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TOXICOLOGIE

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SPECIAL THEME

POST-BREXIT SAFETY AND TOXICOLOGY

- REACH AFTER BREXIT, WHAT CHANGES FOR REGISTRATION AND SAFETY?
- BREXIT REGULATORY BULLETIN BOARD
- IMPACT OF BREXIT ON (TOXICOLOGY) STUDENTS AND SCIENTISTS

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Colofon

**Toxicologische Communicatie,
Data en Documentatie**

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TCDD
TOXICOLOGIE

Inhoud

TERUG NAAR INHOUD

Editorial

The year 2021 is a couple of months old and most of us hoped that a lot would have changed. Now that the Covid-19 year 2020 is over we wanted to look forward, however until now not much has changed. But hopefully, the vaccination program could help us to start thinking about the future. One thing that has changed is our relationship with the island across the canal. The year 2021 marks the start of a new period in which the UK is officially not a part of the EU anymore. In our first issue of 2021, we will try to help you understand the implication of this break, for REACH, for plant protection regulation, for GLP status of work conducted in the UK and for European Registered Toxicologist in the UK.

We will also bring you a new section, ‘What’s Next’, about all the jobs that you might end up in as a Toxicologist. And we will help you to figure out if you need to be scared of 5G or need to welcome it with open arms. We hope you enjoy reading the new edition as much as we did writing it.

This first edition of 2021 will also mark my last, as I will be leaving the editorial team. For me, 2021 will be the year that marks the start of a new adventure (if you are curious, you can find more on it here). If you are interested in a place in the editorial team, please send us a message at redactie@toxicologie.nl.

On behalf of the editorial team,

Jasper Woutersen

Photo by Jess Bailey on Unsplash

News from the board

Welcome to the latest issue of TCDD, with as main theme 'Post-Brexit Safety and Toxicology.' On behalf of the Board, we wish you all the best during this prolonged period of lockdown, which I realize is affecting us all, both in terms of lack of physical interaction with colleagues as well as our state of mind and productivity.

We do hope to see many of you at our virtual NVT Annual Meeting which will be held on **June 9-10 2021, at Reehorst, Ede.** We have developed an exciting online programme around the theme "*The (r)evolution of toxicological models – how to address safety in target species.*" As in previous years, the first day will be specially tailored to our students and PhD candidates, while the second day (June 10) will be for all members of our society.

Please note that we are looking for evaluating all the exciting PhD dissertations published in 2020 and will be accepting nominations for the **Joep van den Berckenprijs** up to **March 1, 2021**. Please see the website for more details Joep van den Berckenprijs - Nederlandse Vereniging voor Toxicologie

For any of you interested in **joining the NVT board** and playing a role in the important work of our Society in the coming years, we are looking for volunteers! We have positions available for general board member as well as member secretary ('secretaris van de vereniging') from June 2021 on. Please contact me for more information.

Kind regards

Juliette Legler, president NVT

NVT 2021 Announcement

"The (r)evolution of toxicological models – how to address safety in target species"

As toxicologists we aim to assess the safety of substances in the species we wish to protect, *i.e.* the target species. However, often we cannot simply conduct toxicity testing in the target species itself. This forces us to use model systems, traditionally animal models and nowadays also *in silico* and *in vitro* models. Obviously, these models are a proxy of the truth and have their own pros and cons. While animal models have many advantages, there is an urgent need for replacements. The Dutch government strongly promotes the reduction of animal testing. In addition, the U.S. EPA announced that they will stop conducting or funding mammalian animal studies by 2035. During the upcoming NVT Annual Meeting, we will talk about safety assessment and toxicity testing in target species and discuss the challenges that we face in applying alternative models into (regulatory) practice. What are the best models for the target species of interest? Can we measure within the target species itself? When do we have sufficient information to predict safety in target species? How do we implement innovative and predictive models in regulatory risk assessment? Join our discussion on these important issues during the hybrid NVT Annual Meeting on **June 9-10th**, **2021**, in the Reehorst, Ede and online.

SECTIE FARMACEUTISCHE TOXICOLOGIE

22nd and 29th of April 2021

Scientific meeting

We are delighted to invite you to the Webinar-based Scientific Meeting of the Section Pharmaceutical Toxicology of the Dutch Society of Toxicology (NVT). The Meeting is entitled **"Clinical and toxicological aspects of novel antitumor drugs"**. It will take place in two 2-hour sessions, **on the 22nd and on the 29th of April 2021, both from 4-6PM.**

We have composed an exciting program (see table for preliminary program) with national experts focusing on clinically and toxicologically relevant aspects of novel oncolytics, including the personalized applied clinical dosing, impact of transporters on kinetics as well as impact of the microbiome and the evaluation of these drugs from a regulatory point of view. Speakers from (university) hospitals and government will share their perspectives.

Further details of this Symposium will be released soon. Save this date, so you won't miss the opportunity to gain knowledge on novel antitumor products.

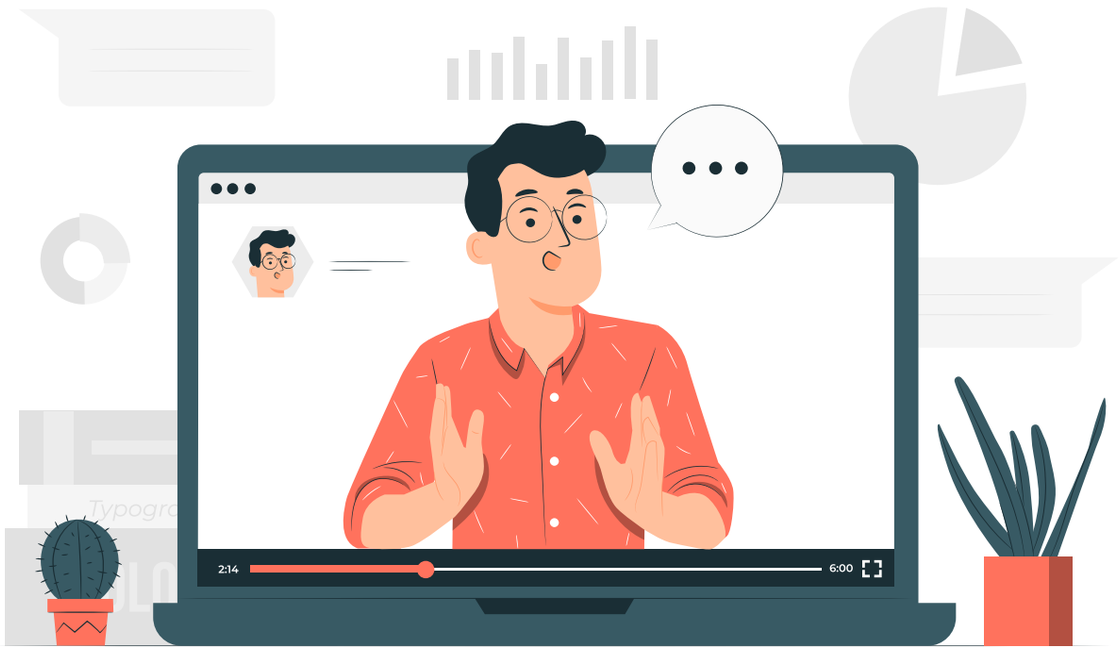
Best regards,

Section Pharmaceutical Toxicology: Daan Touw (chair), Kris Siezen (treasurer), Yolanda Ponstein (secretary), Sylvia Le Dévédec, Damiën van Berlo, Ilonka van Hoof, Lambert Creuwels.

Part 1 – Thursday 22nd April:		
15.45 -15.50 h	Opening Scientific Meeting	Chair Section Pharmaceutical Toxicology
15.50 – 16.20 h	TBD	General introduction new developments on oncolytics
16.20 – 16.55 h	Dr. N. van Erp (Radboud UMC / DPOG)	Personalized dosing instead of Flat dosing of targeted oncolytics
16.55 – 17.00 h	Short break	
17.00 – 17.30 h	Dr. Mark van Bussel (CBG)	Research outcome: dose finding and safety new oncolytic products
17.30 – 18.00 h	Dr. J. de Haan (UMCG)	The microbiome & oncolytics
18.00 h	Closure	

Part 2 – Thursday 29th April:		
16.15 -16.20 h	Opening Scientific Meeting	Chair Section Pharmaceutical Toxicology
16.20 – 16.55 h	Dr. A. Schinkel (NKI)	Impact of transporters on the pharmacokinetics of novel anticancer drugs
16.55 – 17.30 h	Dr. B. Venhuis (RIVM)	Oncolytics in surface water
17.30 - 18.00 h	PhD Students	Poster pitches & election best poster (by audience: through poll)
18.00 h	Closure	

SECTIE ARBEIDSTOXICOLOGIE
EN SECTIE RISICOBEOORDELING



Webinar
Flatten the curve

Beste NVT-lid,

Hier vinden jullie het programma voor het webinar van de Nederlandse Vereniging voor Toxicologie, sectie Arbeidstoxicologie en sectie Risicobeoordeling (NVT) i.s.m Contactgroep Gezondheid en Chemie (CGC).

Het webinar vindt plaats op donderdag 18 maart 2021 van 13.20 tot 16.30 uur. De link ontvang je uiterlijk 24 uur van te voren.

Het onderwerp is: **Flatten the curve. Hoe vertalen piekblootstellingen zich in gezondheidsrisico's en hoe beheers je die?**

Aanmelden voor het webinar kan hier.

Noot: de link is **alléén voor NVT-leden** en mag niet doorgestuurd mag worden.

Collega's die geen lid zijn van de CGC, kunnen een mailtje sturen aan het secretariaat: cgc@epsnet.nl

Graag tot 18 maart 2021.

NVT - sectie Arbeidstoxicologie en sectie Risicobeoordeling

New PET course:
Current topics in toxicology

When: 2-3 December 2021
Coordinator: Prof.dr.ir. Juliette Legler
Location: Utrecht

This new course is intended for (registered) toxicologists who would like to keep up to date on the latest developments in the field of toxicology. The course will consist of 3 parts, namely an afternoon, evening and subsequent morning session in which new insights and perspectives in key current topics in toxicology will be presented.

https://www.toxcourses.nl

TERUG NAAR INHOUD

REACH after Brexit

What Changes for Registration and Safety?

By *Barae Jomaa and Jasper Woutersen*

A downward spiral of loosened safety regulations designed to give businesses a competitive advantage is a potential outcome of Brexit. The balancing act that plays out between the various countries of the European Union has often resulted in more thoughtful regulations that incorporate various points of views. This high standard that has so far been achieved in Europe for food, plant protection products, biocides and chemicals is under threat in post-Brexit UK. REACH is one of the European safety regulations that has been lauded across the globe for its clarity and risk-based approach. Will the so-called UK REACH follow the EUs shining example or chart its own course by doing away with what has been touted by Brexiteers as a slow, inefficient, inflexible and bureaucratic system?

The withdrawal of the UK from the EU occurred on the 31st of January 2020, after long Brexit talks between the EU and the UK and the eventual signing of the EU (Withdrawal Agreement) Act 2020. The transition period for the withdrawal was valid up to 31 December 2020 and from that date onwards the UK was no longer a participant in the European Union Customs Union and European Single Market. The withdrawal has a diverse range of implications on a lot of different sectors. One of the sectors that is of interest to us toxicologists, is the chemicals sector and with that the REACH regulation. The UK government has decided that the UK will not participate in European Chemicals Agency (ECHA) and in the EU regulatory framework for chemicals[1]. It is suggested that the UK will design their own UK REACH regime. The regime is initially designed to be UK-wide, however as Northern Ireland is still part of the EU in Northern Ireland EU REACH regulations will continue to apply. In Great Britain the Health and Safety Executive (HSE) is now established as the UK Chemicals Authority and with that taking over the function of the ECHA. The goal is to have the UK REACH regime replicate the EU system as much as possible and with that, maintaining the fundamental aims and purposes of REACH. However, the industry and environmental NGO stakeholders have voiced their concern that the new way of registration will not be workable and would be too costly to work with. The exact nature of the UK REACH regime and the level of cooperation with ECHA seems to be still a little unclear.

For the chemicals industry, one of the bigger implications of the separation between UK and EU REACH will be that any UK-based company wanting to register a substance in the EU will need an EU-based company as duty holder. The other way around holds true as well, all the EU based companies that want to put chemicals on the market in the UK need to have a UK based company as duty holder for UK REACH registration. The transition period for this has already expired at the end of last year (2020). In the discussions on the Comprehensive Free Trade Agreement between the UK and EU it was discussed how the new UK guidelines for chemicals will be implemented. In the Annex 5-E of this document it is stated that the UK and EU will be cooperating on chemical compliance, however the UK →

included that they keep the right to “setting its own priorities on chemicals regulation, including establishing its own levels of protection in respect of the environment, and human and animal health” in the future. All the present needs for registration, evaluation, authorization and obligations as well as the labeling and classification rules based on the UN globally harmonized system will continue to apply under UK REACH.

There is a saying that imitation is the best form of flattery and the fact that REACH has been replicated in countries as near as Turkey and as far as Korea can indeed be interpreted as a compliment. Unlike classification and labelling regulations or inventory-based systems, REACH includes a clear set of physical, human and environmental safety endpoints that must be tested and evaluated. Moreover, the approach of this European regulation provides the chemicals industry with tiered testing requirements that are easier and less costly to achieve at lower volumes and increasingly stringent and costly at higher volumes. Ths gradual increase in requirements helps businesses grow from R&D to mass market and to ensures that the widespread use of certain chemicals (higher environmental exposure) is given priority in comprehensive safety assessments. At the same time, small and medium-sized enterprises (SMEs) producing substances in smaller amounts (lower environmental exposure) are not overburdened with costly and time-consuming testing.

Central to REACH is the chemical safety assessment performed when chemicals are placed on the market at 10 or more Tonnes per year. This assessment is documented in the Chemical Safety Report (CSR), which is the basis for exposure scenarios communicated to users as well as a foundation for other REACH processes such as subatance evaluation, authorisation and restriction. A chemical safety assessment uses hazard data from relevant endpoints and factors in exposure to produce a risk characterization ratio (RCR), which should always be below 1 for the risk to be deemed as adequately controlled. According to ECHA, the RCR is intended to, where available, cover all endpoints, all populations, all exposure routes and all time scales[2]. In other words, RCRs can be perceived as a quantitative set of descriptors of the risks associated with a certain substance. The formula is as follows:

RCR = PEC/PNEC or EXPOSURE / DNEL

Where PEC is the Predicted Environmental Concentration, PNEC is the Predicted No-Effect Concentration and DNEL is the Derived No-Effect Level. In brief, the predicted/derived no effect concentrations/levels are obtained by dividing dose descriptors with an assessment factor which takes into consideration the differences between the experimental condition (e.g. effects on rodents) and the target condition (e.g. human effects) and/or to account for differences within a test (e.g. interspecies differences/route extrapolation/data quality). For environmental endpoints, the PEC/PNEC ratio is calculated, while for human health endpoints Exposure/DNEL is the method used to characterize risk (at least for threshold effects).

What changes UK REACH would implement, long-term, is currently unknown. However, there will be many avenues where differences could occur. The US Environmental Protection Agency (EPA) for example stated that it will reduce its requests for, and funding of, mammal studies by 30% by 2025 and eliminate all mammal study requests and funding by 2035. Animal tests, raise ethical concerns and only offer limited predictivity for human health. Alternative *in vitro* and/or *in silico* methods as well as testing strategies on the other hand, have improved substantially since the early days of REACH. The UK is not bound by the EU consensus-seeking bureaucracy anymore and could find it easier to follow the US EPAs lead on the elimination of animal testing for regulatory purposes. Such a shift would clearly put pressure on the ECHA to enact similar measures. This is just the tip of the iceberg since the UK could choose to opt-out of certain required endpoints in a way that is similar to how the UN model system for classification and labelling follows a building block approach – countries choose which hazard categories need to be implemented and, in some situations, countries choose their own hazard classes (e.g. combustible dust classification). Will the UK pay less attention to endocrine disruptors or nanomaterials? The UK joined the European Community in 1973 so we are clearly at the beginning of a new journey and a new dialogue that will certainly continue to play out in the realm of chemical safety.

1. Rhodes, C., Rough, E. & Hutton, G. End of Brexit transition: chemicals regulation (REACH). (2021).

2. European Chemicals Agency. *Guidance on information requirements and chemical safety assessment Part E: risk characterisation.* (ECHA, 2016).

Brexit Regulatory Bulletin Board

By *Carolien Schophuizen*

Regulation of plant protection products (PPP)

From 1 January 2021, Great Britain (England, Scotland and Wales) will run their own pesticides regulatory regime. New decisions taken under the EU regime will not necessarily be taken over by Great Britain. This concerns new EU plant protection product (PPP) legislation as well as active substance and maximum residue level (MRL) decisions. The Health and Safety Executive (HSE) will continue as the national regulator for the whole of the UK, on behalf of the UK government and the decentralized administrations. The HSE has published a guidance for anyone working with PPPs. It is designed to help you understand how Brexit may affect PPP regulation.

CLP – Classification, labelling and packaging of substances and chemicals

The classification of chemicals placed on the market in Great Britain are regulated by the GB Classification, Labelling and Packaging Regulation, known as GB CLP. For more information and specifics, please follow this link: https://www.hse.gov.uk/chemical-classification/index.htm

Biocides - Authorisation of biocidal substances and products

The European Biocidal Products Regulation (EU BPR) has been copied into the law of Great Britain. However, amendments have been made to allow it to apply for Great Britain. Although most of the content of the EU Biocidal Products Regulation has remained the same, it now works as a detached system, named the GB Biocidal Products Regulation (GB BPR). For more information and specifics, please follow the link: https://www.hse.gov.uk/biocides/brexit.htm

Pharma, Medicines and medical devices

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK's standalone medicines and medical devices regulator. Various guidances are available from the website of the MHRA, indicating the medicine and medical device requirements now the Brexit transition period has ended. Furthermore, the National Institute for Biological Standards and Control (NIBSC), one of the three centres of the MHRA, has published on information for manufacturers of biological medicines.

Food and animal feed safety in the UK

The responsibility for assessing food and animal feed safety in the UK has been taken on by the Food Standards Agency (FSA) and Food Standards Scotland (FSS). Currently the food and feed safety rules have not changed much, since European legislation has moved into UK law. However, when rules on food and feed marketed in Great Britain (GB) need to change the UK will apply their own risk analysis process rather than the EU's process. Furthermore, the FSA uses a four-nation approach throughout the risk analysis process. The four nations (England, Northern Ireland, Scotland and Wales) will work together when changes to food and feed safety rules are needed. Regular discussions will be held by the FSA and FSS on issues going through the risk analysis process, ensuring that advice is effective for the UK as a whole, or individual nations as needed.

Food contact materials (FCM) legislation

In preparation for Brexit, a piece of legislation called the "The Materials and Articles in Contact with Food (EU Exit) Regulations 2019" was passed in the UK. This regulation has been prepared to ensure that there is continuity after the 'EU Withdrawal Date' which now has passed. The reassignment of responsibilities that were previously held by the EU to the UK regulator is layed out, and a roadmap is provided by which the UK legislation can be updated to keep it in line with EU measures.

GLP status of non-clinical studies conducted in the UK

According to Article 2 of Directive 2004/10/EC, when submitting results of non-clinical studies, the laboratories referred to in Article 1 of that Directive shall certify that the tests have been carried out in conformity with the principles of Good Laboratory Practice (GLP). Following Decision C (97)186/Final of the OECD Council on the Mutual Acceptance of Data in the Assessment of Chemicals, data generated in the testing of chemicals in an OECD Member Country (including UK), in accordance with OECD Test Guidelines and the OECD principles of GLP, are accepted in other OECD Member Countries. For more information and EMA Practical guidance for procedures related to Brexit, visit: EMA/478309/2017 Rev. 51.

Impact of Brexit on (Toxicology) Students and Scientists

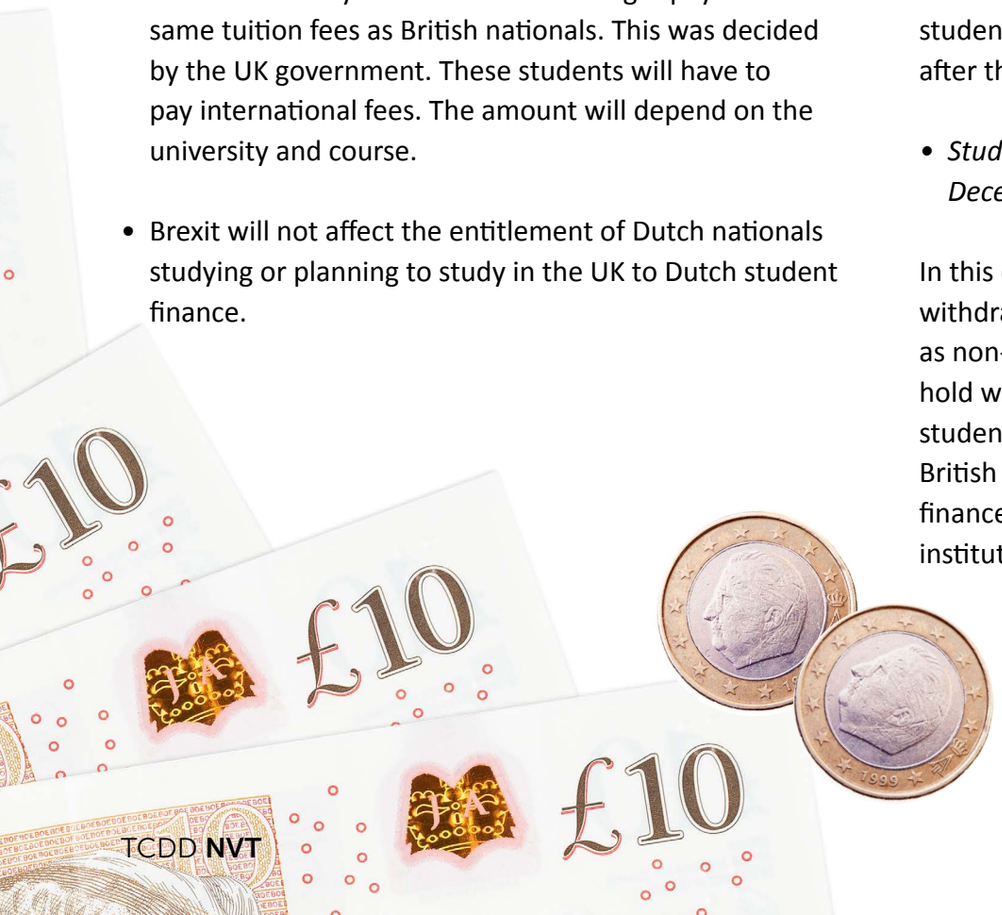
By *Maaike Steenhof*

Dutch students in the UK - Impact of Brexit on tuition fees and student finance[1]

- The UK government has announced that tuition fees for EU students in the UK will not change as a result of Brexit in the 2020/2021 academic year. These EU students will pay the same tuition fees for the entire duration of their course.

- EU nationals who start studying in the UK in the 2021-2022 academic year or later will no longer pay the same tuition fees as British nationals. This was decided by the UK government. These students will have to pay international fees. The amount will depend on the university and course.

- Brexit will not affect the entitlement of Dutch nationals studying or planning to study in the UK to Dutch student finance.



British students in the NL - Impact of Brexit on tuition fees and student finance[1]

- *Students already living in the Netherlands on or before 31 December 2020*

In this case, British students fall under the withdrawal agreement. For British students who are living in the Netherlands before the transition period ends on 31 December 2020 nothing will change with regard to the entitlement to pay statutory tuition fees and receive student finance. This applies even if you start a new course after the transition period ends.

- *Students coming to live in the Netherlands after 31 December 2020*

In this case, British students do not fall under the withdrawal agreement. British nationals will be treated as non-EU/EEA citizens. The type of residence permit you hold will determine whether you are entitled to receive student finance and pay statutory tuition fees. In most cases British students will be not be entitled to receive student finance and pay statutory tuition fees, and will have to pay institutional fees.

Impact of Brexit on Erasmus/Horizon programmes[2,3]

It was clear for a long time that the UK will continue to participate in the Erasmus+ (2014-2020) and Horizon 2020 (2014-2020) programmes upon completion of the projects. Until the Brexit deal, however, it was not clear whether the UK would be able to participate in the upcoming Erasmus+ (2021-2027) and Horizon Europe (2021-2027) programmes. As a true cliffhanger, the answer came just one week before the 1st of January deadline. Luckily it has ended with a favorable outcome for U.K. researchers. The deal includes a hoped-for provision for science—a relief for many scientists in the UK as well as for their international collaboration partners. In exchange for a contribution to the EU budget, the United Kingdom will join the forthcoming Horizon Europe research program, which will spend €85 billion over the next 7 years.

The trade deal means that the United Kingdom will become an ‘associate’ member of Horizon Europe, which formally started January this year but will not issue its first grants until March or April. This means UK-based researchers will be able to take part in the programme in the same way as their EU colleagues — for example, by competing for prestigious grants from the European Research Council and Marie Skłodowska-Curie Actions programmes. But UK researchers and firms will be excluded from Horizon Europe’s new European Innovation Council Fund, which is designed to support start-up and university spin-off firms. →

The UK will pay into Horizon Europe a sum that is proportional to its gross domestic product, and this cash will boost the programme's overall budget, although the figure has yet to be announced. If, for two consecutive years, the country takes out more than it puts into the programme, by an amount that exceeds 8% of its contribution, it will have to reimburse the EU to cover the difference. An agreement defining the fine details of the association must now be made, and UK researchers will not be able to participate in the programme until this happens. A committee of UK and EU representatives will discuss and approve the terms of association.

European Registered Toxicologist (ERT) status[4]

Before Brexit, members of the UK Register of Toxicologists (UKRT) gained automatic membership of the EUROTOX Register of Toxicologists and were entitled to use ERT as a post nominal. The UKRT have sought guidance from EUROTOX regarding the effect of Brexit on members and their ERT status. Reassurance has been provided that EUROTOX is not a political organisation and that the recognition of ERT as a professional qualification is completely independent of the European Union and will thus not be affected by any Brexit-related outcome. Thus, British ERTs keep their ERT status and new UKRTs still gain automatic EUROTOX membership and can use ERT as a post nominal.

References

1. https://www.government.nl/topics/brexit/impact-of-brexit-on-higher-education-and-research
2. Nicholas Wallace. *Science* 08 Jan 2021: Vol. 371, Issue 6525, pp. 110-111. https://doi.org/10.1126/science.371.6525.110
3. Elizabeth Gibney. *Nature* 05 Jan 2021: Vol. 589, 179.https://doi.org/10.1038/d41586-021-00009-y
4. https://www.rsb.org.uk/careers-and-cpd/registers/uk-register-of-toxicologists

Development, validation and application of a novel bioengineered intestinal tubule

By *Paul Jochems, Utrecht Institute of Pharmaceutical Sciences - Department of Pharmacology*

On the 13th of January 2021, I (Paul Jochems) successfully defended my PhD thesis entitled "Development, validation and application of a novel bioengineered intestinal tubule". During my PhD, I developed a novel small intestinal in vitro model to subsequently use for (alternative) dietary protein source testing. We focused on safety and biological effects of these protein sources in our model. In this article I share insights into my technology, experience, and future plans.

Over the last decade *in vitro* model development has gained a lot of attention. Novel technologies are bringing us slowly, step-by-step, closer to modelling the *in vivo* situation in an *in vitro* system. In the first period of my PhD I was performing such a step-by-step approach to eventually develop the bioengineered intestinal tubule [1]. In comparison to the current gold standard, cultivation of Caco-2 cells on Transwell™ inserts, we incorporated 3-dimensional tube structured membranes, an extracellular matrix coating and physiological relevant shear stress (figure 1).

Figure 1. Graphical representation of the bioengineered intestinal tubule

These changes in microenvironment improved the physiological resemblance of the Caco-2 cell towards the small intestinal phenotype [1]. We discovered the Caco-2 cells cultivated in our bioengineered intestinal tubule format differentiated into different specialized epithelial cell types. In comparison to the gold standard, known to solely differentiate into absorptive enterocytes, we showed differentiation towards absorptive enterocytes, goblet-, Paneth-, enteroendocrine- and stem cells [1]. Additionally, exposing the Caco-2 cells to physiological flow resulted in the formation of villi-like structures [1]. These villi-like structures are essential for the enlargement of the absorptive surface area *in vivo*. The development of *in vitro* models closely mimicking the physiological environment, like the bioengineered intestinal tubule, is relevant for multiple aspects. It improves compound evaluation early in the R&D pipeline resulting in more accurate predictions and R&D cost →

reduction. Furthermore, is it essential for the effective reduction and replacement of animal experimentation, a hot topic on the political agenda.

After we developed the bioengineered intestinal tubule we used it to test (alternative) dietary protein sources for safety and biological efficacy [2]. The search for alternative food sources is ongoing as the ever-growing world population puts a pressure on global food security. We evaluated a wide diversity of protein sources (*e.g.* lesser mealworm, yeast and pea protein) in both a healthy and diseased state (modelling a *Clostridium difficile* infection) [2,3]. The effect on intestinal biological parameters were assessed, like the epithelial barrier, cell viability, brushborder enzyme activity and immune responses [2,3]. We believe that the improvement of *in vitro - in vivo* extrapolation is multidisciplinary and data analysis needs to be improved as well. To this end we developed a computational clustering tool. Thereby, we considered all measured biological parameters of a dietary protein at once and clustered different protein sources with similar biological activity together [2]. While using this analysis approach we were still able to pin-point specific characteristics why certain proteins were (or were not) clustered together. This is also useful for other comparisons like different concentrations, different samples along the production pipeline or competitor comparisons.

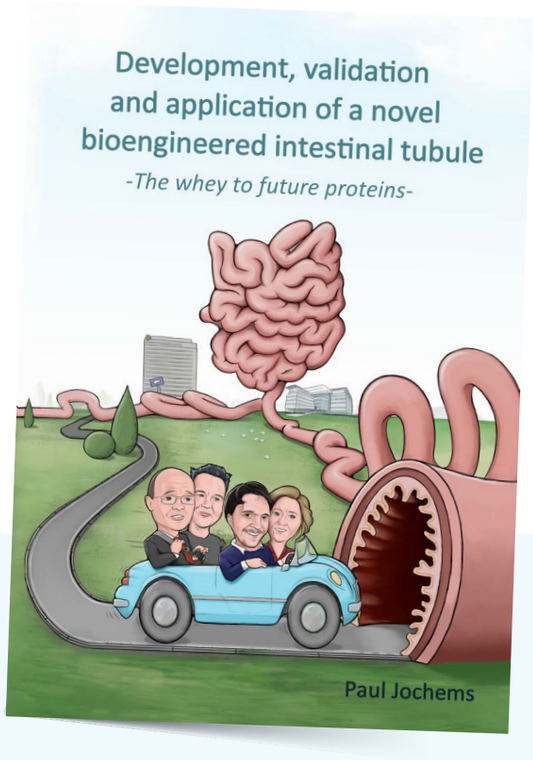
We believe that our bioengineered intestinal tubule and creative analyzing approach is useful for a wide variety of industries like the food-, pharmaceutical- and feed industry. Unfortunately, promising technologies developed in academic research often do not move further than the early concept stage. This is sufficient for publication in peer reviewed journals (which are very much focused on innovation) but not for implementation for regulatory testing or screening approaches. The potential of our intestinal model is underlined by awarded research grants aiming to explore different markets and further development. Personally, I have entrepreneurial aspirations and as follow-up to my PhD research we are now exploring the possibilities to form a start-up company called GUTS BV. We perform a professional service where we help customers to analyze compounds. Examples are whether your compound is absorbed in the small intestine. But also in a broad sense: If you have no clue where to start looking and are looking for a first lead. In addition, we aim to create two commercially available cell culture platforms where customers can conduct these analyses themselves. Even though the name of the company is GUTS BV, the platform goes beyond the cultivation of intestinal cells *e.g.* models for bile duct, kidney, and liver. Next to improving intestinal cultures, this approach can benefit other organ systems as well. The platform itself is easily connected in sequence enabling organ-organ interactions, essential to go towards a complete human surrogate. If you have questions, are curious or just want to have a coffee, don't hesitate to reach out through LinkedIn.

References

[1] Jochems et al. Toxicology In Vitro, 2019

[2] Jochems et al. Npj Science of Food, 2020

[3] Jochems et al. Nutrients, 2020



REGISTRATIE CIE

Inschrijving register

Voorletters	Achternaam	Datum inschrijving	Datum afloop registratie
N.	Timmer	16-12-2020	16-12-2025

Inschrijving TiO

Voorletters	Achternaam	Opleider	Datum inschrijving
A.I.	Saarloos	Prof.dr.ir. I.M.C.M. Rietjens	16-12-2020
P.C.C.	Sijnesael	Prof.dr. P.J. Boogaard	16-12-2020

AIO toxafette - Fleur Froeling

By *Fleur Froeling*

Can you introduce yourself?

Hi, my name is Fleur Froeling, originally from South Africa. I moved to the Netherlands 9 years ago to attend Maastricht University college. I have a Bachelor's Degree in Liberal Arts and Sciences after which I continued my studies to obtain myMaster's Degree in Global Health. I started working at the Institute for Risk Assessment Sciences (IRAS) department of population health sciences in April 2019. In the next two years I will be focusing on researching the effects of woodsmoke on the respiratory health of people with and without COPD/Asthma.

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

This is a great question considering that my project is aimed at collaborating with laypeople! I am working on a Dutch citizen science project where we want to involve citizens in the development and execution of an epidemiological study about woodsmoke. Our interest in this subject stems from the increase in the public's interest in woodsmoke. Many Dutch people are concerned about the possible health effects of woodsmoke. Scientifically, there is still a lot to learn about this subject, hence our interest from a scientific point of view. Hopefully with the help of citizens throughout the course of the project we will be able to answer some of the questions that are of societal concern regarding woodsmoke.

What was your motivation to start a PhD program?

I wanted to further develop my academic skills in a challenging, curious and stimulating environment. So, I thought a PhD would be the perfect opportunity to do so.

Why did you choose a subject in toxicology?

I chose to do my PhD on this topic for two reasons:
I loved the interactive nature of this topic using citizen science to actively engage with citizens to co-create more socially relevant research.
The field of toxicology and environmental health is so diverse and multidisciplinary, with many topics that overlap with interests I discovered during my Global health master.

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

As far as I know, this is the first time we are using co-created citizens science to conduct an epidemiological study of this scale. I think both researchers and citizens will learn a lot from this experience and from each other. Hopefully this project stimulates other researchers to incorporate elements of citizen science in their own studies. As for the social impact, I hope that whatever the result may be, the study was of social relevance due to the fact that it was designed and conducted with the help of Dutch citizens.

What is the best advice that you have received as a PhD student or would like to give to another PhD student?

"You cannot edit a blank page!" This is a quote my dad used to say whenever I had to start writing something, but I feel like it could translate to anything one does in a PhD. It just means you have to start somewhere. The first word of an article, the first participant to be recruited in your study, or even just an idea of what you want to research. Just start! You can always edit and evolve as you learn.

How do you combine your PhD project with your personal life? Are there choices you have to make?

I know it sounds like a cliché but it's all about balance. I think every PhD candidate will struggle with balancing their personal life and work at one point or another. But it is important (and okay!) to make time for the things that are important to you. For me personally it's the first hour of the day after I wake up. I use that hour to listen to a podcast whilst taking my dog for a walk in the forest to kickstart my day.

What is the biggest challenge for you in doing PhD research?

Conducting a citizen science study during a global pandemic. The last year we have had to adjust our plans and come up with creative solutions to build and maintain relationships with citizens digitally. Though the constant adjustments and problem solving may be one of the biggest challenges I will have to face it is also what makes this project so fun. →

Do you keep up to date regarding developments in your field? How?
Yes! I try to keep up to date with developments in my field of research with personalized Mendeley search alerts (weekly emails that provide me with a list of possibly relevant research articles) and by attending digital lectures.

What goals do you have regarding your career after your PhD? Would this be inside or outside academia, and why? Would you consider going abroad?
Definitely something with citizen science! Whether in a post doc function or in a global health setting, I would love to use citizen science in an innovative way to enhance knowledge generation. I would definitely consider going abroad, but I would also love to go back to South Africa if the opportunity would present itself.

Please answer the question from the last toxafette PhD-candidate: What are important insights you gained while performing citizens science that we (more conventional researchers) can learn from?
Communication is key. Even though citizens may not be academically trained in conducting research we all enjoy learning new things. Especially those of interest/concern. So, I would encourage all researchers to publish their findings in places accessible to the lay public such as newspapers, social media etc. But communication goes both ways. I think it is also very important to provide citizens with a platform to communicate their ideas, concerns, critique or questions. We have had some amazing insights from citizens that allowed us to edit and adjust our research design before data collection started.

Call for Proposals for the International Congress of Toxicology 2022 Scientific Program

The International Congress of Toxicology (Maastricht, **September 18-22, 2022**) is a joined meeting **of IUTOX and EUROTOX** (www.ict2022.com) organized by the **Netherlands Society of Toxicology**. The theme of the 2022 ICT ***"Uniting in Toxicology"***, reflects our desire to address topics dealing with different disciplines.

GENERAL GUIDELINES FOR SCIENTIFIC PROPOSALS

- Submit your scientific proposals via the **submission platform** making sure to include the organiser details, the recommended speakers, and a brief presentation for the proposal.

- Proposals will be evaluated based on the following criteria:
  - **a:** Scientific excellence of the proposed individual talks and the session overall.
  - **b:** Relevance of the topic of the Symposium to the overall theme of ICT XVI.
  - **c:** Balance of the scientific content with respect to the utility and relevance of the information presented for improving human and environmental health in countries with both robust and developing research and regulatory enterprises
  - **d:** Speaker diversity with respect to the geographical area represented, gender, and sector (government, industry, academia, other).
  - **e:** Availability of support for speaker travel to ICT XVI. [This criterion is not a requirement, but a strong encouragement.]

- The Congress Organization strongly encourages interaction between Academia-Industry-Regulators and interdisciplinary approaches (basic research, clinical/ epidemiological, regulation) therefore we ask that you make every effort to include speakers from all mentioned organizations.

SPECIFIC GUIDELINES FOR SCIENTIFIC PROPOSALS

SCIENTIFIC SESSIONS:
Aims to be topical or cutting-edge scientific knowledge exchange with experts in the area presenting data from their research and answering questions from the audience. A Chair and a Co-Chair should be included.

- Should last a total of 120 minutes and have a maximum of 4 speakers setup as a workshop or symposium.
- The first speaker should set the scene for the symposium by explaining briefly the background to the topic before presenting his/her data.
- Presentations should be 25 minutes with 5 minutes for questions for a total of 30 minutes per speaker.
- Proposal for 60 minute round table sessions will also be considered.

CONTINUING EDUCATION COURSE (CEC):
An educational session with 3-4 experts on a particular topic presenting a balanced view of established principles. Proposers/Chairs should ensure they work with individual speakers to achieve balance and prevent topic overlap. Scheduled Sunday, September 18 from either 9h00 to 12h00 or from 13h – 16h00. A full day format including coffee and lunch breaks may be proposed.

Please note: All fields of toxicology are welcome as topics for a CEC, except Regulatory Toxicology and Immunotoxicology.

What's Next?

In the world that we currently live in, career opportunities are basically endless, making it difficult to decide on a specific path. This is especially true for fresh graduates entering the job market as they have not yet developed a professional network to guide them in finding the right job. For those who are struggling, or just curious about what careers are out there in the field of toxicology, a new section has been taken up in the TCDD named: "What's Next?". A section created specifically to provide toxicologists with insights into career paths chosen by their peers.

We will kick-off this new section in our journal by illustrating the work of a Study Director. *By Héloïse Proquin, Jasper Woutersen, Martje de Groot and Maaike Steenhof, who are currently working, or have worked as Study Director.*

When explaining the job to an uncle or aunt during a family gathering, it can be described as being a project manager. A study director oversees studies (being *in vitro* or *in vivo*) to test the potential toxicological effects of pharmaceutical products or industrial products according to known guidelines such as OECD, ICH, or ISO. As a study director you are the single point of control of the study, and you are responsible for all the decisions that need to be made during the study and for all the work that is performed as part of the study. A study director prepares the study by making the protocol and contacting and instructing all individual and/or principal scientists involved in the study. A study director makes sure that all is well organised and prepared to start, execute, and finalise the study. While the study is running, the in-life phase for *in vivo* studies and experimental phase for *in vitro* studies, the study director verifies that everything is going well and according to plan and GLP standards. Sometimes, the study director needs to make difficult decision like euthanising animals or stopping a study. A study director always keeps good communication with the Sponsor – which is the client requesting the study - and involves him/her in the decisions to make. When the study is finished, a study director, often with the help of a study assistant, checks the raw data if they are all according to GLP standards, and writes the report. When the report is checked by different parties, it can be finalised and archived after approval of the Sponsor.

A study director works on several studies at the same time, with the studies being at different stages (I.e. preparations, in-life, reporting, etc.). Studies can have different duration as well, a lot of *in vitro* studies will need 5 to 6 weeks from start to finish whereas *in vivo* carcinogenicity studies could take up to a couple of years. If you want to work in a multi-disciplinary setting, on many projects at the same time, are interested in the commercial aspect of research and want to troubleshoot a lot during your workday, being a Study Director might be the right job for you.

Martje de Groot: *"For me the greatest challenge of being a study director is to not take it personally when there are challenges in a study, and everyone is looking at you since you are the single person responsible. At the same time, it is the greatest reward if a client is satisfied with the final report, despite all challenges that you faced along the way."*

Jasper Woutersen: *"I really love my job as a study director when things go wrong. Of course you do not hope things go wrong, but I like the challenge of finding the best solution to continue the study. The challenge of finding the right people with the right knowledge that can help you solve the problem. The other part I really like is contact with sponsors, being able to help them solve a problem and being able to just work a little harder to exceed their expectations."*

Maaike Steenhof: "The part that I loved most: to collaborate with so many different skilled and committed people, biotechnicians, laboratory technicians and scientist from different labs (PK/TK, clinical pathology and biochemistry, pathology etc.). It's great to experience that you share the same priorities (the best animal welfare, smooth study conduct and high quality scientific study reports) and that by working together as one big team you can make the (sometimes very tight) deadlines for the study reports. What I found the most challenging was handling the last minute requests for adding additional parameters or changes in study design. How to find the balance between best scientific design (sometimes less in more 12), pleasing the sponsor and the work load for the people in the labs (e.g. a biomarker that has to be measured in fresh specimen 16 hours after dosing could implicate that several people have to work until around midnight)."

5G – faster, better, more dangerous?

By *Damiën van Berlo*

The advent of the newest generation of telecommunication technology, known generally as 5G (for fifth generation) sparked a lot of attention among the general public and in the media. 5G offers increased data transfer speed compared to its predecessors, clearly benefiting society in many ways. However, its safety has been questioned. For instance, in 2017, a petition was sent to the EU by scientists from 30 countries, requesting to halt the rollout of 5G. A similar initiative is the international EMF appeal, calling upon the UN and the WHO to provide greater health protection from EMF exposure. As of January 2021, 255 scientists working on electromagnetic radiation have signed the appeal. Slovenia actually stopped the rollout of 5G in March 2020, to investigate possible health effects. And we should also keep in mind that wireless radiation (including 5G) is classified by the International Agency for Research on Cancer (IARC) as a group 2B carcinogen, which means possibly carcinogenic.

Meanwhile, the telecommunications industry and the experts associated with it emphasize that there is no reason for concern and accuse scientists who think otherwise of “fear mongering”.

The electromagnetic power of radiation is determined by its frequency and wavelength: higher frequency and lower wavelength are associated with higher power. 5G used higher frequency radio waves than previous networks: the low band range is around 600-850 MHz (similar to 4G), the high range currently is as high as 25-39 GHz. Although this is a clear step towards the wrong side of the spectrum from a health perspective, this is still far removed from the frequencies that characterize ionizing radiation, which we consider as (potentially very) harmful to people. The high energy of ionizing radiation is capable of breaking chemical bonds in the DNA and turning atoms into ions. Actually, the frequency of ionizing radiation is in the petahertz (PHz) range, rather than the GHz range that is reached by 5G. To put this into perspective: 1 PHz is 1×10^6 GHz. Because of the still relatively low frequency and energy, one would not immediately expect 5G radio waves to have an adverse impact on health. However, one should keep in mind that ionization is not the only mechanism by which radiation might elicit health effects. In particular, heating has been observed at frequencies far below those associated with ionization. In humans the power levels emitted by mobile and wireless telecommunications can produce temperature rises of a few tenths of a degree in tissue. The relevance of this temperature increase is uncertain. When considering effects beyond human health, it should be noted that it is likely that smaller organisms such as insects will be more affected by RF-induced heating because of their much smaller size.

Many experimental studies have been performed investigating the possible adverse health effects of wireless radiation; although there is some evidence for biological effects (even at intensities considered as too low to cause heating), solid evidence for toxicity in humans is still lacking. Of course, those studies mostly investigated the effects of →

previous standards (3G, 4G etc.); the availability of data on 5G is still limited. Also, there has been criticism of the experimental procedures carried out to investigate effects of 5G radiation: Kostoff et al. (2020) argue that the experimental conditions do not mimic real-life conditions. For instance, the pulsing and modulation of the signal is absent from the experimental setting. The authors also point out that synergy with other forms of toxic stimuli is not considered.

Briefly summarizing the above: there currently is no good reason to assume that 5G is dangerous to people. But this has not been shown conclusively yet, which could be considered as worrying considering the current worldwide rollout of the technology.

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Let op met servies van bamboe en melamine

De Nederlandse Voedsel- en Warenautoriteit (NVWA) adviseert om melamine kunststof serviesgoed waarin bamboe en/of maisvezels zijn verwerkt, niet (meer) te gebruiken. Bij gebruik bestaat een kans dat er te veel formaldehyde in het voedsel of drinken terecht komt. De NVWA laat importeurs en aanbieders van deze producten weten dat zij de producten direct uit de handel moeten halen. De autoriteit treedt handhavend op als de producten in Nederland worden aangeboden. Daarnaast adviseert het Voedingscentrum om ook servies dat voor 100% van de kunststof melamine is gemaakt, niet te gebruiken voor heet eten en drinken voor kinderen tussen 0 en 3 jaar.

Verkennend onderzoek

Bamboe-melamine serviesgoed is in opkomst vanwege de vermeende duurzaamheid. Hoewel het wordt verkocht als ‘bamboe’, zijn deze materialen vervaardigd uit melamine kunststof waaraan bamboevezels zijn toegevoegd. Bovendien geven ze stoffen als formaldehyde en melamine af die bij te hoge hoeveelheden schadelijk zijn voor de gezondheid.

Op basis van signalen uit de EU heeft de NVWA een eigen verkennend onderzoek gedaan naar melamine kunststof serviesgoed met bamboevezels. Het ging hierbij om hard, slijtvast, kunststof serviesgoed dat kan worden hergebruikt. Er zijn bekers, kommen en mokken bemonsterd en onderzocht. Daarbij bleken bij een aantal artikelen behoorlijke overschrijdingen van de zogenoemde migratielimiet voor formaldehyde. Dat wil zeggen dat er bij gebruik van het servies te veel formaldehyde vrijkomt in eten of drinken. →

Nieuwsbericht 15-02-2021

Risicobeoordeling
Bureau Risicobeoordeling & onderzoek (BuRO) van de NVWA, is vervolgens gevraagd wat het risico is van het gebruik van dit soort veel toegepast serviesgoed. BuRO onderzocht vanaf welk afgifteniveau van formaldehyde er sprake is van een gezondheidsrisico. En het heeft onderzocht of van de afgifte van formaldehyde van de producten uit het verkennende onderzoek effecten op de gezondheid worden verwacht. Het bleek dat bij aanwezigheid van bamboe in het onderzochte servies de afgifte van formaldehyde hoger was; daardoor kunnen effecten op de gezondheid door formaldehyde in voedsel en drinken niet worden uitgesloten.

Een te hoge inname van formaldehyde kan leiden tot maagirritatie en maagzweren. Op basis van de risicobeoordeling adviseert BuRO om alle kunststof serviesgoed waarin bamboe en/of maisvezels zijn verwerkt niet (meer) te gebruiken. Ook zouden dergelijke producten van de markt moeten worden geweerd. BuRO wijst er bovendien op dat bamboe- en maisvezels als toevoeging aan kunststof serviesgoed niet is beoordeeld door de EU-voedselveiligheidsautoriteit (EFSA); de veiligheid kan daarom niet worden gegarandeerd. Het toevoegen van bamboe- en maisvezels aan kunststof gebruiksartikelen zoals serviesgoed is daarom niet toegestaan.

Nederlandse Voedsel- en Warenautoriteit
Ministerie van Landbouw, Natuur en Voedselkwaliteit

Van de markt halen
Vanuit de Benelux-landen is een brief aan de importeurs en leveranciers van deze artikelen gestuurd waarin hen wordt opgedragen bamboe-melamine kunststof servies per direct van de markt te halen. De 3 Benelux-landen kondigen in de brief ook aan dat voortaan zal worden gehandhaafd op het verbod op niet toegelaten (bamboe-) toevoegingen in kunststof gebruiksartikelen.

Consumenten die dergelijke producten nog aantreffen op de Nederlandse markt kunnen dit melden bij de NVWA. De NVWA zal handhavend gaan optreden als dergelijke producten in Nederland worden aangeboden.

Jonge kinderen
Op basis van de risicobeoordeling adviseert de NVWA de minister voor Medische zorg en Sport om de huidige zogenoemde specifieke migratielimiet (SML) voor formaldehyde (15 mg per kg) voor melamine kunststof serviesgoed (met of zonder bamboevezels) te verlagen. Deze biedt nu onvoldoende bescherming bij gebruik door kinderen vanwege hun geringere lichaamsgewicht. Consumenten en gebruikers van dit soort servies moeten bovendien actief over deze risico's (vooral voor baby's en kinderen) worden voorgelicht.

Het Voedingscentrum adviseert in afwachting van de verlaging van de norm om ook serviezen gemaakt van 100% melamine (dus zonder toevoegingen van bamboe en/of mais), niet te gebruiken voor heet eten en drinken voor kinderen tussen 0 en 3 jaar.

Bron:
Let op met servies van bamboe en melamine | Nieuwsbericht | NVWA

Oplossing en winnaar van de kerstpuzzel / Christmas puzzle solution and winner

Congratulations to our now regular Christmas puzzle winner:

Peter van Kessel

He correctly solved the Christmas puzzle 2020 as follows:

Across:
4: clock
6: midnight
7: feast
8: times
10: grapes
13: in
14: weight
18: up
20: giveup
23: resolutions
24: baby
26: january
27: fit

Down:
1: fizzy
2: ringin
3: stars
5: champagne
7: first
9: eve
11: sip
12: fireworks
15: hogmany
16: bells
17: bubbly
19: holiday
21: party
22: toast
25: on

TERUG NAAR INHOUD

TCDD is de nieuwsbrief van de Nederlandse Vereniging voor Toxicologie (NVT).