufficient time to discuss and ask questions to the speakers and other attendees. We hope it will be an inspiring, thought-provoking, and informative meeting.

WEDNESDAY AFTERNOON APRIL 24, 2024

Utrecht Science Park, Ruppertgebouw, zaal Rood

Address: Leuvenlaan 21, Utrecht

	PROGRAM
13.15 – 13.30	Business meeting (Huishoudelijke vergadering), Section Pharmaceutical toxicology members only
13:15 – 13.50	Registration, coffee and tea
13.50 – 14.00	Welcome & Instructions *Day chair: Daan Touw, UMCG*
14:00 – 14.30	Management of (geno)toxic impurities – a view from pharma industry *Dr. Miranda Cornet, Director Non-Clinical Safety at UCB Biopharma*
14.30 – 15:00	Ames Test assay parameters important for the detection of N-Nitrosamine mutagenicity *Anthony Lynch, Head of Genetic Investigative Toxicology at GSK*
15:00 – 15:30	Break
15:30 – 16:00	Regulatory experience with nitrosamine impurities in pharmaceuticals. *Dr. Leon van Aerts, Senior non-clinical assessor at CBG*
16:00 – 16:30	Nitrosamine: communication to patients and consumers. *Feyzullah Mermi, pharmacist at KNMP*
16:30 – 16:50	Discussion & wrap-up
16:50 – 17:30	Social get together and drinks

Registration:

- Deadline: 15th of April
- Email to: Wianda Goense (w.a.goense@umcg.nl), with subject "Registration NVT spring symposium – 24 April"
- Please indicate: Name and affiliation

There will be no charge for attending this symposium

A certificate of attendance will be sent within a few weeks after the symposium.

SECTIE ARBEIDSTOXICOLOGIE

Sectie Arbeidstoxicologie zoekt versterking

De sectie Arbeidstoxicologie van de NVT kan na het vertrek van enkele bestuursleden weer versterking gebruiken. We zijn nu met z'n vieren, waaronder een (interim) voorzitter. We kunnen daarom twee extra leden gebruiken.

De belangrijkste activiteit van de sectie, is het organiseren van een jaarlijks middagsymposium, in samenwerking met de Contactgroep Gezondheid & Chemie. Hiervoor bedenken we gezamenlijk met de CGC wat een interessant en actueel thema zou kunnen zijn, stellen we het programma samen, en zoeken we sprekers daarbij. Ook dragen we zorg voor de organisatie van de dag en voor de verslaglegging. Daarnaast draagt de sectie soms bij aan de invulling van de jaarvergadering van de NVT, aan de website van de NVT, en bespreken we allerlei actualiteiten.

Wat we vragen is enig inzicht en ervaring in het werkveld van de arbeidstoxicologie, en enthousiasme om bij te dragen aan interessante activiteiten. Belangrijk is verder, dat de voertaal in de sectie Arbeidstoxicologie in het algemeen het Nederlands is.

Als je belangstelling hebt, kun je een bericht sturen aan Jeroen Terwoert: jterwoert@nlarbeidsinspectie.nl.

Is organic food free of pesticides or pesticide residues?

By *Héloïse Proquin*

For the past 70 years, mixtures of plant protection products have been used to increase production yield and reduce the presence of pests and diseases. What was seen as a revolution at the outset has led to a decline in wildlife, such as birds, and posed risks to human health, including an increased likelihood of cancer risk. A recent study estimated that 60% of the farmland birds have declined over the last 40 years, primarily due to pesticides and fertilizers[1].

All over Europe, the transition to organic farming has begun and is regulated by the EU through regulation 2021/1165 of 15 July 2021[2]. The regulation states that synthetic phytochemicals cannot be used in organic farming, only natural ones. However, derogation can be requested from the member states, and this is regularly done.

Among the natural products used in organic farming, some are known to have a certain toxicity and/or impact on the environment, such as copper and sulphur. Copper is used against a fungal infection (mildew) in potato crops, tomatoes, etc. It is not biodegradable, accumulates in soils and has an impact on the life expectancy of worms. It is classified as a substance which can be in a nanomaterial form and is toxic to aquatic life with long lasting effects[3]. The second controversial chemical is sulphur, it can be used in a number of ways: to prevent a fungus like powdery mildew or as a curative for some vine diseases and parasites. It is considered to have low toxicity for humans and environment, but it is mostly produced from gas and petroleum[4]. It is also classified as a substance known to also be used in a nanomaterial form.

Even with the derogations and the use of controversial pesticides, a meta-analysis from 2014 showed that synthetic pesticides were detected in 11% of organically farmed produce as compared to 46% of conventionally farmed produce (especially fruit) [5].

Additionally, concentrations of total nitrogen, nitrate and nitrite were respectively 10%, 30% and 87% lower in organic crops than in conventional farming. Effects on the presence of heavy metals were also observed with significantly lower levels of heavy metals in organic crops (up to 50% lower for cadmium). Lastly, this study showed that concentrations of antioxidants such as polyphenols are 18% to 69% higher in organic crops. The limits of this meta-analysis were the absence data regarding the natural pesticides as well as minerals and vitamins.

These results were confirmed with recent studies in Europe. In Europe, out of 340 EU agricultural topsoil samples, the total pesticide content in organics was 70–90% lower than in conventional ones. Of these total pesticides, organic soils contained mainly mixtures of 2–5 residues (maximal 5 residues/sample) while >70% of conventional soils had mixtures of pesticide residues, (maximal 16 residues/sample) including glyphosate and its main metabolite AMPA, and pendimethalin. In France, samples were taken between 2019 and 2020 and showed that 8.8% of organic fruit, vegetables and cereals contain pesticide residues compared with 63.1% of their conventional counterparts[7].

These analyses clearly demonstrate that even with the presence of natural pesticides and some derogations for synthetic ones, organic farming has much less impact on the environment and, with organic food, exposure to synthetic pesticides, fertilizers and heavy metals is drastically lowered. ►

Mildew (Oidium lycopersici) on tomato
CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=228293

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From protest to progress:

how CRISPR can impact agricultural challenges

On the 6th of February of this year, The European Commission, led by President Ursula von der Leyen, proposed to withdraw plans to halve pesticide/insecticide use by 2030, citing it as a “symbol of polarisation” amidst farmer protests over rising costs among other concerns. This decision aims to acknowledge the challenges faced by farmers, emphasizing the need for agriculture to transition towards a more sustainable model while ensuring profitability in the long term. Protests by farmers have highlighted concerns over rising costs, taxes, cheap food imports, and climate change initiatives. The European farmers’ lobby, COPA-COGECA, welcomed this move, viewing it as recognition of the need for a revised approach towards achieving sustainability in agriculture (1).

By *Jelmer Faber*

In contrast, the emerging technology of CRISPR-Cas gene editing offers a promising alternative to traditional pesticides. The CRISPR technology allows for precise, targeted changes to the DNA, utilizing a guide RNA to direct the CAS enzyme to specific DNA sequences for modification. The technology’s simplicity, efficiency and versatility make it a powerful tool in the hand of a researcher. CRISPR-Cas could revolutionize the way we protect crops from pests by making plants inherently resistant to diseases and pests, reducing the reliance on chemical pesticides. This biotechnological advancement presents a sustainable approach to addressing agricultural challenges, promoting crop resilience through genetic enhancements rather than chemical interventions. Such innovations not only promise to decrease the environmental footprint of agriculture but also align with the global push towards more sustainable and eco-friendly farming practices. The use of the CRISPR-Cas technology has already been successfully implemented in various crops to increase yield and decrease pesticide use. Take the family of whiteflies. Under the microscope they might look harmless but pose a substantial agricultural threat. This little fly feeds on the undersides of leaves but in doing so can transmit up to four different viruses to the crop. To make matters worse, the whitefly has become resistant to a plethora of insecticides (2). The viruses transmitted by the whitefly commonly affect the eukaryotic translation initiation factor eIF4E through

association of this protein with the viral-encoded VPg protein. Targeted eIF4E gene knockout in cucumbers with use of the CRISPR-Cas technology led to resistance to the whitefly-transmitted *Cucumber vain yellowing virus, Zucchini yellow mosaic virus* and the *Papaya ring spot mosaic virus*, illustrating that gene editing with CRISPR can make crops resistant to viruses resulting in less insecticide use and therefore less human exposure (3).

The decision by the European Commission to reconsider pesticide reduction goals in light of farmer protests underscores the complex balance between agricultural sustainability and economic viability. The exploration of CRISPR-Cas gene editing as an alternative to traditional pesticides offers a promising path forward. Though it is imperative to weigh the benefits of increased crop resilience against potential ethical concerns, such as genetic diversity and long-term ecological impact.

The Greenhouse Whitefly (*Trialeurodes vaporariorum*), image from Wikipedia, courtesey of Gaucho.

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Genetically modified vegetables: **Scary or not**

For many years, humans have used selective breeding to modify the DNA of plants to create better crops. Advancements in scientific research have found ways to alter the DNA in lab settings, resulting in a more efficient and faster procedure to enhance crops. Plants that are altered in this way are referred to as Genetically Modified Organisms (GMOs), Genetically Modified (GM) crops, transgenic plants, or Genetically Engineered plants. An often-used definition for GMOs is organisms containing detectable genetic material that has been modified through certain lab techniques and cannot be created through conventional breeding or found in nature. The FDA defines a GMO (genetically modified organism) as a plant, animal, or microorganism that has had its genetic material (DNA) changed using technology. Genetic modification involves the introduction of specific beneficial genes into an organism's genome. This process allows for the transfer of single genes from one organism to another, whether within the same species or across different species.

By *Marcha Verheijen*

In 1994, in the United States, the first GM ingredients were approved for human consumption, but to date you will not find many GMO fruits or vegetables in the supermarket. GM ingredients are mostly used in animal feed and in processed foods such as cereal and snack chips. Overall, only a handfull of GM crops are currently grown (e.g., soybeans, corn, sugar beets, canola, and cotton), though nearly 90% of corn, cotton, and soybeans planted in the US were GM. As of 2017, GMO crops are grown in 24 countries around the world and each country has its own rules and regulations for the GM crops approval process. But no matter where you are, the rules and regulations are all based on the same objective: GMOs should be safe for human and animal health and the environment.

But why do we need GM crops at all? It is estimated that in the year 2050, the global population will have increased to nine billion. It will be hard to feed all these people by just using the agricultural land that we use now. Furthermore,

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the climate is changing, meaning that plants that can now grow in a specific area might not be able to survive there in the future. Through genetic modification, it is possible to produce the same amount of food with substantially less land and water. Plants can be engineered to grow faster, grow bigger, contain more nutrients and vitamins, with less water, less effort and even less pesticides. If GM crops are so amazing, why aren't all crops modified by now? That is because there is a divided vision on the safety of these GM crops for both human consumption and the environment. Introducing a new gene or trait into an ecosystem can result in unintended consequences. Creating crops that have been enhanced with insect resistance means that less pesticides are needed to protect the crops. This means less soil and water contamination, but also fewer health concerns for those who consume it. There are currently several crops that have been enhanced using insecticide gene found in the bacteria Bacillus thurengensis (Bt). This gene encodes the CRY toxin that is relatively specific and disrupts gut digestion of caterpillar and beetle pests that eat the crops.

Opponents of GMOs argue that beneficial insects, such as butterflies, may also be endangered by the toxin. Furthermore, risk to beneficial insects may be increased when the newly introduced genes spread through the ecosystem and are transferred to wildflowers and weeds. This is not only the case for the intended traits. The process of incorporating a gene in an organism is paired with the use of selectable traits. Selectable traits are most often antibiotic resistance or herbicide tolerance and are used to select the plants that have successfully undergone the modification process. Transfer of these traits may result in widespread antibiotic resistant microbes or super weeds. Supporters of GMOs view these issues differently. Selectable traits can be removed from GM crops through a multitude of techniques, including the CRE-LOX method. Furthermore, the concern of gene flow of introduced traits actually precedes the GM crop era. The use of pesticides and herbicides already favored plants that acquired tolerance naturally or through selective breeding methods. Finally, also the use of conventional pesticides goes hand in hand with harming unintended creatures, which may extend beyond butterflies to include insects like worms that reside near crops but do not consume them.

Overall, the FDA reports that GMO foods are as healthy and safe to eat as their non-GMO counterparts. If employed correctly, they can bring a multitude of benefits to the world, but we should be vigilant of possible risks to food safety and environmental impacts. Therefore, it is necessary to thoroughly investigate benefits and drawbacks of traits introduced in GM crops.

Text was based on these sources:
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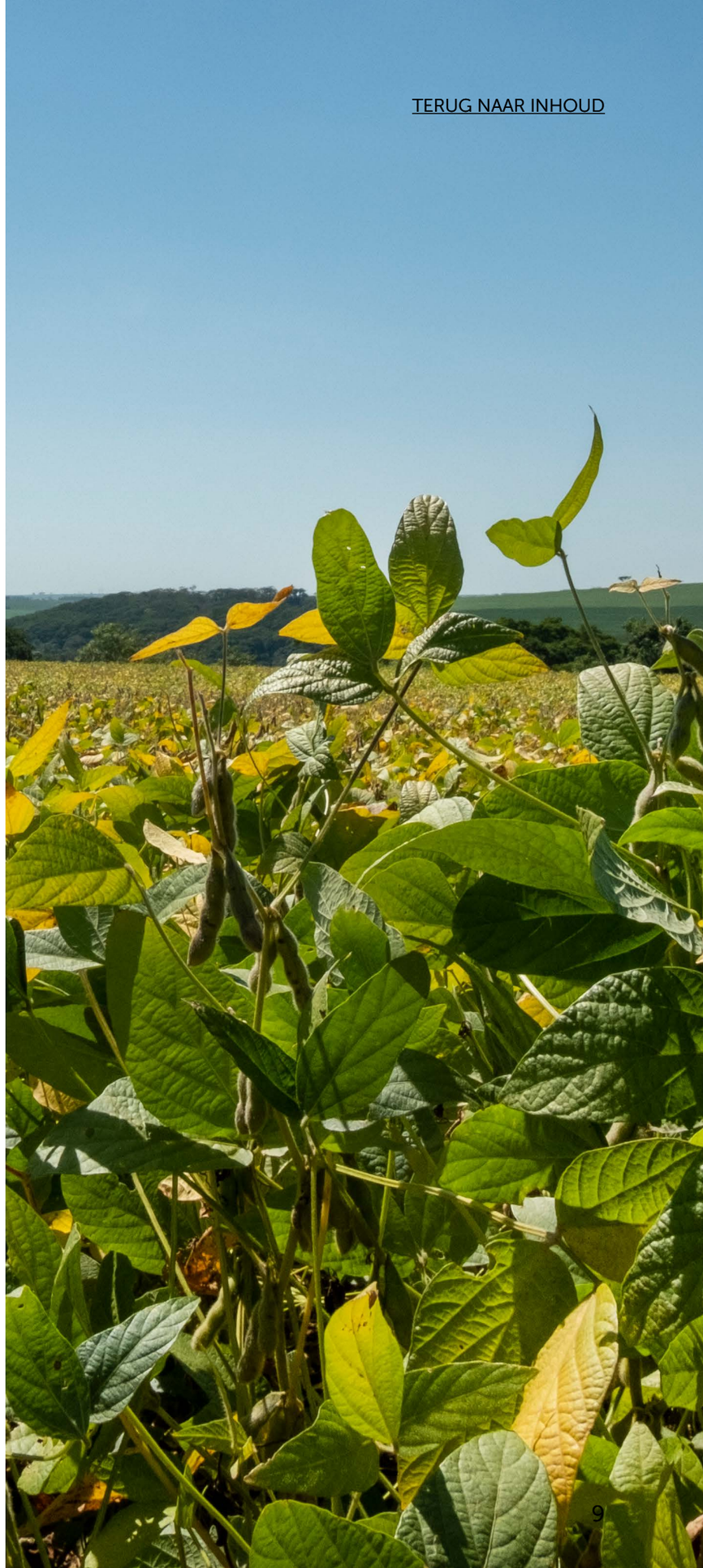

Soil pollution in relation to agriculture and food safety

By *Carolien Schophuizen*

In the 1980s, it became increasingly evident that soil contamination could significantly affect crops and animal products. Chaney et al. introduced the 'Soil-Plant Barrier' model to outline the general risk patterns associated with soil elements. [1] Some elements remain largely insoluble in soil or bound within plant roots, preventing them from reaching dangerous levels in plant shoots for humans, livestock, or wildlife. Others, though highly toxic to plants at low concentrations and not easily translocated to shoots, fruits, or tubers, pose minimal hazard to animals and humans as they are unlikely to enter the food chain. However, under specific conditions, a select group of elements can be absorbed and transported by plants from contaminated or mineralized soils, posing a threat to livestock, wildlife, or humans. [2]

Since then, there has been a growing interest in soil quality, contamination, and management. This interest has been driven not only by ecological and environmental concerns but also by considerations related to agriculture, food safety, and public health. Our understanding of the persistence of certain chemicals or elements and their long-term effects has underscored the ongoing relevance of this topic.

Origins of Contaminants:

In farmland soils, contamination primarily stems from industrial production and various human activities. [2] Consequently, areas with the highest concentrations of soil heavy metals are often those where human activities, particularly industrial production and transportation, are most intense. [3] Extensive research indicates that heavy metals in soils are influenced by both natural background levels and human activities. Natural sources primarily involve parent materials and the weathering of rocks. [4] Human activities contributing to heavy metal contamination include industrial emissions, mining and smelting operations, the use of fertilizers and agrochemicals, sewage irrigation, sludge application, and vehicle exhaust. [5]

Contaminants linked to manufacturing industries vary depending on the products and processes involved. In less regulated countries, agrochemical manufacturing poses significant threats to soil health due to emissions and waste. Legacy issues from pesticide production (or use) persist, with hazardous products like organochlorine pesticides remaining in soils even after bans due to their lasting environmental and health impacts. Lead-acid battery recycling, particularly prevalent in developing countries, emits lead pollution due to inadequate pollution controls. Copper smelters and steel plants release polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDD/Fs), contaminating nearby soils and cattle. Aluminum production generates substantial waste and emissions, posing environmental risks without proper management. Textile and leather industries discharge dangerous substances in effluents. [5]

New-emerging contaminants are also gaining attention. Pharmaceuticals and personal care products encompass a wide range of substances, including prescription and over-the-counter medications. These compounds can enter the environment through various pathways, including wastewater discharge. PFAS manufacturing leads to widespread environmental contamination through spills, emissions, and improper waste disposal. Microplastics, Endocrine disrupting chemicals and nanomaterials are all adding to environmental pollution and other contaminants. The toxic potential of some of these new contaminants are not always known, nor do we always understand their behaviour in soils, sediments and vegetation. [6]

The absorption of contaminants by plants, food contamination risk or remedy?

Food contamination originating from soil, such as the presence of elements like arsenic and cadmium in rice, is a notable example. These elements can be absorbed by plants and subsequently transferred to food products. They often mimic essential nutrients required by plants, facilitating their uptake. Particularly in rice and rice-based foods, high concentrations of arsenic and cadmium can pose significant health risks. [7]

Arsenic tends to be mobilized under reducing soil conditions, primarily in wetland sediments, through microbially-mediated reductive dissolution of arsenic-bearing iron oxide minerals. This process is further enhanced by the addition of organic

matter. In flooded rice paddies, mobilized arsenic becomes readily available to plants and can be absorbed by rice roots, ultimately accumulating in the grain and posing risks to human health. The speciation of arsenic in soil solutions determines its uptake pathway, localization, and impact on humans. In contrast, cadmium uptake in rice occurs under non-flooded conditions. [8] However, plant absorption does necessarily need to be a problem. Several remediation methods based on plant-absorption have been developed, with phytoremediation garnering increasing attention due to its potential application in agricultural settings. Phytoremediation involves using plants to mitigate soil contaminants and can address both organic pollutants and heavy metals. [8]

Phytoremediation encompasses various techniques, including phytoextraction, which is a method that uses plants, especially hyperaccumulators, to absorb and accumulate contaminants like heavy metals from soil or water. Once the plants absorb the contaminants, they are harvested and removed, reducing pollution levels. This approach is part of phytoremediation, which utilizes plants to mitigate environmental pollution. Phytoextraction of heavy metals may be limited by plant physiological constraints and long remediation durations. [8]

Is there cause for concern?

Findings from the LUCAS Topsoil Survey indicate that the vast majority of agricultural land in Europe is generally safe for food production. However, there are significant areas where precautionary measures are warranted. Various regulatory frameworks and legislative actions are in place to safeguard public health and the environment from the consumption of contaminated food. [9]

The EU has several directives and regulations that address soil contamination and its impact on the environment. One of the key pieces of legislation is the Soil Framework Directive (2004/35/EC), which aims to protect soil and prevent its degradation. [10] Member states are required to identify and manage contaminated sites under this directive. Furthermore, EU legislation also governs the management of waste, including contaminated soil. The Waste Framework Directive (2008/98/EC) sets out rules for the management of waste, including its disposal, treatment, and recycling. [11] The EU has established the European Food Safety Authority (EFSA) to provide independent scientific advice on food safety issues. The EU sets maximum residue limits (MRL)s for pesticides, veterinary drugs, and other contaminants in food products through Regulation (EC) No 396/2005. [12] These MRLs ensure that food placed on the EU market is safe for consumption and that contamination levels are kept within acceptable limits. These contaminants include, but are not limited to: Pesticides, Veterinary Drugs, Environmental Contaminants such as heavy metals (e.g., lead, cadmium, mercury) and persistent organic pollutants (POPs) like dioxins and polychlorinated biphenyls (PCBs). The establishment of MRLs helps ensure that food placed on the EU market is safe for consumers and that contamination levels are kept within acceptable limits to protect public health. Individual Member states are responsible for monitoring and enforcing regulations related to soil and food contamination. They conduct regular inspections, sampling, and analysis to ensure compliance with EU laws and standards.

In conclusion, the problem of soil contamination raises concerns regarding its potential effects on ecosystems and the food chain. Several remediation strategies are available, such as actually harnessing plants' capacity to absorb contaminants. Although regulations target safeguarding public health in the commercial food industry, privately cultivated crops might still pose risks related to soil contamination. Generating public understanding of the correlation between soil health and food safety may be seen as a vital initial step towards food- safety awareness.

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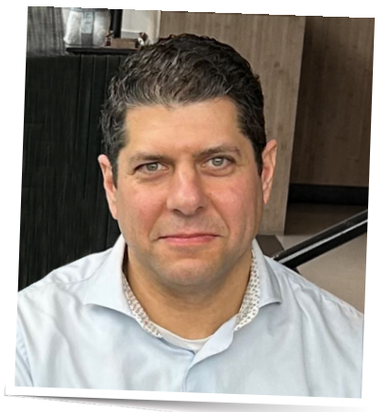
The Big Beef

Why hormones get into meat and what that means to consumers



By *Barae Jomaa*

The import of beef containing growth hormones has been banned in the EU since 1989 and the UK has retained the ban even after Brexit. Considering that the UK is trying to join the 11-nation Comprehensive and Progressive Agreement for Trans-Pacific Partnership (CPTPP), Canada, one of the members, is said to be putting pressure on the UK to drop this ban[1]. Many CPTPP member countries don't see any scientific basis to the EU's fear of hormones in beef. Even more, they claim that the EU is in effect using the hormone ban as a trade barrier.

There are six hormones that are the centre of this debate, namely, estradiol, progesterone, testosterone, zeranol, melengestrol acetate and trenbolone acetate. The first three also occur endogenously whereas the last three are synthetic hormone drugs. All six are allowed in the US and Canada as hormonal growth promoters for beef cattle but not the EU. According to Health Canada, the effect of hormonal growth promoters is to increase lean tissue growth, reduce fat deposition and increase food conversion efficiency. "The result is a healthier product which is produced at a lower cost to the consumer."[2]

The US Food and Drug Administration (FDA) distinguishes between natural and synthetic hormones. And while it has set safe limits for synthetic hormones, it has not set safe limits for naturally occurring hormones saying that people are "not at risk from eating food from animals treated with these drugs because the amount of additional hormone following drug treatment is very small compared with the amount of natural hormones that are normally found in the meat of untreated animals and that are naturally produced in the human body." On the other hand, the FDA says that synthetic hormones are required to undergo extensive toxicological testing and have a safe level determined, before they are approved. Moreover, the manufacturers are required to show that the amount of hormone left in meat after treatment is below the safe level[3].

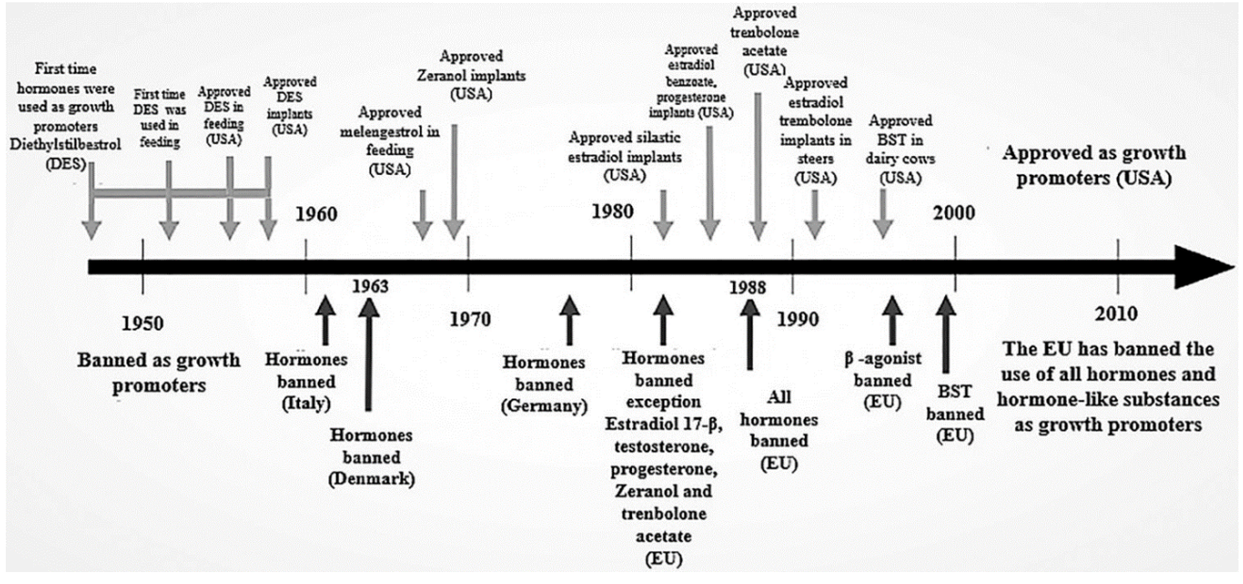


Figure 1. Timeline or history of anabolic growth promoters. This figure is for the EU below and above the line for the U.S.A. situation. Adapted from Ronquillo and Hernandez (2017) and from Herago and Agonafir (2017).[4]

The diverging regulations mean that US and American beef that is treated with hormones cannot be imported into the EU. This has naturally created tensions between the trading partners with some media outlets calling it a "Beef War"[5]. In 1998, the dispute between the US and Canada on one hand and the EU on the other, was brought to the World Trade Organization (WTO) which found that "the European Communities did not actually proceed to an assessment, within the meaning of Articles 5.1 and 5.2, of the risks arising from the failure of observance of good veterinary practice combined with problems of control of the use of hormones for growth promotion purposes. The absence of

such risk assessment, when considered in conjunction with the conclusion actually reached by most, if not all, of the scientific studies relating to the other aspects of risk noted earlier, leads us to the conclusion that no risk assessment that reasonably supports or warrants the import prohibition embodied in the EC Directives was furnished to the Panel."[6]

An EU scientific risk assessment was eventually made in 2002 by the Scientific Committee on Veterinary Measures relating to Public Health (SCVPH). They found that 17-beta estradiol remains in the tissue, has to be considered as a "complete carcinogen", and may therefore pose a potential risk to human health whereas for the other hormones, there was a lack of evidence that would "allow a quantitative estimate of risk"[7]. Nonetheless, the scientific committee found that carcinogenic, genotoxic, endocrine, developmental, neurobiological, immunological as well as immunotoxic effects "could be envisaged", with prepubertal children being the most susceptible.

What we know about the hormonal substances utilized in cattle for growth promotion is that they vary in their safety profile. Estradiol-17β, primarily targeting intracellular receptors, enhances weight gain and feed efficiency but raises concerns regarding genotoxic and carcinogenic potential based on animal studies showing increased tumor incidences. Progesterone, administered in combination with estradiol benzoate, displays structural similarity to endogenous progesterone and, while exhibiting poor oral absorption and inactivation, poses potential carcinogenic risks evidenced by animal studies. Testosterone, despite tolerability in humans, raises concerns for potential carcinogenicity based on experimental animal studies. Zeranol, a non-steroidal anabolic agent, shows estrogenic activity and, while inducing weak estrogenic effects in long-term toxicity studies, poses potential carcinogenic risks in rodents. MGA, a synthetic progestogen, improves feed efficiency but exhibits reproductive toxicity and embryotoxic effects in animal studies. TBA, a synthetic anabolic steroid, enhances feed efficiency but raises concerns for carcinogenicity based on animal studies indicating liver hyperplasia and islet-cell tumors[8].

The European Food Safety Authority (EFSA), issued an opinion in 2007 showing that residues of the six hormones do occur though exposure "cannot be quantified". EFSA conceded that epidemiological studies associating the consumption of beef from hormone-treated animals and human health risks are lacking, which they claim is a situation that will most likely not change due to methodological obstacles. The best that EFSA could do is point to a loose association between general meat consumption and hormone-dependent cancer[9].

From an animal welfare perspective, there has been relatively little interest to know how hormone treatment could negatively impact the cattle with the bulk of studies focused on growth parameters. As an Australian study has shown, this could be an area that needs more attention, as they found that hormone treatment could affect the heat tolerance of cattle[10].

Despite the trade war that the EU ban on hormones in meat has prompted, the jury is still out in terms of a conclusive risk assessment in the EU's favour. The growth promoting hormones that may be given to food-producing animals certainly carry serious hazards but whether or not residuals in meat lead to any significant exposure in humans is still up for debate.

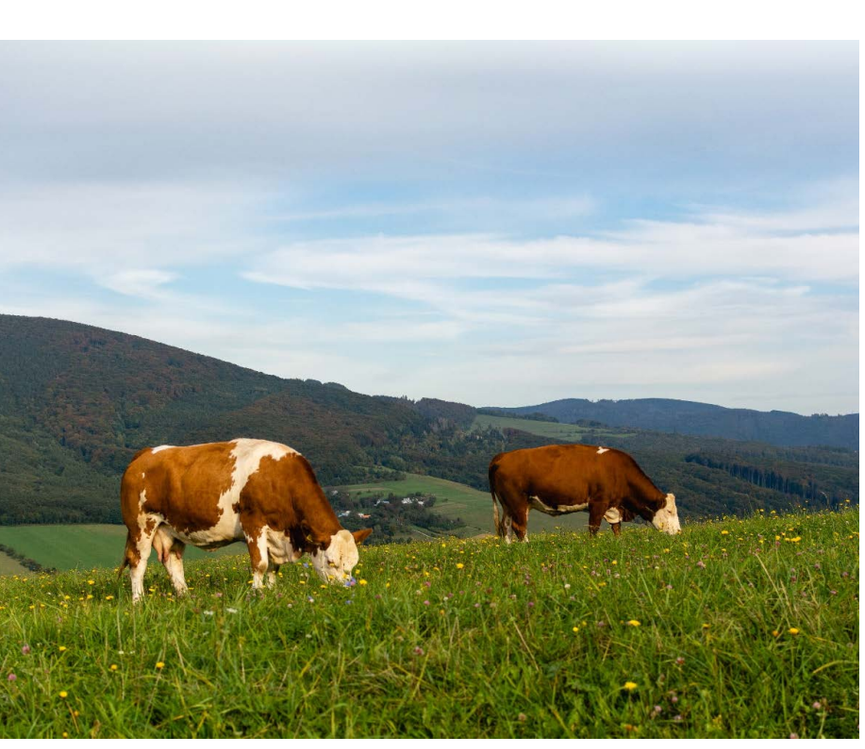


Fig. 2. Free from added hormones, cattle graze freely in the Czech Republic *(image courtesy of Martin Vorel)*

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A Day in the Life of a Toxicologist

How I use toxicology to manage regulatory requirements

I was asked to describe what I do in order to give aspiring toxicologists an idea of some of the different jobs toxicologist end up doing. At first it seemed pretty straight forward but then I had to stop and think; what kind of a toxicologist am I? Among the choices I had are clinical toxicologist, developmental and reproductive toxicologist, environmental toxicologist, forensic toxicologist, occupational toxicologist, pharmaceutical toxicologist, regulatory toxicologist and risk assessment toxicologist. I work at a chemical company that produces surfactants so I quickly realized that I'm working as both a regulatory toxicologist and a risk assessment toxicologist.

By *Barae Jomaa*
Toxicologist at Colonial Chemical, Inc.

The registration of chemicals within regulatory frameworks such as EU REACH is perhaps the easiest part to describe. Chemicals come out of research and development with great function and all the chemists are extremely excited about the prospects. However, before reaching the market, we need to figure out if they're safe if used as intended. That's where I come in. I screen for safety using quantitative structure-activity relationship (QSAR) models and then see if any of the predicted hazards are acceptable for the use of the chemical in an end product. Once we're content with the screening level safety profile and my colleagues at marketing see potential EU demand for this new chemistry, I lead the effort to register the chemical within REACH.

"Before reaching the market, we need to figure out if they're safe if used as intended. That's where I come in."

As with most chemical companies, safety testing is outsourced to external labs. So, part of my work is liaising with labs, checking study protocols and reviewing study reports. Along the way I have learnt quite a bit about the various standardized test guidelines.

In an ideal world, all the required tests are clearly laid out and external labs just carry out the required work. In real life though, there are often multiple tests that can be conducted for one endpoint. The choice of test may, for example, depend on the type of chemical. Moreover, a test battery whose results are interpreted as part of an integrated testing strategy is sometimes required if one is to avoid animal testing.

Once all the hazard data has been generated, the question is; what are the uses expected within a product's life cycle? To answer this question, one has to cover all the steps ranging from the manufacture of the chemical, its formulation into products and its end use. All this information will help establish the expected exposure. ►

As you might have expected, the final step is to ensure that the risk is managed. Where necessary technical measures or protective equipment might have to be used so that the risk is contained. In cases where a risk is not contained by the provision of practical safety measures, then the use is advised against.

Even though regulations will differ across the world, the basic principles remain the same. The main challenge is to understand where the differences lie and to adjust accordingly. To give you an example, I find it very interesting that in Canada one often gets the opportunity to engage with the government toxicologists that are working on your chemical registration dossier whereas in the EU, the process is much more streamlined and leaves somewhat less room for personal interactions. These different approaches are by design. In Canada there is what's called a pre-notification consultation where you discuss the dossier with the regulator before you submit it. In the EU, a chemical registration dossier is submitted and then the regulators will come back with comments, sometimes years later, as part of what's called a compliance check. The name compliance check sounds quite intimidating compared to consultation. Having said that, I do prefer REACH, though there are likely aspects in which the various regulators can learn from each other.

Ensuring that chemicals are safe by design is a challenge for sure but if you enjoy a good challenge like I do, then working as a toxicologist for a chemical manufacturer is the job for you!

ECHA launches new chemicals database

ECHA CHEM is the new solution for publishing information on chemicals. The first release, available now, includes information from all REACH registrations – and there is more to come.

Helsinki, 30 January 2024 – ECHA maintains the largest chemicals database in the European Union (EU), combining industry-submitted data with information generated in the EU's regulatory processes. ECHA CHEM is the new solution to share with the public the growing amount of information hosted by the Agency.

In the first version of ECHA CHEM, you can find information from all the over 100 000 REACH registrations that companies have submitted to ECHA. Later this year, the database will be expanded with the redesigned Classification and Labelling Inventory, followed by the first set of regulatory lists.

Mercedes Viñas, ECHA's Director of Submissions and Interaction said:
"ECHA CHEM is a significant step forward in enhancing our service for sharing data on chemicals gathered through ECHA's current activities. It makes the information available online within a stable system and in a user-friendly manner."

Kai Taka-aho, Director of Information Systems said:
"ECHA CHEM has been designed to be flexible technical platform capable of handling large amounts of data, and adjustable for different needs arising for example from new tasks to be assigned to ECHA. So, one could say with the technological choices made ECHA CHEM is really a future-proof solution."

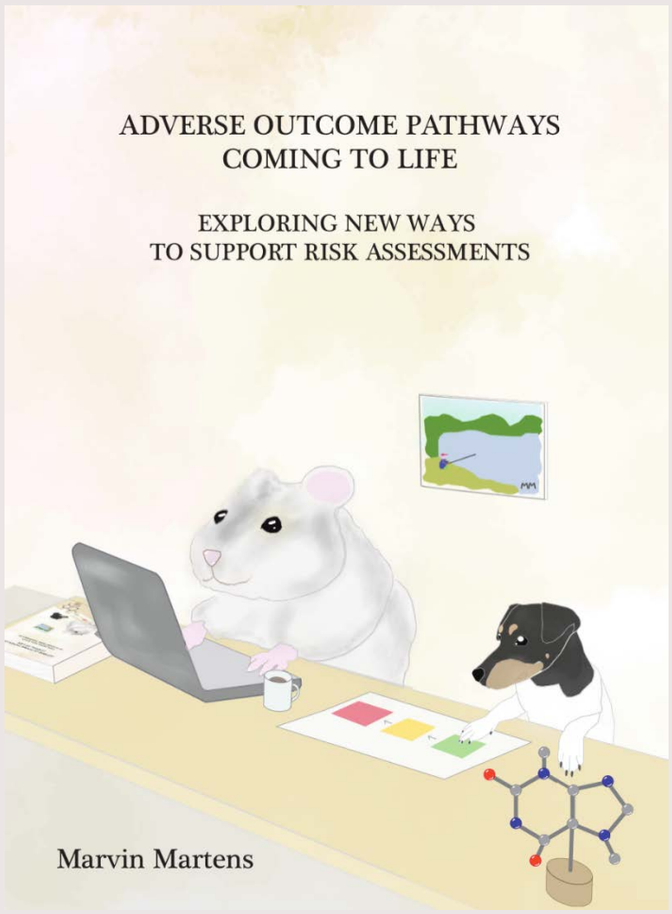
Background
ECHA's current Information on chemicals platform, launched in 2016, grew rapidly and contains today information on over 360 000 chemicals. In 2022, ECHA announced that it would create a new system for publishing chemicals data. ECHA CHEM allows the Agency to better handle the growing diversity and quantity of data, while taking advantage of technological advancements.

Try it yourself: https://chem.echa.europa.eu/

Adverse Outcome Pathways come to life -
Exploring new ways to support risk assessments

By *Marvin Martens*

The ever-growing number of chemicals requiring assessment poses significant challenges for risk assessors. Moreover, the ethical and practical constraints associated with animal experiments have initiated efforts towards a transition to more efficient and humane methods, such as *in vitro* assays, *in silico* models, and human data integration, to drive risk assessments and promote human and environmental safety. However, this transition is accompanied by the complexities that come with developing novel techniques as alternatives to the traditional animal testing.



One pivotal concept in supporting risk assessments is the Adverse Outcome Pathway (AOP) framework. AOPs serve as a structured means to capture and organize mechanistic toxicological knowledge derived from literature, thereby guiding the paradigm shift towards alternative models. By delineating the cascade of biological perturbations into smaller, measurable effects known as Key Events (KE), AOPs provide a roadmap for assessing and documenting chemical risks.

Despite the increasing adoption of AOPs in risk assessments, challenges persist in validating and incorporating *in vitro* assays and, of importance of the presented PhD thesis, large-scale omics datasets into testing strategies. Transcriptomic data, while promising for understanding molecular processes underlying toxicological responses, face obstacles related to reproducibility and acceptance within the risk assessment community.

To address these challenges, my doctoral research[1] had two main goals: enhancing AOP usability, and developing a method for analyzing and interpreting transcriptomic data to gain better insights into KE activation, ultimately aiming to strengthen the acceptance of transcriptomic data in risk assessments.

Improving AOP Usability

The research started with an exploration of the overall usability of AOPs, primarily housed in the AOP-Wiki (aopwiki.org), and their interoperability with molecular pathways in WikiPathways (wikipathways.org), a molecular pathway database. This endeavor involved assessing the coverage of KEs in AOP-Wiki compared to molecular pathways in WikiPathways, revealing opportunities for creating connections between the two databases. Subsequently, efforts were made to make the AOP-Wiki more FAIR (Findable, Accessible, Interoperable, and Reusable) by employing semantic web technologies and producing an RDF version of the data. This work resulted in the creation of a flexible, reproducible workflow in a Jupyter notebook for accessing and analyzing AOP-related data, leveraging semantic web versions of AOP-Wiki, AOP-DB, and WikiPathways alongside other services from the OpenRiskNet project.

Extending AOPs with Molecular Pathways

Building upon the established AOP-Wiki and WikiPathways integration, the research introduced a method for analyzing transcriptomic data, using WikiPathways as an integrative platform. The proposed molecular AOP model aimed to bridge the gap between AOPs and molecular pathways, enabling

the interpretation of transcriptomic data in the context of KE activation. Case studies on liver steatosis and mitochondrial complex I inhibition underscored the potential of this approach to analyze and interpret transcriptomic data, although with acknowledged challenges in modeling molecular AOPs and working with transcriptomic datasets.

Impact of the Research

The overarching goal of this research was to harness existing mechanistic knowledge in AOPs and leverage large-scale omics approaches to drive the transition away from animal testing in chemical risk assessments. The increased accessibility and interoperability of AOP-related knowledge and data make AOPs more FAIR, and could pave the way for more effective risk assessment strategies, ensuring human and environmental safety. Furthermore, the proposed method for analyzing transcriptomic data using molecular AOPs holds promise in bridging big data approaches with the risk assessment community, providing a clear model for assessing KE activation.

In conclusion, my research represents a significant step towards enhancing chemical safety assessment methodologies. By improving the usability of AOPs and integrating transcriptomic data analysis, the research opens new avenues for more efficient and ethical risk assessments, ultimately contributing to a safer world for both humans and the environment.

[1] Martens, MTLJ. 2024. Adverse outcome pathways coming to life: Exploring new ways to support risk assessments. Maastricht University. DOI: 10.26481/dis.20240129mm

Congratulations!
Gratuliere!
Félicitations!
Congratulazioni!
Gratulerer!
Gefeliciteerd!
Parabéns!
Felicitaciones!

The answer to the Christmas puzzle was “Lets toast to yesterdays achievements and tomorrows bright future”.

Thanks for all the participants but there can only be one winner, and the winner is…

Wim Best!

AIO toxafette - Marjolein van Borselen

In the toxafette, Ph.D. students specializing in toxicology exchange insights gained from their research projects. Each edition features a fresh participant who responds to a set of inquiries before passing the torch to another doctoral candidate. In this instance, Marjolein van Borselen, affiliated with the Pharmacology and Toxicology division at Radboudumc in Nijmegen, steps forward to elucidate her project, which integrates elements of both pharmacology and toxicology.

Can you introduce yourself?
I am a second year Ph.D. student and directly started my Ph.D. after getting my medical degree. I studied in Nijmegen and I am happy that I got my Ph.D. position in Nijmegen as still many friends live here. And of course, I am enjoying the research…

How would you explain the subject of your research to a layperson?
My Ph.D. project is focused on drug dosing recommendations for children with obesity. As children aren't tiny adults, they are at risk of drug toxicity or drug therapy failure. In addition, we don't completely understand the effect of obesity on the physiology of children and how this will affect drug disposition. With my project, we hope to get a better understanding of the obesity-related physiological changes. I will use this information to develop a computer model of children with obesity. This virtual population will be used to simulate dosing recommendations.

How is your research related to the field of toxicology?
My research is focused on the prevention of drug toxicity and harmful effects of the wrong dosages in children with obesity.

What was your motivation for starting a Ph.D. program?
Already during my bachelor, I enjoyed the idea of performing research besides being a medical doctor. This motivation grew during my clinical rotations. I am very happy that I got the opportunity to start in Ph.D. research.

How do you see the future of your research topic (follow-up research / social impact)? What do you hope for?
I hope that with the results of my research, the understanding of obesity-related physiological changes will grow, and that this knowledge will improve clinical care for children with obesity.

What is the best advice that you have received as a Ph.D. student or would like to give to another Ph.D. student?
Enjoy your time and take your time as a Ph.D. student as this is the moment that you have the most TIME.

Is there an experience that you had that you would like to share with other PhD student in case it happens to them?
I had the opportunity to attend an international conference with the sole purpose of meeting three experts who were presenting there. Since my supervisor couldn't attend, she encouraged me to go alone. As a first-year Ph.D. candidate, I was a bit anxious about meeting these prominent figures, but it turned out to be the best conference experience! So, if you have the opportunity, go to a conference by yourself as you can have so much more interaction with other researchers.

What advice would you like to give to the more senior/experienced people in your field?
Although time is becoming sparse and your schedule is loaded, take some time for yourself for your own research, and use it to scroll through PubMed or do your own experiment as you are trained to be a researcher and not a manager. So, schedule time for yourself and don't be afraid to waste it on something seemingly irrelevant as you had the time during your Ph.D.

What goals do you have regarding your career after finalization of your PhD? Would this be inside or outside academia, and why?
I am enjoying research at the moment and thinking about an academic career instead of a medical one. It would also be possible to try a combination, but I believe that research is not a side job.

Please answer the question from the last toxafette PhD-candidate: What qualities do you think are important to have as a PhD candidate?
In my opinion, a PhD candidate needs to be curious and should enjoy sinking one's teeth into a project.

Join us for the 45th edition of the annual meeting of the Dutch Society of Toxicology

on June 18 and 19, 2024 at “De Reehorst” Ede

This Lustrum edition will take you on an journey through Toxicology’s evolution. Many developments including the emergence of artificial intelligence, the shift from traditional animal experiments to *in silico* and *in vitro* New Approach Methodologies, the rise of three- dimensional organoids and (multiple) organ-on-a-chip models, and the widespread availability of toxicological data.

During the upcoming annual meeting we will reflect on the field of toxicology: What lessons does the past offer? Are all changes improvements, and what lies in our near future? The overarching question beckons: Do we need an entirely new toxicology framework, or should we seamlessly integrate these innovations into the existing one?

Abstract Submission

If you are a PhD candidate, Bachelor/Master student or (young) professional you can submit an abstract for the annual NVT meeting. In addition to the regular PhD platform and speed presentations, we will have a dedicated session for (young) professionals to present their project. Therefore, professionals from all fields and disciplines of toxicology are encouraged to submit an abstract for this session. The best abstracts will be selected to participate in these sessions. Everyone with a submitted abstract will get the opportunity to showcase their research through a poster presentation. A jury will award the best oral and poster presentation a small prize during the award ceremony.

Abstract submission and registration is now open and available on the website:
www.meeting2024.toxicologie.nl

Abstract submission for oral presentations will close the 19th of March and registration will close on the 19th of April.

We look forward to seeing you at the meeting!

The NVT organizing committee

Website: www.meeting2024.toxicologie.nl
Contact: nvtmeeting@gmail.com

See the next page for our programme!

JUNE 18TH	PROGRAMME		
08:30-09:00	Welcome/Registration		
09:00-09:10	Opening		
09:10-10:00	Keynote lecture 1		
10:00-10:30	Break		
10:30-12:00	Interconnected hazards: Bridging disciplines in Toxicology	ToxTalk: Short communications from the field	
12:00-12:30	Lunch		
12:30-13:30	Poster session	Sponsor stands	
13:30-15:00	Fit for Purpose Testing: Opportunities and Challenges in experimental models	PhD platform	
15:00-15:30	Break		
15:30-17:30	Data visualisation	Weighted correlation net-work analysis	Career session
17:30-18:30	Drinks & networking		
18:30-20:00	Dinner		
20:00-00:00	Party		

JUNE 19TH	PROGRAMME	
08:00-09:00	Breakfast	
08:40-09:00	Welcome/Registration	
09:00-09:50	Keynote lecture 2	
09:50-10:15	Break	
10:15-11:45	Public perception and data availability: the risk of quantity over quality?	The Toxicologist's Guide to the Regulatory Landscape
11:45-12:45	Joep van den Bercken award 2023 + 2024	
12:45-13:15	Lunch	
13:15-14:15	Poster session	Business meeting
14:15-15:45	Computational Frontiers in Toxicology: Unveiling *in silico* Horizons	Speed presentations
15:45-16:15	Break	
16:15-16:45	Grand finale	
16:45-17:00	Award ceremony and closing	

WANTED: Active members to participate in future proofing working groups

Who is interested to join one of the working groups to support NVT in becoming ready for the future?

As introduced earlier in the TCDD the NVT board has launched a working group to evaluate what is needed to make sure our society continues to have a good fit with our members' interests and has the right organizational structure to stay close to scientific developments and toxicological practices.

The future proofing-working group started last year by Anne Kienhuis and Joanne Salverda from the NVT board, and several of our esteemed members offered their valued support, including Lambert Creuwels, Anja Slikkerveer, Margriet van der Zee, Iris van de Gevel, Kelly Caris and Charlotte Pauwels. Main input for the working group were the results of the NVT questionnaire and the outcome of a round-table session held by the sections.

After several fruitful brainstorm sessions, three topics were identified for further evaluation:

1. **Subdivision of sections – lead by Anja Slikkerveer**

This working group will make a proposal for a new / improved structure for the sections of the NVT, that takes into account the current topics in toxicology. Is the current section structure the best structure to share information and learn from each other? Do we need to create new sections? Or is there a more future proof alternative?

2. **NVT and communication – lead by Margriet van der Zee**

To maximise the benefits of our collective expertise, we plan to enhance the flow of information among our organisation's members. We will develop a strategic communication plan that outlines our objectives (e.g. informing, advertising), defines our target audiences (e.g. existing members, new members, broader community), and specifies the channels we will use to communicate them (e.g. website, LinkedIn, social media platforms). We will also estimate a budget and timeline for implementing different components of the plan and will consider engaging a professional communication expert to execute some of the tasks involved.

2. **Positioning NVT – lead by Iris van de Gevel and Kelly Caris**

This working group will further investigate how we can better position the NVT in service to and in close collaboration with its members. Where can we professionalize the NVT for instance in supporting the sections and members? What can we learn from other professional associations? What is the framework within the NVT must position herself? Besides these more general topics, we will also look at the need to further balance applied and scientific topics, or what can we do to recruit new members?

After the initial steps were taken in terms of launch and scoping, we now would like to ask your input and your active participation in one of the working groups.

Interested? Please contact us!
Anne.Kienhuis@rivm.nl
Joanne.Salverda@nouryon.com

TERUG NAAR INHOUD