

TCDD

TOXICOLOGIE

NUMMER 2
MEI 2020

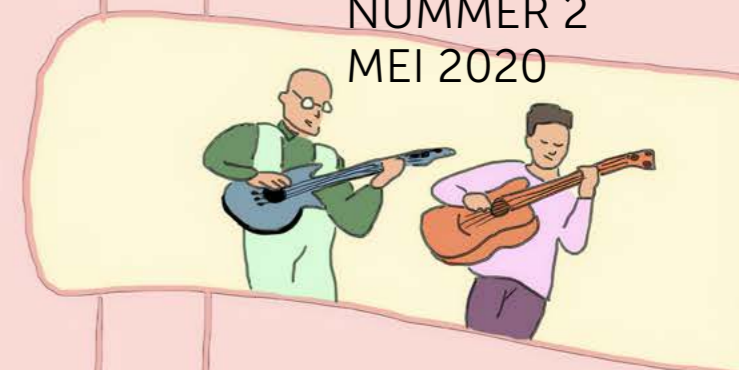
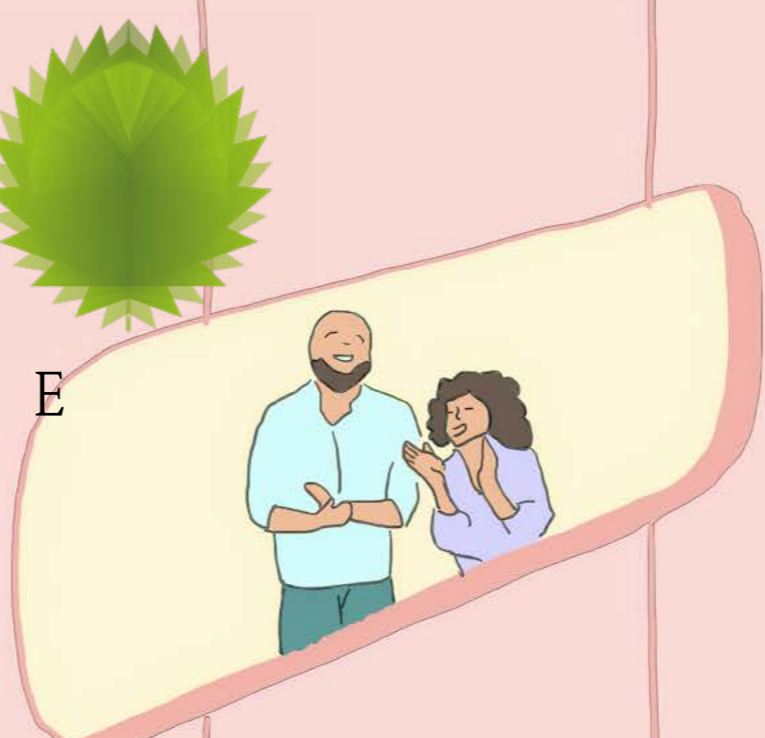


SPECIAL THEME

CORONAVIRUS

- RISK MITIGATION AND 3R CONSIDERATION FOR *IN VIVO* BASED RESEARCH IN CRISIS SITUATIONS
- TONIC CAUSES A STIR

- CORONAVIRUS: THE GOOD, THE BAD AND THE UGLY ADVICE
- HOW RESPIRATORS ENDED UP IN HOSPITALS



Colofon

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Editorial

Het zijn vreemde tijden, hele vreemde tijden. Een wereldwijde pandemie houdt ons allen in zijn greep. Het Corona-virus drukt een stempel op 2020: Het virus verdeelt ons (vaak letterlijk) en tegelijkertijd verbindt het ons op bijzondere manieren. Als redactie wilden wij in deze editie van de TCDD ook aandacht besteden aan Corona, beschreven onder verschillende namen, waaronder het nieuwe Corona-virus, COVID-19 en SARS-CoV-2. Een Corona-editie dus, zonder enkel nieuws te herhalen dat zovelen van jullie al horen en lezen via andere media, maar ook binnen beperkte tijd en met beperkte middelen. Voor ons als redactie dit keer geen face-to-face redactievergadering, maar een video-meeting, vanuit verschillende huiskamers. U herkent deze meetings inmiddels vast; Soms met een verrassend kijkje in de "mens" achter uw collega, klant of concurrent. Voor de content dit keer geen interviews met onze leden over relevante

vraagstukken, maar gesprekken via telefoon of mail. Het is voor ons allemaal wennen en aanpassen, samen leren roeien met de riemen die wij hebben – en dat allemaal op gepaste afstand.

Desalniettemin denk ik dat wij erin geslaagd zijn er weer een interessante editie te maken: In deze TCDD vindt u namelijk een interview met het hoofd van het NVIC, prof. dr. Dylan de Lange, over Toxicologen in vitale sectoren, spreekt onze voorzitter Juliette Legler ons toe in nieuws van het bestuur en vindt u een thema-artikel over adembescherming door Barae Jomaa. Als u ook wat luchtiger nieuws kunt gebruiken, lees dan vooral ook het stuk van ons redactielid Damiën van Berlo over alle Corona-adviezen op sociale media. In deze TCDD ook aandacht voor verschillende evenementen die vanwege de Corona-maatregelen zijn verplaatst of geannuleerd. Daarnaast vindt u ook onze bekende rubrieken, zoals de AiO Toxafette en twee nieuwe

Proefschrift Promopraatjes. Interessant om bij deze laatste te noemen: virtueel je proefschrift verdedigen is een feit!

Een speciale dank aan alle leden die bij hebben gedragen aan deze editie van de TCDD. Ondanks dat de balans tussen werk en privé nu lastig te bewaren is, waren velen van jullie bereid iets aan te leveren of onze vragen te beantwoorden. Bedankt! Rest mij nog u veel leesplezier te wensen, maar bovenal: veel gezondheid en sterkte.

Namens de redactie,

*Martje
de Groot*



News from the board

On behalf of the board of the NVT, I would like to reach out to all of our members to express our best wishes and gratitude. With the recent announcement that COVID-19 measures will be extended, more than ever it is clear that our health is of paramount importance. I hope you are all well, and I wish you the best in coping with the challenges of working from home and keeping your work (and spirit) going. For all of our members involved in patient care or other vital tasks, we are especially grateful for your efforts to combat the virus and help those affected.

On behalf of the NVT annual meeting organizing committee, I am very sorry to inform you that due to the COVID-19 measures, we have decided to postpone the annual NVT 2020 meeting, which was planned for June 10-11, 2020 in Ede. We aim to transfer the program of the NVT annual meeting with this year's theme: "The (r)evolution of toxicological model - How to address safety in target species" in its entirety to the NVT annual meeting next year, which will take place in spring 2021. We hope you are all enthusiastic to join the NVT annual meeting in 2021!

We will let you know as soon as we have more information on the date of the NVT annual meeting 2021.

We would like to thank the participants who already put time and effort into preparing and submitting an abstract. Please note that registration refunds for the NVT annual meeting 2020 have not yet been processed but we will begin to process these soon. For any additional enquiries on the NVT annual meeting, please mail us at the following mail address: nvtmeeting@gmail.com.

Please note that though the face-to-face annual meeting will be postponed until 2021, we will still hold a virtual meeting of NVT members ('algemene ledenvergadering') on June 11, 2020, from 13:00-15:00. Please save the date! Look forward to 'seeing' you all then!

All the best and take care!

Juliette Legler
President NVT



SAVE THE DATE!

June 11, 2020
13:00-15:00 uur

(VIRTUAL)
**NVT
General
Meeting**



SECTIE RISICOBEOORDELING

Uitnodiging najaarsbijeenkomst: 'Alles wat u altijd al heeft willen weten over PFAS'

Nieuwe datum: 5 November 2020 (13.00 – 17.00 uur)

Locatie: NVWA, Graadt van Roggenweg 400, Utrecht

Voorlopig programma:	
13.00-13.20	Registratie
13.20-13.30	Welkom
13.30-13.50	Algemene inleiding – Prof. dr. Annemarie van Wezel (UVA)
13.50-14.20	Afleiding van PFAS risicogrenzen in bodem – Dr. Arjen Wintersen & Dr. Piet Otte (RIVM)
14.20-14.50	Consequenties voor bodembeleid – Drs. Marije Schouwstra (I&W)
14.50-15.10	Pauze
15.10-15.30	Via bodem naar (drink)water – Dr. Frederic Béen (KWR)
15.30-15.50	Via water naar landbouwhuisdieren naar consument – Dr. Krista Bouma & Dr. Jacqueline Steenbergen – Biesterbos (NVWA)
15.50-16.30	Discussie & afsluiting
16.30-17.30	Borrel



Source: NOS

U kunt zich aanmelden door een email te sturen naar Monique Nagtegaal (m.nagtegaal@nvwa.nl). Vermeld hierbij "Deelname NVT najaarsvergadering – 5 november" in het onderwerp. Vermeld ook uw naam en affiliatie in de mail.



SECTIE ARBEIDSTOXICOLOGIE

Oproep Kennisdeling Arbeidstoxicologen

Arbeidstoxicologie is een specifieke tak van sport binnen de toxicologie. Aangezien veel arbeidstoxicologen als zelfstandige- of als enige binnen deze functie in een bedrijf werkzaam zijn, is het prettig om in contact te staan met andere arbeidstoxicologen.

We zijn op zoek naar arbeidstoxicologen die enkele keren per jaar samen willen komen om casussen te bespreken. Het idee is om een paar keer per jaar een bijeenkomst van 2-3 uur te organiseren op een centrale locatie. Hierbij zullen 2 of 3 personen een casus indienen om te bespreken. Dat kunnen casussen zijn waarmee men worstelt en waarover andere deelnemers tips en adviezen kunnen geven, maar het kunnen ook casussen zijn waarbij men nieuwe kennis heeft opgedaan of nieuwe methoden heeft toegepast waar anderen van kunnen leren. Uiteraard zullen binnen de groep afspraken

worden gemaakt over het vertrouwelijk omgaan met eventueel bedrijfsspecifieke informatie die mogelijk gedeeld wordt.

Ben je op zoek naar andere arbeidstoxicologen voor het opdoen en delen van kennis? Of ben je een ervaren arbeidstoxicoloog die graag kennis en ervaring overbrengt op de nieuwe generatie? **Geef je dan voor eind mei op via één van onderstaande mailadressen**

o.v.v.:

- Naam
- Werkgever
- Woonplaats
- Of je evt. een ruimte ter beschikking hebt voor een bijeenkomst voor max. 10-12 personen
- Of je mogelijk al een casus in gedachten hebt om voor te leggen (incl. korte toelichting inhoud).

Kelly Caris (kelly.caris@arbounie.nl)

Ina Dijkman (ina.dijkman@cosanta.nl)

Aankondiging middagsymposium Arbeidstoxicologie van de circulaire economie

Op 8 oktober 2020 organiseren de NVT sectie Arbeidstoxicologie en de Contactgroep Gezondheid en Chemie in Eindhoven een middagsymposium onder bovenstaande titel.

Verduurzaming van de economie en circulariteit, zijn brede begrippen. Het omvat onder meer: 1) energietransitie, ofwel de omschakeling naar vernieuwbare of oneindige vormen van energie (hout, zonne-, wind-, en getijde-energie, aardwarmte), 2) de inzet van zgn. 'biobased' grondstoffen in de chemie, 3) duurzamer bouwen en 4) recycling, of liever: het streven naar een 'circulaire economie' ("waste is food"). Deze ontwikkelingen zijn niet per definitie ook "veilig en gezond" voor de betrokken werknemers. In dit middagsymposium willen wij ons focussen op de arbeidstoxicologische aspecten hiervan. De middag begint met een overzicht van

de voornaamste ontwikkelingen, waarna drie cases worden behandeld. Hebben de voorvechters van verduurzaming en de innovatieve bedrijven voldoende aandacht voor blootstelling aan stoffen? En kunnen arbeidstoxicologen daarin nog iets betekenen?

Het volledige programma tref je te zijner tijd op de website aan.

Plaats:

Aristo Meeting Center, Vestdijk 30,
5611 CC Eindhoven, op 5 minuten
loopafstand van NS-station
Eindhoven Centraal

Tijdstip:

Donderdag 8 oktober 2020,
van 13:00 tot 16:30 uur

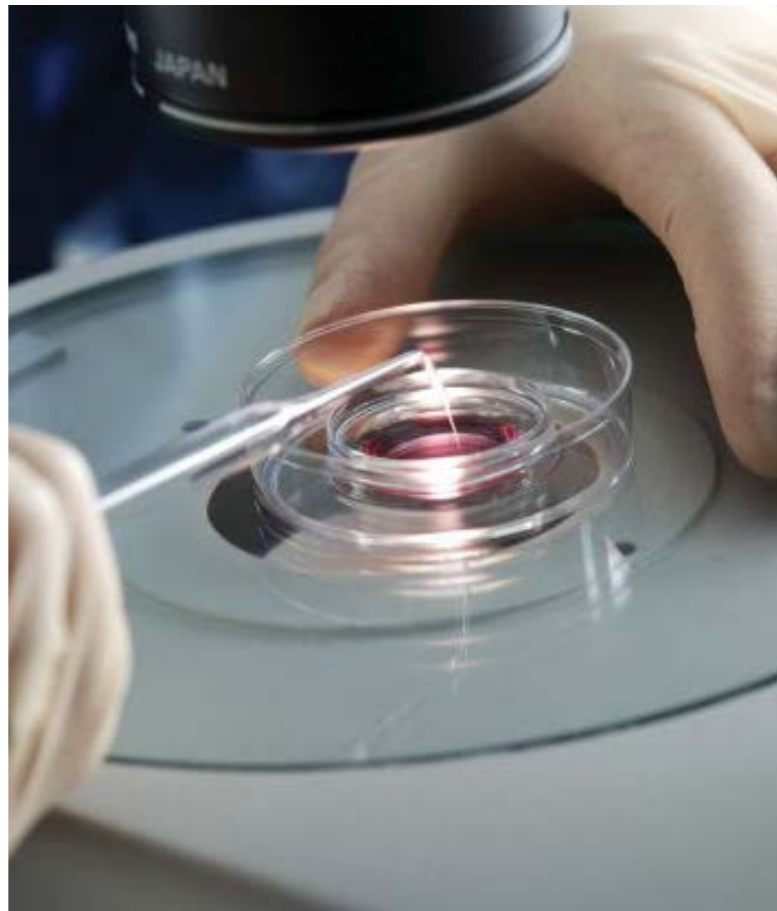
Risk mitigation and 3R consideration for *in vivo* based research in crisis situations

By Carolien Schophuizen and Jean Cozzi

As countries worldwide are dealing with the COVID-19 pandemic, we all face the uncertainties that surround the measures taken to prevent further spread of the disease. Though the type of containment procedures may differ by country, many research facilities (universities and laboratories) scale back operations since scientists must observe work-from-home orders.

Some scientists may be able to continue working in their laboratory, albeit under somewhat altered conditions which consider the social-distancing precautions. Others may be faced with unforeseen loss of capacity in their facilities, causing delays and the subsequent need for alternative solutions.

Given the uncertainty surrounding COVID-19, those of us involved in animal research have been considering strategies to mitigate risk and consider the 3Rs for genetically engineered mice and rats, and other valuable rodent colonies. Some researchers may have had to reduce breeding, cull animals and cut other experiments short. However, studies that have been ongoing for years would be difficult and expensive to do over. Where possible, institutes aim to keep critical rodent colonies going. Nevertheless, when operating with a skeleton or a reduced crew, choices need to be made.



Q & A Session

Jean Cozzi, Innovation Manager, Genetically Engineered Models and Services Europe of Charles River Laboratories has recently presented a Q & A Session: Securing Transgenic Colonies and Considering Next Steps. Among others, the following two strategies for maintaining transgenic rodent lines were discussed:

1. For standard mouse lines (up to two mutations and a clearly defined genetic background): Sperm cryopreservation: A cost-effective solution requiring just two males.
2. For complex mouse lines (more than two mutations or a non-clearly defined genetic background) and transgenic rats: Custom breeding: During non-crisis periods, embryo cryopreservation is a good solution for rats and complex mouse lines but obtaining enough animals of relevant genotype(s) for embryo cryopreservation may not be possible given short timelines.

An overview of the requirements for sperm and embryo cryopreservation is taken up in Table 1 →

The main message of the Q&A session was one that many scientists should keep in mind; crisis situations may lead one to make quick decisions on how best to outsource (rodent) line securitization. However, if rushed into a decision, one might incur both scientific and economic risks.

The session is available [online](#). ■

Table 1: Comparison of Sperm and Embryo cryopreservation

Cryopreservation	Sperm	Embryo
Description	<ul style="list-style-type: none"> Sperm collected from cauda epididymis is cryopreserved in straws. Storage in liquid nitrogen. Quality controls: running IVF – sufficient fertilization rate should be obtained (50% at least) and fertilized embryos should develop to 2-cell stage. 	<ul style="list-style-type: none"> <i>In vitro</i> fertilization (IVF) is preferred method to obtain large number of embryos. Embryos are frozen in straws – standard service includes freezing of 150 embryos containing the mutation(s) of interest.
Timelines	<ul style="list-style-type: none"> 2-4 weeks 	<ul style="list-style-type: none"> 12 weeks
Number of Mice	<ul style="list-style-type: none"> 2 healthy reproductively active males. 	<ul style="list-style-type: none"> 2 healthy reproductively active males. Females can be WT or transgenic. Depending on breeding scheme and objective 15-30 females are required.
Age of Mice	<ul style="list-style-type: none"> Males: 12-24 weeks 	<ul style="list-style-type: none"> Males: 12-24 weeks Females: 8-24 weeks
Amount Generated	<ul style="list-style-type: none"> 15 straws including one QC straw. 	<ul style="list-style-type: none"> Cryoarchive 150-300 embryos per line (6-12 straws) according to breeding scheme.
Further Details	<ul style="list-style-type: none"> Rapid. Preserves one-half genome. IVF needed for line revitalization. Recommended mostly for single mutation on a common inbred background. Generating large cohorts of mice possible via IVF for rapid line amplification. 	<ul style="list-style-type: none"> Preserve entire line genotype (mutations & genetic background). Recommended for homozygous, multiple unlinked mutations, unique genetic background.



A gift to science: Upper picture shows the bark of the cinchona tree (photo credit: Ji-Elle); bottom picture depicts the fluorescent properties of the quinine contained in tonic water (photo credit: Joseph Blosser).

Tonic Causes a Stir

By Barae Jomaa

Quinine is a potentially toxic ingredient in tonic and now its analogue hydroxychloroquine is touted as a potential treatment for COVID-19.

Malaria has been around since pre-history and Europe was feeling the bite until one fateful day when the Jesuit missionaries learned from Andean civilizations the secret of the cinchona tree. Jesuits have been spreading their faith to the world since their inception, a journey that took them to Peru in 1568. What they witnessed there was a godsend. Incas were using the bark of the cinchona tree to treat shivering¹. It didn't take long before the Jesuit Order brought back the good news to the old continent. By the late 17th century, the so-called Jesuit's powder was increasingly being used to treat the intermittent fevers that were later attributed to malarial parasites.

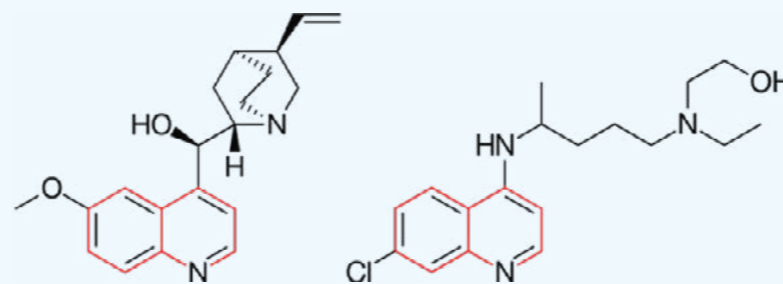
In the language of the Incas, quina means bark and in English the word quinine has been in use to describe the compound since it was first isolated in 1820. Around that time, British officers stationed in India would make the bitter anti-malarial quinine powder more palatable by mixing it with sugar and soda.

Despite the fabulous origin of quinine, it does come with serious side effects. Death has been reported as a →

result of quinine intake² and today the EU limits quinine in tonic to only 100 mg/L. Quinine used to be given at a daily dose of 650 mg of quinine given three times daily in a 75 ml solution of tonic (half a glass)³. Today's tonic is approximately 87 times less concentrated than the original drink!

Quinine toxicity is associated with severe nervous system effects such as optic and auditory nerve damage. Cinchonism, which is the excessive or prolonged use of quinine, is characterized by headaches, tinnitus, blurred vision, and on some occasions even deafness and anaphylactic shock. By stimulating the central nervous system, quinine causes fever and delirium as well as an increased rate of ventilation. However, this progresses to coma and respiratory depression. In terms of cardiovascular toxicity, quinine can lead to peripheral vasodilation, myocardial depression and an increase in action potential duration. Other reported effects include gastrointestinal symptoms, hemolytic anemia and renal failure⁴.

Hydroxychloroquine is a less toxic synthetic analogue of quinine which is also used to treat malaria. Just like quinine, hydroxychloroquine can cause life-threatening arrhythmias as they both block IKr potassium as well as other channels⁵. Also similar to quinine, hydroxychloroquine can lead to gastrointestinal symptoms, headaches, tinnitus, anemia, renal impairment as well as central nervous system effects such as delirium⁶. Both substances have also been shown to induce retinopathy^{6,7}.



Structural diagrams: quinine (left) and hydroxychloroquine (right)

Promising *in vitro* results showing hydroxychloroquine to be effective against SARS-CoV-2⁸ have spurred interest for the anti-malaria as a potential cure for COVID-19. Soon thereafter, a French non-randomized clinical trial with only 42 patients⁹ caught media attention with its claim that hydroxychloroquine was indeed an effective treatment for the disease. The results of the study caused a stir in the scientific community and were later disputed¹⁰. The French study seemed to receive an endorsement on the 5th of April from US President Donald Trump¹¹. The president had been touting the drug's benefits for weeks even mentioning that it is "not going to kill anybody". Unfortunately, one couple listened to the president's promotion of the drug and decided to self-medicate. They ingested toxic amounts of a fish tank cleaner containing chloroquine phosphate – another analogue of quinine. Both had to go to the hospital within 30 minutes of ingestion and one of them died as a result¹².

As of the time of publication, not all the data is in yet from the various clinical trials being carried out around the globe. However, a high dose arm of a Brazilian clinical study has been stopped due to safety concerns¹³, and the US FDA has issued a statement warning healthcare professionals of the risks of off-label use of hydroxychloroquine which include life-threatening cardiac arrhythmias¹⁴. ■

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Coronavirus: the good, the bad and the ugly advice

By Damiën van Berlo



This piece has been written to brighten up this coronavirus-themed issue (and these dark times) somewhat. It is *not* intended to inform you about which advice is good and which is not; you know that *at least* as well as I do. The below information is a scientists' perspective on the information circulating on the social media. This cannot be described without some light-heartedness.

Virus pandemics are common subjects for movies and popular novels. In a significant proportion of these movies (e.g. *28 Days Later* and its sequels, *I Am Legend*, *World War Z*, *the Omega Man*), people change into zombie-like beings upon infection and prey on the non-infected. There are also a couple of more realistic movies that try to sketch an often terrifying picture of a global pandemic caused by a dangerous virus. Examples of this category are the Korean movie *The Flu*, the recent Indian movie *Virus*, Hollywood production *Outbreak* and the current favourite: Steven Soderbergh's *Contagion*, which shows many parallels to what the world is currently experiencing with COVID-19. In *Contagion*, an unknown virus is transferred from bat to pig and subsequently to human. The first patient ends up in the hospital with a violent cough, and dies a particularly unpleasant death. If you want to scare people into keeping 1.5 m distance at all times, showing them this movie might work. If you want to avoid more panic, it might not. →

So why am I discussing movies here? We are in a very real situation, where we have people starting fights over toilet paper¹, stealing disinfectant and respirators from hospitals² and even someone throwing an old lady to the ground using a bag of garden earth³. No Hollywood script writer would dare to include that in a film script (“Oh come on, think of something more realistic!”), except the Monty Python crew maybe... In some cases, reality exceeds human imagination.

Unfortunately, there is some horrible and bizarre advice circulating on the internet, often with many supporters jumping on the hype bandwagon. These “treatments” and “preventive strategies” for COVID-19 and the coronavirus SARS-CoV-2 appear to be Hollywood-inspired; I’ll get back to that later.

To be clear: useful advice for dealing with the COVID-19 pandemic is being shared on social media. The main things, as you have probably heard many times in the last weeks: keep 1.5 meters distance from others, stay home as much as possible, wash your hands on a regular basis and take great care around individuals particularly vulnerable to the virus. The latter includes the elderly, people with pre-existing cardiovascular disease and heart patients with co-morbidities (diabetes, lung disease, obesity etc.). This all makes a lot of sense; *good advice*. The following “anti-viral” advice however, should never have gone *viral*:

ADVICE: “EAT GARLIC”.

A lot of Facebook posts are advocating garlic consumption as it would have antiviral properties and would help against SARS-CoV-2, according to proponents.

Actually, garlic is considered as a healthy food by the WHO and *might* even have some anti-viral potential^{5,6}. This has not been shown convincingly, however. There is limited evidence that garlic consumption might be preventive for the common cold⁷. Unfortunately, that does not mean that it has an effect against SARS-CoV-2; there is no evidence.

Also, dosing can be a bit of an issue. Generally, around 4 grams (or 1 to 2 cloves) is recommended in the literature⁸. Consumption of excessive amounts of garlic however, can lead to gastrointestinal problems, unpleasant body odor and flatulence.

Or worse: a Chinese woman had to be hospitalized with severe throat inflammation after consuming 1.5 kg (!) of garlic over a 2-week period⁹. I do not doubt that it will greatly facilitate keeping people at a distance of >1.5 meters, but 10 grams a day would also have done that job, I’d reckon.

Rating: BAD advice at high doses (and UGLY for people with hyperosmia – highly sensitive sense of smell)



ADVICE: “TAKE MIRACLE MINERAL SUPPLEMENT (MMS)”, I.E. REBRANDED CLO2.

Taking the so-called “Miracle Mineral Supplement” was recommended by a certain Jordan Sather, who is mainly known for having a YouTube channel with quite a few followers. The main active component of MMS is chlorine dioxide (ClO₂). Mr. Sather has claimed the following via Twitter: “not only is chlorine dioxide (aka MMS) an effective cancer cell killer, it can wipe out coronavirus too”. An impressive boast, but is there any truth to it? Not much. ClO₂ is an effective biocide that kills bacteria, fungi and viruses and has even been called “the ideal biocide”¹⁰. It has been investigated as an antiseptic as well and is sometimes used as such; but sterilization of e.g. surgical instruments is something very different from oral treatment in patients. There is no basis for its use as a treatment for COVID-19 patients; it does not penetrate deeply in larger organisms¹¹ and thus it is unlikely that oral intake would have beneficial effects in the lungs, or even systemically. Although ClO₂ is not very toxic for human beings compared to other biocides¹², it is certainly not harmless; the US EPA has set a maximum level in drinking water of 0.8 mg/L and OSHA has set an 8-hour permissible exposure limit of 0.1 ppm (0.3 mg/m³) in air for workers exposed to ClO₂. Taking it as an MMS supplement is very unwise; the FDA has even issued a warning against it¹³.

Rating: UGLY advice →



ADVICE: "DRINK COLLOIDAL SILVER¹⁴".

A suspension of tiny silver particles in a liquid is called colloidal silver. There has been a movement of "silver drinking" proponents on Facebook, who claim that because it is an antiseptic and can boost the immune system, it can be an asset in the fight against SARS-CoV-2. Possibly the best known of these proponents is TV evangelist Jim Bakker. In fact, you can easily buy colloidal silver from a major online shopping platform in the Netherlands, where it is marketed as "anti-viral"¹⁵.

It is true that it works as an antiseptic, and for instance wound bandages with a silver component added to them do in fact exist. But again, an antiseptic is very different from a medicine; antiseptics are administered to a surface that is to be sterilized, a medicine is to be administered to a patient. In this case, drinking significant amounts of silver puts one at a risk of developing kidney damage, seizures and argyria.

And it seems that some people confuse the oesophagus with the trachea, or think that they are both the same channel; after drinking colloidal silver it does not end up in the lungs, but in the stomach.



Image: 92-year old man with argyria (right)¹⁶

Rating: BAD advice, UGLY at higher doses

ADVICE: "DRINK WATER EVERY 15 MINUTES¹⁷".

The same applies here; one tube goes to the stomach, the other to the lungs. By drinking water, one obviously cannot wash the virus from the lungs towards the stomach, where the stomach acids could theoretically kill it. Even if this *would* happen, viruses are quite resilient. For instance, the MERS-CoV virus, a related coronavirus that was responsible of the outbreak of Middle East Respiratory Syndrome (MERS) between 2012 and 2017, is known to be very resistant to the acidic gastric environment¹⁸.

On the positive side, it would be difficult to cause harm to yourself when applying this advice. *The dose makes the poison* and it is difficult to overdose on water (unless you drink more than a liter of water per hour. Excessive water intake results in cerebral oedema and death). At least when taking it in via the oral route; the respiratory route is slightly more problematic.

Rating: BAD advice, mainly because it can give a false feeling of security

**ADVICE: "EXPOSE YOURSELF TO HEAT TO KILL THE VIRUS".**

There are a number of different variants of this advice circulating on social media. A well-known source of such information is a woman who calls herself Mary Wilson, who claims to be lecturer at Koforidua Technical University in Ghana. She has put a video on Facebook that has been circulating since 17 March 2020, in which she says that doctors treating COVID-19 patients recommend the use of hair dryers and sauna baths to "prevent this coronavirus"¹⁹.

It is true that high temperatures can kill SARS-CoV-2; but you do not want to expose your body to such temperatures, which are as high as 5 minutes at 70°C²⁰. That is much higher than a comfortable bath temperature, and very dangerous. To be fair, this advice is not completely without basis, because flu epidemics are known to slow down or stop altogether in summer. This could be because aerosols produced by coughing cannot travel far enough to infect someone else, or *influenza* might be exquisitely sensitive to temperature increases. We do not yet know how this works for SARS-CoV-2, but we do know that countries with hot climates can have many COVID-19 patients.

Rating: BAD advice; UGLY when taking this too far →

ADVICE: "TREAT PATIENTS OR STERILIZE YOUR HANDS WITH UV RADIATION".

The use of UV light has been promoted on social media to clean your hands, destroying SARS-CoV-2 that might be present. In fact, POTUS Donald J. Trump also proposed something similar to Dr. Deborah Birx during a press briefing: *"So, supposing we hit the body with a tremendous - whether it's ultraviolet or just very powerful light, and I think you said that hasn't been checked but you're going to test it. And then I said, supposing you brought the light inside of the body, which you can do either through the skin or in some other way. And I think you said you're going to test that too. Sounds interesting."*²¹

Such ideas are probably based on the well-known facts that UV radiation can kill viruses and that some viruses (e.g. *influenza*) appear to be less active in summer²². Many people think UV is relatively harmless because it is part of sunlight. However, the type of UV radiation used to sanitize and sterilize is UV-C; this short wavelength UV radiation is much more dangerous than UV-A and UV-B (of which sunlight consists). All or nearly all UV-C is blocked by the ozone layer along with most UV-B; the earth probably would not be able to sustain life otherwise. Although UV-C radiation is so potent that it can indeed kill viruses (including MERS-CoV²³), it would be extremely unwise to for instance dismantle a commercially available air purifier to get access to the UV-C lamp inside, which is then used to "sterilize" skin. Using a solarium (which

nowadays is usually UV-A only) or exposing yourself to sun radiation for prolonged periods is less harmful, but still not harmless. The WHO has warned people against the use of UV light to sterilize hands or any other area of the skin.

Rating: BAD advice in general; UGLY when using UV-C lamps intended for disinfection

ADVICE (MORE ACCURATELY: SUGGESTION): "INJECT DISINFECTANT".

During the same official press conference mentioned in the UV radiation paragraph, a governmental official presented some data from a study by the US government that showed that bleach can destroy SARS-CoV-2 in saliva or respiratory fluid in five minutes; isopropyl alcohol acts even quicker than that. After he communicated the idea to irradiate patients with UV, the US president came up with another suggestion: *"And then I see the disinfectant where it knocks it out in a minute. One minute. And is there a way we can do something like that, by injection inside or almost a cleaning? So it'd be interesting to check that."*²¹

As with some of the previous advice involving virus-destroying agents, it is not a good idea to "clean" patients internally with bleach, disinfectant or any other aggressive chemicals. On the positive side: it would probably reduce their chance of dying from COVID-19, because the proposed "cure" would get them first.

Trump continued as follows: *"I'm not a doctor. But I'm, like, a person that has a good you-know-what."* I won't be the judge of the "you-know-what" of Donald Trump, but I can say with some certainty that it's not a good idea for him to bring wild suggestions to a SARS-CoV-2 conference on national TV, watched by millions and millions of Americans. Even if afterwards, he claims that he was being "sarcastic".²⁴

Rating: UGLY advice →



Photo by Charles Deluvio on Unsplash

ADVICE: "TAKE A DUNG BATH AND DRINK COW URINE²⁵".

At this point it gets wild; in India, some people claim that taking a bath in bovine feces and drinking cow urine protects against SARS-CoV-2. This advice provides *fertile ground* for a paragraph.

The claim is made by people who follow the Hindu religion and consider cows to be holy animals; some Hindus even attribute medicinal properties to their waste products. Unfortunately, there is no scientific basis for the anti-viral properties of stool dipping.

On the upside: similar to what would be expected for excessive garlic consumption, it will certainly be easier to stimulate people to keep at least 1.5 m distance when you regularly take fecal baths. If the smell won't chase them away, the dense cloud of flies surrounding you should achieve that.

Still, if they consider cow products to be potently curative, I wonder why they aren't simply drinking cow milk? Am I missing something crucial here?

Rating: CRAP advice; in more ways than one



ADVICE: "DRINK LOTS OF ALCOHOL".

This one is a bit of a crowd-pleaser. Alcohol is used to disinfect, so some people developed the idea that drinking alcohol helps against SARS-CoV-2. It would help build immunity against the virus or kill it outright, so they claim. Inhalation would seem more logical, but as mentioned before, not everyone manages to distinguish the two pipes going down from the oral cavity, towards stomach and lung. What is true, is that a sanitizer with at least 60% alcohol can sanitize your hands and thus protect against SARS-CoV-2²⁶.

Finally, heavy drinking can downregulate your immune system, making you more vulnerable to SARS-CoV-2²⁷... Although this advice is clearly nonsensical, it could explain some of the advice above; it could have been conceived by people who took this last advice very, very seriously.

Rating: UGLY advice



ADVICE: "PERFORM PRE-BEDTIME RECTAL ADMINISTRATION OF VIOLET LEAF OIL²⁸",

according to a cleric from Iran. A cotton ball is dipped in violet oil and, once soaked, inserted rectally. In fact, this particular gentleman doesn't only claim that this procedure can cure coronavirus, but also that it will increase brain mass and can reverse Down syndrome. I will refrain from another Medline search for fact-checking; this idea is just off-the-scale ridiculous. At least violet oil smells better than some of the advice we have discussed previously... Still, someone who spreads such nonsense deserves to have their cotton ball soaked in something else than violet oil.

Rating: UGLY advice →



Conclusion: social media can help to keep people together at a distance in a situation such as the one we are currently experiencing. And good advice is circulating via these media; but it is also very easy to distribute “fake news” and utter nonsense. What is very unsettling is how easy it is to gain a following with such bizarre claims. In my opinion, much is - and will be - learned in this period on how to deal with social media in crisis situations; I hope this will lead to new fact checking strategies and services.

You might ask, what about the connection to movies? Indeed, much of the bad and ugly advice above appears to be inspired by movies. The fascinating thing is, that it is not the realistic movies about pandemics that inspire people. The inspiration comes from somewhere else. “Eat garlic. Drink silver. Expose yourself to heat. Use UV radiation. Expose to daylight.” These “curative strategies” also feature in movies about vampires and werewolves... when fighting a monster you don’t know (i.e. SARS-CoV-2), people seem to look at how monsters are fought that we *do* “know”. I just hope they stay from the bit with the pointy sticks, inserted intracardially (an effective means to dispose of vampires, according to Hollywood). There is just too much *at stake* (pun intended). ■

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False Information. We are all glued to our mobile devices seeking information about the crisis but a lot of false information is spreading as fast as the virus itself. This piece aims to make people think twice before sharing and reposting myths about COVID19. Image created by Ruth Burrows. Submitted for United Nations Global Call Out To Creatives - help stop the spread of COVID-19.

How Respirators Ended Up in Hospitals

The COVID-19 pandemic has brought particulate respirators to the forefront of a public health crisis

By Barae Jomaa

Respirators, which are indispensable protective equipment for workers exposed to air contaminants, have gained public attention due to the COVID-19 pandemic. While respirators take on many forms, including respirators that protect against certain gases and vapours, the ones consumers mostly find in hardware stores are disposable particulate filter half masks. Filtering facepiece respirators (FFPs) are meant to protect against airborne particles and come numbered from 1 to 3 with the higher numbering indicating better protection. FFP2 is analogous to the US N95 filter¹ whereas FFP3 is analogous to US N99. Even though such masks are mostly used in mining, industry and fire services², they have gained popularity in healthcare due to pandemics. The use of respirators in a hospital setting started during the pneumonic plague outbreak of 1910. This article revisits historical and functional distinctions between industrial and medical respirators in order to shed some light on their use, and associated shortage, during the ongoing COVID-19 pandemic.

Historical perspective

The use of masks for respiratory protection from dust is likely a pre-historic activity. Ancient African engravings show men with only eyes indicating that male face coverings, known as Lithams, have likely existed for millennia. Lithams serve a vital functional purpose by protecting their wearer from inhaling dust³. Pliny the Elder, a Roman author and naturalist, was the first to record the use of primitive face masks while describing the manufacturing of an orange-red pigment called minium (lead tetroxide) in AD 23 - 79⁴:

“Persons employed in the manufactories in preparing minium protect the face with masks of loose bladder-

skin, in order to avoid inhaling the dust, which is highly pernicious.”

Since dried animal bladder is not readily permeable to air, the mask was likely used in conjunction with a sackcloth filter as described by Julius Pollox a century later⁵.

We now know that lead tetroxide is indeed highly pernicious as it may damage fertility or the unborn child, causes damage to organs through prolonged or repeated exposure, is harmful if swallowed, is harmful if inhaled, is suspected of causing cancer and may cause harm to breast-fed children⁶. The suitable respirator in this case



Caption: A Tuareg wearing the Litham. Image from the book *Timbuctoo Across the Centuries* by Felix Dubois, 1896.

would be a half mask that can filter 99.97% or more of airborne particles⁷ (FFP3 in EU, N100 in US).

The first documented, yet rudimentary, filtering facepiece intended to protect firemen from smoke was developed in 1825 by the Italian physician Giovanni Aldini who described the use of a mask made of asbestos fibres⁸. The modern respirator was developed with incremental improvements by various inventors a few decades into the second industrial revolution (1848 – 1874). In 1848, Lewis Haslett patented the first respirator with a one-way clapper valve to allow for easy exhalation⁹. A few years later, John Stenhouse pioneered the use of activated →

charcoal which allowed, for the first time, the filtering of toxic organic gases and vapours¹⁰. Today, there are numerous gas cartridges for use with respirators that are specifically suited to different types of gases. However, the basic principle remains and these cartridges still contain activated charcoal which is additionally impregnated with a relevant chemical agent. The perfection of gas masks and their specialized cartridges was quickly accelerated during World War I with the ascent of chemical warfare.



Caption: Stenhouse's mask. Image from Edward L. Youmans' Class-Book of Chemistry, New York, 1858

Surgical masks were first worn by doctors in 1897, however, these masks are mainly worn to protect the patient from the doctor's breath during surgery. Filtering facepiece respirators that would protect doctors during a pandemic had to be much more efficient at filtering out pathogens. These were first used in healthcare in China in 1910 by Dr. Wu Lien-teh in an effort to protect healthcare workers from the pneumonic plague. Concerned with the pandemic, Dr. Wu Lien-teh wrapped his nose and mouth with multiple layers of gauze and cotton¹¹. They were so effective that he later oversaw the production of 60,000 masks during the second pneumonic plague pandemic (1920).



Caption: Healthcare workers wearing Dr. Wu Lien-teh's cotton and gauze mask during second pneumonic plague pandemic (1920).

Meant mainly for industry, respirators were seldom used in hospitals prior to 1990. However, between 1988 and 1993 tuberculosis-related deaths of healthcare workers led to a change in mindset. In 1994 the US Centre of Disease Control issued guidelines recommending the use of respirators at healthcare facilities for tuberculosis infection control¹².

When the poison is the cure

Not only were respirators made from asbestos in ancient Rome but most World War II gas masks had filters containing asbestos¹³. The practice of using harmful asbestos fibres in gas mask filters continued well into the 1980s¹⁴. The use of vintage gas masks is now advised against, even for educational purposes unless they can be shown not to contain asbestos¹³. A 40-year follow-up study also found significant excess mortality from ovarian and lung cancer in a group of women working in the manufacture of asbestos-containing gas masks during World War II¹⁵.

Activated carbon is now the preferred gas filter material for organic vapours and is impregnated with metal oxides for polar or low molecular weight gases including chlorine, ammonia and sulphur dioxide. Such metal impregnating agents include copper, silver and chromium¹⁶. The use of hexavalent chromium as an impregnating agent in gas mask canisters has come under scrutiny. While the risk has been deemed acceptable by the US army in 1989¹⁷, US OSHA deemed such use unacceptable as alternatives exist and stopped approving the use of chromium-impregnated sorbents on the 1st of September 1990¹⁸. Moreover, the classification of these compounds under EU REACH as category I or II Carcinogenic, Mutagenic or Reproductive toxicants has led manufacturers to discontinue the sale of chromium-impregnated respirators in European markets¹⁹.

Today, particulate-filtering facepiece masks such as FFP2/N95 masks as well as surgical masks are deemed safe to use and are made from melt-blown nonwoven polypropylene fabric.

Factors to consider

Protection Factor (PF) = concentration outside / concentration inside

Workplace Protection Factor (WPF) = PF measured on employees in an occupational setting

Assigned Protection Factor (APF) = lower 5th percentile point estimate of the WPF distribution (generally a log-normal distribution)²⁰, in other words, 95% of users are expected to exceed this protection

Maximum Use Concentration (MUC) = APF x Occupational Exposure Limit (OEL) →

$$MUC_{(Mixture)} = [Concentration_1 / MUC_1 + Concentration_2 / MUC_2 + \dots Concentration_n / MUC_n]$$

For example, an FFP2 respirator has an APF of 10 and dust has an OEL of 5 mg/m³ so the MUC will be 50 mg/m³. The APF is derived for various types of respirators at a national level and can vary between countries!

The COVID-19 crisis

With the COVID-19 pandemic, it became increasingly important to understand the difference between surgical masks, FFP2/N95 masks and surgical N95 masks. As previously mentioned, surgical masks are intended to protect the patient during surgery from the surgeon's respiratory emissions. In addition, surgical masks have an outer blue or green water repellent layer to protect the wearer from bloodborne pathogens potentially splashing from the patient during surgery. They are not meant to filter viruses as they are loose fitting and they are not subject to the same standards as FFP2/N95 masks. N95 masks are tight fitting, designed for optimal particle collection efficiency and are rigorously tested. They are meant for construction or industrial use. A surgical N95 mask is a medical device that has the best of both worlds, it filters out small particles ($\geq 95\%$ of 0.3 μm -sized particles) and at the same time has a water repellent layer. For reference, bioaerosols that remain in the air are 1.0 to 5.0 μm ²¹. According to the FDA²², a surgical N95 respirator "contains coating technologies unrelated to filtration (e.g., to reduce and or kill microorganisms)." One such mask is the BioFriend BioMask N95 surgical respirator which has an inner layer, treated with copper and zinc ions, which inactivates viruses including Coronavirus 299E (the surrogate for the 2002 SARS-CoV-1 epidemic) using

different mechanisms of action²³.

Due to the COVID-19 induced shortage of medical-grade N95 masks, on the 2nd of March, the FDA allowed "emergency use" of non-FDA approved respirators meant for industry²⁴. The main reason for the shortage is that N95 respirators are disposable since they are ineffective after an 8-hour workday. While mask decontamination technologies have been developed to extend the lifetime of N95 respirators up to 20 times²⁵, such systems are not yet widespread. This means that industries are currently forced to compete with an increased demand for respirators from the healthcare sector. ■

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Toxicologen in vitale processen

Werkzaamheden van het NVIC ten tijde van Corona

De rijksoverheid heeft een lijst opgesteld van cruciale beroepsgroepen en vitale processen voor COVID-19¹. Zoals alle lezers ongetwijfeld weten, heeft de beroepsgroep toxicologen de lijst niet gehaald. Echter, zoals reeds aangehaald door onze voorzitter in de rubriek "News from the board", er zijn wel toxicologen werkzaam aan vitale processen. Zo ook de medewerkers van het Nationaal Vergiftigingen Informatie Centrum (NVIC). In deze bijzondere tijden was het hoofd van het NVIC, prof. dr. Dylan de Lange, bereid om tijd vrij te maken voor een TCDD interview. Hieronder volgt een "kijkje in de keuken" bij het NVIC ten tijde van Corona.



Prof. Dr. Dylan de Lange, Hoogleraar Klinische Toxicologie, toxicoloog-intensivist UMC Utrecht, hoofd van het Nationaal Vergiftigingen Informatie Centrum (NVIC)

TCDD: Wat zijn de reguliere werkzaamheden van het NVIC?

Om uit te leggen wat we allemaal doen, moet ik eerst kort uitleggen hoe het Nationaal Vergiftigingen Informatie Centrum (NVIC) in het UMC Utrecht is gekomen. Het NVIC is een informatiedienst die gezondheidsmedewerkers (denk aan artsen, verpleegkundigen, apothekers, ambulancepersoneel, dierenartsen, etc.) adviseert over de diagnostiek en behandeling van mogelijk geïntoxiceerde mensen en dieren. In 1959 startte professor Lammers een adviesdienst vanuit het Rijksinstituut Volksgezondheid (RIV), de voorloper van het huidige RIVM. In het begin werden er nog uittreksels over toxische stoffen rondgestuurd naar apothekers en artsen, maar later werden deze stofmonografieën in een kaartenbak verzameld. Gezondheidsmedewerkers gingen bellen

om deze informatie te krijgen. Vanaf de jaren '60 van de vorige eeuw ging deze adviesdienst samenwerken met de "afdeling Reanimatie" van het Academisch Ziekenhuis Utrecht. Ook de telefonische adviesdienst verhuisde mee naar het ziekenhuis. Hierdoor werd de band met de kliniek versterkt zodat er altijd een medicus als achterwacht kon oordelen over de intoxicaties en de adviezen die gegeven werden. Vanaf de jaren '90 werd alles gedigitaliseerd in een computersysteem.

Naast de informatiedienst voor gezondheidsmedewerkers, is een andere belangrijke taak van het NVIC het adviseren van de overheid bij calamiteiten waarbij chemische stoffen betrokken zijn. Daarnaast brengen we rapporten uit over nieuwe en opvallende blootstellingen aan chemische producten. Hiermee informeren we overheidsinstanties zodat zij beleid kunnen maken op basis van deze gegevens. Het UMC Utrecht heeft een Calamiteiten Hospitaal voor de opvang van slachtoffers van rampen

en grote incidenten. Het NVIC draagt een steentje bij met advies over hoe dergelijke patiënten behandeld zouden moeten worden indien er blootstelling is geweest aan chemische stoffen.

TCDD: Zijn de reguliere werkzaamheden van het NVIC aangepast vanwege COVID-19?

De medisch specialisten die normaliter voor het NVIC werken als toxicoloog zijn momenteel ook ingezet voor de behandeling van COVID-19 patiënten. Daar gaat momenteel veel tijd in zitten. Echter, er is altijd een arts die beschikbaar blijft voor vragen over patiënten die blootgesteld zijn aan chemische stoffen en/of medicamenten. Het schrijven van rapporten en het doen van wetenschappelijk onderzoek kan grotendeels vanuit huis gedaan worden. We hebben dagelijks een teleconferentie om de opvallendste bevindingen te bespreken. De ruim 40 medewerkers →

van het NVIC werken dus grotendeels vanuit huis. Alleen de telefoonbeantwoording kan niet vanuit huis. De informatiemedewerkers aan de telefoon zijn nog altijd 24/7 aanwezig. Om besmettingen te voorkomen werken zij nu wel in aparte ruimtes. Kortom, het is een "uitgeklede" afdeling geworden.

TCDD: Zijn er nieuwe werkzaamheden bijgekomen die gerelateerd zijn aan COVID-19?

Uiteraard houden we in de gaten of, nu iedereen thuis zit, er een verandering optreedt in het aantal en soort intoxicaties. Daarnaast zijn er allerlei experimentele medicijnen voorgesteld die zouden kunnen werken tegen het corona-virus. Voor deze medicijnen is het bewijs nog zeer beperkt, maar er dreigen wel bijwerkingen of overdoseringen bij gebruik. Vandaar dat wij onze stofmonografieën voor deze medicamenten weer tegen het licht gehouden hebben. We anticiperen dus op trends, maar eerlijk gezegd lijkt het heel erg mee te vallen. We worden, tot op heden, niet vaker gebeld over dit soort COVID-19-geassocieerde intoxicaties.

In de kliniek werken we uiteraard mee aan onderzoek over de uitkomsten van COVID-19 patiënten en doen we mee aan farmacokinetisch onderzoek naar verschillende experimentele COVID-19 medicamenten.

TCDD: De overheid adviseert om momenteel zoveel mogelijk thuis te werken. In hoeverre is dat mogelijk voor NVIC medewerkers?

Zoals ik al zei is onze afdeling grotendeels gereduceerd tot enkele verplicht aanwezige medewerkers. Zij zitten aan de telefoon en beantwoorden de ruim 130 vragen per dag. Maar ook de digitale infrastructuur (computers, servers, telefonie, back-ups, e.d.) moet blijven draaien dus ook onze ICT-ers zijn regelmatig aanwezig om alles te onderhouden. Heel veel andere zaken kunnen vanuit huis gedaan worden. Gelukkig hebben we alle medewerkers de mogelijkheid gegeven vanuit huis in te loggen op onze afdelingscomputers. Hierdoor is het mogelijk om alle wetenschappelijke onderzoeken, tellingen en rapporten gewoon door te laten gaan.

Helaas kan niet alles op afstand gedaan worden. Sommige software draait alleen op bepaalde computers. Dan moeten de medewerkers toch gewoon naar hun werkplek komen. Ook staat sommige informatie in oude handboeken en die kan je alleen maar inzien op locatie. Dus af en toe komen de medewerkers wel naar de afdeling om hun werk te kunnen doen. Wat wel echt helemaal stilgevallen is, is onderwijs. Normaliter hebben we eigenlijk altijd wel iemand die stage bij ons loopt, onderzoek doet of mensen in opleiding tot medisch specialist die bij ons onderwijs in klinische toxicologie volgen. Dat is nu gestopt. We hopen dat dit in de nabije toekomst weer mogelijk wordt.

TCDD: Welke speciale maatregelen gelden er voor NVIC medewerkers als ze op kantoor aanwezig zijn?

Het UMC Utrecht heeft de normale ingangen afgesloten en alleen medewerkers die gezond zijn (en geen

griepachtige klachten hebben) mogen het ziekenhuis in. Heb je wel klachten dan moet je je laten testen en mag je niet het ziekenhuis in. In het ziekenhuis houden we ons aan dezelfde regels als iedereen thuis: houd afstand van elkaar, was je handen regelmatig, maak je werkplek schoon als er na je een andere medewerker komt werken. We dragen geen mondkapjes. De bedrijfskantine is gesloten en vergaderen doen we tegenwoordig online.

TCDD: Wat vindt u van de nieuwe manier van werken vanwege COVID-19 (afstand houden van elkaar, veelal online in plaats van direct contact etc.)?

Ik moet wel zeggen dat ik mijn collega's erg mis! Het lol hebben met elkaar, het delen van frustraties en het brainstormen over nieuwe dingen is toch een wezenlijk onderdeel van ons werk. Je merkt dat "online werken" dat niet vervangt. Omgekeerd lukt het ook om bepaalde zaken goed te doen zonder vergaderingen en bijeenkomsten. Vergaderingen die we nu niet missen, hoeven we in de toekomst niet meer te herintroduceren. Zo leren we ons werk toch ook efficiënter te maken.

TCDD: Enige tijd geleden kwam in het nieuws dat het Calamiteiten Hospitaal nu 19 IC bedden heeft voor COVID-19 patiënten. Heeft dit effect op (de uitvoering van) de werkzaamheden van het NVIC?

Het Calamiteiten Hospitaal, een groot noodhospitaal dat snel geopend kan worden als er sprake is van een grote ramp of een incident, heeft IC-bedden gereed staan. Het UMC Utrecht maakt nu gebruik van deze →

ruimtes en wordt daarbij geholpen door militaire artsen en militair verpleegkundigen. Omdat het NVIC letterlijk naast het Calamiteiten Hospitaal huist, zien we veel artsen, patiënten, en militairen deze ruimtes betreden. Dat maakt de ernst van deze COVID-19 pandemie erg tastbaar. Behalve de medisch specialisten die werken op deze COVID-afdelingen hebben wij, als NVIC, daar geen bemoeienis mee.

Ten tijde van het interview was het Calamiteiten Hospitaal geopend voor COVID-19 patiënten, inmiddels is deze noodvoorziening weer gesloten.

TCDD: In de NVIC jaarverslagen wordt altijd het onderwerp “Trends in het afgelopen jaar” besproken. Verwacht u dat COVID-19 nieuwe trends in intoxicaties zal veroorzaken?

Wat de gevolgen zijn van de pandemie op het aantal en het soort intoxicaties in Nederland zullen we nog moeten leren. Misschien zorgt onze “thuis quarantaine” wel voor minder arbeidsgerelateerde blootstellingen aan chemische stoffen en meer blootstellingen aan huishoudproducten. We gaan het merken, het zijn bijzondere tijden! ■

Referenties

1. <https://www.rijksoverheid.nl/onderwerpen/coronavirus-covid-19/ouders-scholieren-en-studenten-kinderopvang-en-onderwijs/noodopvang-cruciale-beroepen-en-vitale-processen>

Time-Cumulative Toxicity of Neonicotinoids

Francisco Sánchez-Bayo and I have recently published a study with the title: “Time-Cumulative Toxicity of Neonicotinoids: Experimental Evidence and Implications for Environmental Risk Assessments”.

The quintessence of the publication is that the test guidelines for (eco)toxicological risk assessments need to be revised to get a better picture of chronic toxicity. The toxicity of neonicotinoids is a well-documented example of gross underestimation of chronic toxicity. There is a whole list of data (many of which have been made available by Paul van den Brink) in our publication, showing that the Druckrey-Küpfmüller equation is generally applicable.

This makes it clear that toxicity can be determined by dose and time. The lack of attention to the reinforcing effect of the exposure duration on the toxicity of genotoxic and non-genotoxic substances is probably the biggest shortcoming in the current risk assessments of pesticides and medicines.

If the guidelines are revised, serious consideration could also be given to using laboratory animals only to verify the mechanism of action.



*By Dr. Ir. HA (Henk) Tennekes
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The full article can be accessed for free [here](#). ■

AIO toxafette - Niels Timmer

Please introduce yourself and tell us something about your PhD project

My name is Niels Timmer and my PhD project started in 2012. The last four years I have been working at Charles River Laboratories (formerly WIL Research / NOTOX), while publishing my last manuscripts and finalizing my [thesis](#). And now, after eight years of hard work and endless revisions, I will defend my thesis on 25 May 2020. My project was funded by Unilever and focused on the environmental risk assessment and sorption behavior of positively charged (so-called cationic) surfactants. These are surface-active agents that, due to their molecular make-up, tend to stick to glassware and other laboratory equipment. This means accurate analytical determination of dissolved concentrations can be quite complicated. The first part of my project was focused on finding the proper methods to accurately measure a set of more



than 25 of these compounds. Working together with two fellow PhD-candidates (at that time), I also worked on a mixed-mode micro-sampler that was envisioned to be used in a forensic context (with Hester Peltenburg), and on employing these analytical methods when working with fish gill cells to establish the *in vitro* toxicity of a group of cationic surfactants (with Floris Groothuis). The last part of my PhD project focused on detailed testing microbial breakdown of two cationic surfactants with known biocidal properties. As these surfactants are used in numerous products that are disposed down the drain (e.g. fabric softener, mouthwash, hair conditioner), it is important they are broken down efficiently and effectively during sewage treatment processing to prevent unwanted effects in the environment. My research showed that by applying a small amount of a suitable sorbent (i.e. clay minerals or silicon dioxide), toxic effects to the microbial communities could be prevented while both surfactants remained bioavailable for full breakdown.

What are the major challenges that you have encountered in your project

The major challenge I encountered while still under contract with Utrecht University was a sample extraction tool we were investigating that turned out to give irreproducible results. Due to the difficult test compounds my project focused on, we kept looking at the test compounds as the cause of these inconsistencies. So many elaborate experiments were performed that would have produced lots and lots of meaningful data if we



would have known the sampling tool was the culprit. A second major challenge was finishing my thesis while working full-time at Charles River. Luckily, my new employer has always been very thoughtful and supportive, but it still was no walk in the park.

What did you expect from your PhD?

To be honest, I never knew what to expect. My MSc research project was supervised at the time by what would later become my co-promoters, and when the opportunity to apply for this PhD project presented itself, I felt adventurous and decided to apply because I was so enthusiastic about my MSc research. After that I just went with the flow, and I am quite happy to say the unavoidable moments of regret never outweighed the happy moments. On second thought, one thing I did expect from my PhD was to learn and experience a lot of new stuff. In that respect, I can wholeheartedly state that my PhD truly paid out.

What would you investigate if you have unlimited resources (i.e. time, money, people) in your project?

If I would have had unlimited resources, I would probably have tested my hypothesis regarding microbial breakdown with a much larger additional set of radiolabeled potentially biocidal compounds. This would have helped to provide more insight into the importance of determining biodegradability at environmentally relevant concentrations. With unlimited resources it might also have been possible to test sorption to sediments and bioaccumulation potential in sediment dwelling organisms. These two topics were originally scheduled to be investigated but had to be omitted due to time constraints.

How do you combine your PhD work with your personal life?

I have had the luxury position where my PhD work mostly interfered with my personal life when I chose to let it interfere and it therefore did not have much of a negative impact. I always accepted it when I had to work late at night or during the weekends. Luckily, I have always been able to minimize such impactful moments, and my friends and family have always been supportive if I had to leave early or miss a social event. Since my thesis is now finished my personal life will no longer be impacted, which is something I look forward to very much.

What are your future career plans?

My future career plan is to keep working for my current employer, as they offer me a good perspective to develop my capabilities and I truly enjoy working there. Hopefully, together with my colleagues I will be able to

keep improving and advancing our 'biodegradation and environmental fate' team. If the opportunity presents itself, I would love to supervise a PhD project further in the future, although this is probably something that requires more experience on my end to do successfully.

Are you a member of a society and what do you expect from being a member?

I am a member of the NVT and SETAC. What I expect from being a member is to receive updates of important developments in the field of toxicology, as well as timely communication about events in which I might be interested. Obviously, I expect to be able to attend the numerous meetings and conferences organized by the society. What I also expect as a member is to have the right to vote on important decisions.

Answer to the question of the previous PhD candidate: What would you like to be the impact of your PhD project after 4 years (e.g. for the field of toxicology and/or for the society)?

I would hope that my work is taken into account when existing guidelines for biodegradability testing (e.g. OECD 301/310) are updated, so that biodegradability testing of potentially inhibitory compounds can be performed more cost-effectively, and the resulting changes in allowed experimental procedures may increase environmental relevance of the resulting data. Realistically, I do not expect my PhD research to have a lot of impact for the NVT and its membership, but perhaps my work will help to spark more interest in biodegradation among its members. Environmental toxicology is not always on the forefront, but is still an important piece of the toxicology portfolio.

Do you have a question for the next PhD candidate who will contribute to the Toxafette?

How has the COVID-19 crisis impacted your own perspective of your PhD project?

Who do you propose as future candidate for the Toxafette?

Anke Tukker ■



Photo by Adam Nieścioruk on Unsplash

Occupational Toxicology Topics at INA Congress

Report on the 17th biannual International Neurotoxicology Association Congress (INA) held from September 29 until October 3, 2019 in Düsseldorf Germany.

This report will only cover the occupational-relevant issues of this 5 days congress on behalf of the NVT-AT (occupational toxicology). Anke Tukker already covered mainly *in vitro*, *in vivo* topics, the setting and the social event in TCDD 4 2019 pp 15, 16 whereas Anne Zwartsen covered the session on the neurotoxicity of psychoactive substances in TCDD 1 2020 pp 31, 32.

The Congress traditionally starts on Sunday with the Hooisma lecture, this time the lecture was given by [Deborah A. Cory-Slechta](#) (USA) about "Developmental Ambient Ultrafine Particle Exposures Produce Brain and Behavioral Features of Neurodevelopmental Disorders." In this study, mice were exposed during gestation to concentrated ambient ultrafine particles (UFP < 100 nm) from air pollution. She showed that UFP enter the body not only orally, dermally or by inhalation, but also through the nose directly via the olfactory bulb. UFP easily pass the placenta and blood-brain barrier. She showed several adverse neurotoxic developmental effects and brain damage.

So what could be the occupational relevance of this study results in neurodevelopment? This study showed that UFP from air pollution can reach the brain by four routes

despite the defense mechanisms of the body. It can harm the developing brain of mice. We do not know if we can extrapolate to the human child and adult. Until we know more we have to be very careful with pregnant women occupationally exposed to air pollution.

On Monday, [Anna Bal-Price](#) from the European Commission Joint Research Centre (JRC), Italy, highlighted a "Mechanistic approach applied to evaluation of developmental neurotoxicity (DNT) induced by an exposure to chemical mixture." The obtained data in this study suggest that non-cytotoxic concentrations of a single chemical become neurotoxic in a mixture, especially for those working through a similar mode of action and after long exposure, as shown by several Adverse Outcome Pathways (AOPs) relevant to impairment of learning and memory in children. Here again, this principle of "mixture effects" applies to the human developing brain, but it may play a role in many occupational exposures in the adult nerves and brain. The Monday afternoon session was about the use of imaging data for risk assessment: updates, challenges and future perspectives.

In an Amyloid PET/MRI a case series study [Roberto G. Lucchini](#) NY detected neuritic plaques in a series of World

By Herman Bartstra, Occupational physician, Netherlands Centre for Occupational Diseases, Polikliniek Mens en Arbeid / Solvent team / Neurotoxicology, Academic Medical Centre (AMC)



Trade Center responders (9/11/2001) with cognitive impairment. Results from this case series analyses identified volume loss in brain regions that are well known to be involved in Alzheimer's disease and also identified indications of possible elevations in amyloid in both quantitative as well as qualitative analyses.

These preliminary results are very interesting because cognitive impairment could have a post-traumatic stress syndrome as an explanation. Lucchini may be on track to a neurotoxic explanation.

[Ulrike Dydak](#) (USA) gave us insight into "The potential and limitations of Magnetic Resonance Imaging (MRI) in risk assessment of metal toxicity". MRI is a non-invasive imaging technique that allows to visualize and measure increased accumulation of paramagnetic metals in the human brain. Functional and metabolic imaging techniques have become useful tools for studying the toxic effects of metal exposure on neurochemistry,

neurotransmitter systems, neuronal and axonal integrity, and ultimately neurodegeneration. Thus, MRI may fill an important gap between exposure assessment and measure of effect, with potential to unravel the biodistribution, biokinetics and ultimately the mechanism of biological effects of overexposure to a metal such as manganese. She discussed applications of MRI in the field of metal toxicity, such as measuring exposure-induced loss of olfaction with fMRI, changes in neurotransmitter balances with MRS, or visualizing the distribution of manganese deposition in the brain of welders and relating it to other exposure biomarkers. Understanding how biomarkers of metal exposure, such as toe nail and hair metal levels, relate to brain metal deposition and neurochemical effects is a first step towards individualized risk assessment in metal toxicity.

[Christoph van Thriel](#) et al., Germany, raised and answered the question: “Neurophysiological methods in neuroscience and neurotoxicology – Can they be used in risk assessment?”

In neuroscience great progress could be achieved with respect to non-invasive methods to record electrical activity of the brain (e.g. via electroencephalography, EEG) and more recently to manipulate this activity by non-invasive brain stimulation (NIBS). The presentation described resting-state electroencephalographic (EEG) recordings, time-frequency analysis, and source localization as research tools in neuroscience and pharmacology. Moreover, experiments using NIBS in the context of acute neurotoxic effects of solvents were

summarized. The presentation discussed the sensitivity and specificity of neurophysiological methods and addressed the adversity of changes that are detectable with these methods. Finally, the possible link to electrophysiological *in vitro* methods were illustrated. In a pilot trial in a population of healthy participants without a history of toluene intake, they investigated the behavioral and neurophysiological effects of acute exposure to a peak concentration of 200 ppm toluene, the current STEL for Germany.

In summary, the results of their studies show that acute exposition to toluene within established safety limits alters cortical excitability and neuroplasticity, caused by NMDA receptor block and an impact on cholinergic transmission, and reduces visual functions. The current STEL for Germany for toluene will be lowered because of the results of this experimental study.

These new neurophysiological methods and the toluene experiment constitute very exciting news for our outpatient and research group at the Amsterdam UMC, the Solvent Team; where we investigate patients with the painters disease or chronic solvent induced encephalopathy mainly exposed to solvents.

In the poster sessions two other methods for risk assessment from his research group were presented by [Christine Hucke](#): Neural correlate of intranasal chemical irritation – EEG+ fNIRS as a method for risk assessment (P#17). Second, [Stefan Kleinbeck](#), from the same group worked out a mode of action in the phenomenon of the

Gulf War Illness: the burning eye sensation. Permethrin metabolite triggers adaptive immune response in Gulf War Illness. Eye irritation leads to changes in blinking behavior and to ocular perceptions (i.e. burning eye sensation). Another issue was important for us: [Rita Bast-Petterse](#) (Oslo) and [Gunilla Wastensson](#) (Sweden) did a literature search of neuropsychological effects related to occupational aluminum exposure and there were no clear, consistent findings.

[Valentin Tallandier](#), Cedex, France, worked out a toxicological aspect of styrene in a study of the vestibulotoxicity of styrene by an *in vitro* approach. The current experimental findings show for the first time that styrene may deregulate the K⁺ concentration in the endolymphatic space and alter the functionality of the vestibular system. Wednesday [Qiao Niu](#), from China, did a session on the Interaction of Both Aluminum Exposure and ApoEε4 Gene on Cognitive Functions and ApoER2 Protein Expression in Al-exposed Workers. There was a dose-response relationship. As aluminum exposure levels increased, the cognitive functions were gradually worse. There is an additive interaction between aluminum exposure and ApoEε4 gene. They both can decrease the expression of ApoER2 (LRP8) protein, and the interaction of the two factors may further decrease the expression of ApoER2 (LRP8) protein.

Occupationally, it is interesting how these findings and effects relate to those of Bast-Pettersen and Wastensson. In the Thursday sessions a combination of three speakers shed light on the concerning topic of occupational

pesticide exposure. First [Diane Rohlman](#) (USA) started and startled us with “Occupational Pesticide Exposure Among Egyptian Adolescents: Changes Over Time.”

The goal of this study was to examine the impact of chlorpyrifos (Organophosphorus pesticide, OP) exposure on biomarkers of exposure and neurobehavioral performance in adolescents across an application season. Highly exposed participants had significantly elevated metabolite levels throughout the 10-month study period. Deficits in motor skills and slower reaction times, along with deficits in executive function and short-term memory were found between the high and low exposure groups. Changes in neurobehavioral performance across the application season indicated a pattern of impaired performance among the high exposed compared to the low exposed. Deficits increased during the application season and remained for months after application ended, even when the biomarkers of exposure are reduced. This is particularly important when considering the developmental changes that occur during adolescence. The second speaker was [Fayssal Farahat](#), from Saudi Arabia on an intervention study: “Quantitative risk assessment and effectiveness of protective clothing on reducing OP exposure among pesticide applicators in Egypt”.

The objectives were to assess work practices, quantify relative contribution of dermal and inhalation exposure to the internal dose and assess effectiveness of protective clothing on reducing OP exposure among Egyptian pesticides applicators.

Almost half of the adolescent applicators have bare feet and most of them wore short sleeves clothing. OP doses attributable to dermal exposure and subsequent absorption through skin were estimated to be 94–96% of total dose with legs as the most highly exposed region for all job categories. Safety messages and specifically designed plastic pants from readily available materials were suggested by the focus groups.

They concluded that plastic protective pants and safety messages of spray away, use stick and not hands, clean after spray, are suggested as basic interventions that could be successfully implemented at minimal cost to protect pesticide applicators and similar groups in low income countries.

It is stunning that dermal exposure made up for 94–96% of total dose. We are curious how the intervention measures will turn out over time.

[Pamela Lein](#) (USA), the third speaker talked about a “Preclinical model of chlorpyrifos exposures and effects documented in Egyptian pesticide applicators”. OP-induced neurotoxicity remains a significant occupational health concern, management of which is complicated by the lack of biomarkers that reliably identify at-risk individuals. To address this issue, they used a preclinical model of occupational OP exposure to evaluate the relationship between OP-induced cognitive deficits and expression of conventional and novel biomarkers of exposure and effect. Biomarker analysis suggests that oxidative stress, but not cholinesterase inhibition, contribute to CPF-induced cognitive deficits.

These striking results and elegant prevention intervention are nice examples how international collaboration can highlight the mechanisms and effects of OP and how the workplace can be improved for poor workers in less developed countries. ■



Studying the Role of Estrogen Receptor Alpha in the Developmental Toxicity of Diethylstilbestrol Using Alternative Testing Strategies

By Aziza Hussein Bakheit Adam

From July 2015 to January 2020, I conducted this PhD research at the Toxicology department of Wageningen University. There I worked under the guidance of Prof. dr. Ivonne Rietjens and Dr. Jochem Louisse. My promotion took place via skype on April 20, 2020 where I successfully defended my thesis entitled **“The Role of Estrogen Receptor Alpha in the Developmental Toxicity of Diethylstilbestrol using Alternative Testing Strategies”**.

Diethylstilbestrol (DES) is a synthetic estrogen that has been used between the 1940s and 1970s by pregnant women to prevent miscarriages and premature delivery by stimulating the synthesis of estrogen and progesterone in the placenta. However, use of DES appeared to cause a wide range of adverse effects, such as clear cell vaginal adenocarcinoma in the daughters of women who took the drug, and developmental and reproductive toxicity. These adverse effects have often been attributed to the functional estrogen receptor alpha (ER α), since it has been reported that ER α is needed to induce DES-mediated adverse developmental and reproductive effects in neonates. The question has been raised why



DES behaves differently from the endogenous ER α agonist 17 β -estradiol (E2), even though the molecular dimensions and binding orientations of DES and E2 to the ER α are almost identical. The research described in my thesis aimed to investigate the possible differences in the estrogenicity and developmental toxicity between DES and E2, using different *in vitro* and *in silico* approaches, focussing on the potential role of possible differences in ER α -mediated effects in the underlying mode of action. Accordingly, first the effect of DES and E2 on ER α -mediated reporter gene expression, ER α -mediated T47D breast cancer cell proliferation, and ER α -coregulator interactions and gene expression in T47D cells were evaluated. In addition, the effects of DES and E2 in two alternative developmental toxicity assays (the ES-D3 cell differentiation assay of the embryonic stem cell test (EST) and the zebrafish embryotoxicity test (ZET)) and

the potential role of ER α in these effects were evaluated. Finally, possible dose-dependent differences in internal dose levels of DES and E2 were evaluated with help of PBK modelling, in order to elucidate to what extent possible differences in kinetics could play a role in differential *in vivo* effects of DES and E2. Altogether, the data show that two estrogens E2 and DES differ in their biological effects related to development in a subtle but significant way. At the cellular level, DES and E2 show high similarities in the molecular pathways that relate to ER α -mediated effects with small significant differences that may contribute to the developmental toxicity in part via potential epigenetic effects of DES. The *in vitro* developmental toxicity assays EST and ZET can discriminate DES from E2 in terms of developmental toxicity, but at the same time do not capture the full mode of action underlying DES-induced developmental toxicity. Finally, it was shown that in →

addition to the subtle differences in toxicodynamics, substantial differences in internal concentrations (endogenous E2 concentrations compared to predicted DES concentrations in women that took DES as medication), add to the differential *in vivo* effects of E2 and DES.

My experience with online PhD defence

At the moment I decided to defend my PhD thesis online, I had mixed feelings about having to do my defence online. On the one hand, I am happy that my defence could continue and I now have my doctorate, but on the other hand, it was a very strange experience because of the difficult situation caused by the coronavirus crisis that we are in now and the fact that I had to do it without family, friends and colleagues around me. I missed that support. But luckily, my paranymph and some friends were there with consideration of the social distance.

The university wanted to do everything in the usual way as much as possible. I was very happy to see the rector magnificus, the promotor and the opponents wearing the professional mantle and sitting behind their computers. At 13:30 the beadle pronounced the traditional "hora est" ("it is time"). I started with a presentation and after 15 minutes the rector magnificus opened the ceremony and all the questions by the opponents and answers by me went very well and I was very happy because my promotors were very satisfied with the defence. Again, once the questions and time were finished, the beadle naturally pronounced the traditional "hora est". The PhD committee went into a separate online meeting for 15 minutes, and later they awarded me the doctoral degree. After the rector awarded the doctorate and offered his congratulations to me, my promotor offered a personal speech to me and later I received a congratulation from all the opponents.

Immediately after the defence, I participated in a digital party given by my family, friends and colleagues who all congratulated me, and I received nice flowers from the department and some friends. It was a very nice experience and, despite the situation, it was very special because so many people shared the joy of this achievement with me. ■



REMINDER: SAVE THE DATE!

June 11, 2020
13:00-15:00 uur

(VIRTUAL) NVT General Meeting



The (r)evolution
of toxicological models
How to address safety in target species

Female reproductive health – Species- and ligand-specific endometrial differences to hormones and aryl hydrocarbon receptor activation

Door Annick van den Brand

Annick van den Brand promoveerde op 20 februari 2020 aan de Universiteit Utrecht met het proefschrift getiteld: “Female reproductive health – Species- and ligand-specific endometrial differences to hormones and aryl hydrocarbon receptor activation”. Het promotieonderzoek werd uitgevoerd onder begeleiding van Prof. Martin van den Berg (Universiteit Utrecht) en Prof. Majorie van Duursen (Vrije Universiteit Amsterdam).

Ongeveer 10% van alle vrouwen in vruchtbare leeftijd wordt gediagnostiseerd met aandoeningen aan de reproductieve gezondheid, zoals endometriose, baarmoederkanker en verminderde vruchtbaarheid. Dit soort aandoeningen komen steeds vaker voor en wordt in verband gebracht met de blootstelling aan milieuvervuilende stoffen. Het blijkt echter moeilijk om deze aandoeningen te onderzoeken door de hormonale interactie tussen het brein, de eierstokken en de baarmoeder én verschillen tussen het reproductieve systeem van mensen en proefdieren. Mede door de verschillen tussen mensen en proefdieren is er een gebrek aan goede testmodellen om aandoeningen in het

reproductieve systeem in mensen te onderzoeken.

Tijdens mijn promotieonderzoek is er onder andere gekeken naar de verschillen tussen het endometrium (de binnenwand van de baarmoeder) van ratten en mensen. We hebben hiervoor een humaan relevant endometrium model vergeleken met een endometrium model voor de rat. Dit model hebben we ontwikkeld door verschillende typen primaire cellen uit humaan en ratten baarmoeder weefsel te isoleren en op te kweken in het laboratorium. Vervolgens hebben we deze cellen in een 3D-model weer bij elkaar gebracht, en blootgesteld aan de hormonen oestradiol en progesteron. Op deze manier konden we de het endometrium in verschillende fases van de reproductieve cyclus nabootsen.

Ook hebben we de effecten op endometrium cellen onderzocht van chemische stoffen die de aryl hydrocarbon receptor (AHR) activeren. Deze receptor is vooral bekend als sensor van lichaamsvreemde stoffen en ook als de regulator van de afbraak van deze stoffen. De laatste jaren wordt deze receptor echter steeds meer in verband gebracht met het reguleren van normale cellulaire processen. De geactiveerde



AHR kan bijvoorbeeld ook het oestrogenmetabolisme beïnvloeden. Een verstoring van de hormonale balans via deze receptor kan zodoende een rol spelen bij het ontstaan van reproductieve aandoeningen door chemische stoffen.

Een opvallend verschil tussen de endometrium cellen van mensen en ratten is dat het hormoon progesteron de expressie van de AHR omlaag brengt in het rat →

endometrium model, maar niet in het humane endometrium model. Ook zagen we dat het activeren van de AHR het oestrogeenmetabolisme in de humane endometrium cellen beïnvloedde, maar niet in de endometrium cellen van ratten. Verder zagen we dat de mate van AHR activatie (potentie) van twee liganden tegengesteld was in menselijke en ratten endometrium cellen.

Het onderzoek dat is beschreven in mijn proefschrift toont aan dat er grote verschillen zijn tussen het endometrium van mensen en ratten met betrekking tot hormonen maar ook met betrekking tot mogelijk toxische effecten van chemische stoffen. Deze verschillen in effecten op de baarmoeder tussen diersoorten en chemische stoffen kunnen nog niet goed verklaard worden. Deze verschillen maken het ook moeilijk om een goede vertaling te maken van proefdierstudies naar een menselijke situatie. Om deze proefdierstudies beter te interpreteren is het identificeren van de verschillen tussen mens en knaagdier een cruciale stap. Alles bij elkaar genomen kan worden geconcludeerd dat een rat geen relevant model is om het effect van stoffen op de vrouwelijke reproductieve gezondheid, en dan met name het endometrium, te voorspellen. Dit komt door verschillen in hormonale respons, maar ook door soort-specifieke en chemische stof-specifieke verschillen na het activeren van de



AHR. Om de effecten van chemische stoffen op het endometrium te testen kan er beter gebruik gemaakt worden van primaire humane endometriumcellen.

Je kunt het hele proefschrift lezen via: <https://dspace.library.uu.nl/handle/1874/391078>

En nu?

Sinds maart 2019 werkt Annick bij het Rijksinstituut voor Volksgezondheid en Milieu (RIVM), op de afdeling Voedselveiligheid. Ze houdt zich hier onder andere bezig met risicobeoordeling van chemische stoffen. ■

Note from the editors

As might be expected, there are a lot of changes that are happening to meetings and conferences because of the COVID-19 pandemic so please check regularly on the websites of the respective events for an update.

SLC webinars are viewable online

If you missed the last SLC webinar on Big Data: What Is It and What Does It Mean to Me? presented by Dr. Aric LaBarr and Dr. Alyson Wilson? Don't worry.

You can catch the recorded version from the comfort of your home. All webinars are viewable in a protected format on the [SLC website](#). ■



Call for SP and CEC's

Taking place in Orlando, Florida, the SOT 60th Annual Meeting and ToxExpo will feature more than 80 Featured and Scientific Sessions, 2,000 presentations, 300 exhibitors, and 6,000 attendees. [The Scientific Session and Continuing Education course proposal deadline is June 12, 2020](#). ■



Eurotox 2020 Coronavirus Update

By Heather
M Wallace,
President of
EUROTOX



I am pleased to announce September 26-29, 2021, as the new dates of the [2021 EUROTOX congress taking place in Copenhagen, Denmark.](#)

As previously announced, the EUROTOX Executive Committee in conjunction with the Local Organising Committee (LOC) in Denmark and K.I.T. Group, took the decision to postpone to 2021, the EUROTOX 2020 Copenhagen congress originally scheduled to take place, September 6-9. The decision was not taken lightly, and a number of options were investigated and discussed before agreeing to postpone the congress to 2021.

This is a great disappointment, but with the current uncertainty around the COVID-19 situation, we felt we needed to make a decision in the best interests of all; the speakers, the exhibitors and our delegates.



The Executive Committee and the Scientific Programme Committee will work together in the next few months to prepare the programme for the 2021 congress. Some changes will be necessary due to the availability of speakers, and the timeliness of the session content.

Furthermore, this decision will have knock on effects for congresses already planned in 2021 and 2023. I have been in touch with the Chairs of the LOC for Ljubljana (2021) and Athens (2023) and they were both understanding and supportive.

The current situation is that the next three EUROTOX congresses will be:

2021	Copenhagen
2023	Ljubljana
2024	Athens

The ICT congress in 2022 will remain in Maastricht. The EUROTOX Executive Committee appreciates the disruption this decision may cause all parties involved, but we hope that you understand that it was made to ensure the safety of our EUROTOX family, and maintain the integrity of our annual congress. We hope that we can continue to count with your support as we navigate our way through this situation.

Please keep safe and well. ■

3Rs Science Prize 2020 Call for submissions

The European Partnership for Alternative Approaches to Animal Testing's (EPAA) 2020 3Rs Science Prize is now open for submissions.

EPAA promotes the development, validation and acceptance of 3Rs alternative approaches (replacement, reduction and refinement of testing on animals).

The 3Rs science prize is granted every two years to a scientist with an outstanding contribution to 3Rs.

This initiative promotes positive contributions from industry or academia and encourage more scientists to focus their research on the 3Rs goals. Scientists working on relevant methods for regulatory testing (e.g. safety, efficacy, batch testing) providing an outstanding contribution to the use of the 3Rs may apply for the prize.

The call is available on the EPAA [website](#). Submissions must be sent via email to grow-epaa@ec.europa.eu by 12:00 (noon) **Monday, October 5.** ■



Summer School will take place as a virtual meeting

June 22-25, 2020. Registration is free.

Join students and early-career scientists this summer at the first [North American Summer School on Innovative Approaches in Science](#). The program will feature lectures, in-depth training, virtual laboratory tours, e-poster presentations, and virtual engagement with speakers and attendees. The program is focused on presenting cutting-edge methods to reduce and replace animal tests in toxicology and biomedical science.

This **free** online event features expert speakers from Harvard University, Johns Hopkins University, the National Institutes of Health, the Environmental Protection Agency, the Physicians Committee for Responsible Medicine, and more.

Information about applying is available [here](#). ■



Haalbaarheidstoets voor een grenswaarde voor isocyanaten

De SER start een onderzoek naar de haalbaarheid van een publieke grenswaarde voor isocyanaten



Isocyanaten zijn uitgangsmaterialen voor polyurethaan (PUR), dat onder meer wordt toegepast in vernissen, lakken, schuim en kleefmiddelen. Blootstelling aan isocyanaten komt in vele sectoren voor, waar onder de bouw, de automobiellindustrie, de scheepsbouw, de verfindustrie, bij de productie van plastics en bij de productie van elektronica. Blootstelling aan isocyanaten kan onder andere beroepsastma veroorzaken.

Aan brancheorganisaties wordt gevraagd of een waarde van 0,1 µg NCO/m³, als een gemiddelde concentratie over een achturige werkdag, uitvoerbaar is voor hun leden. Dit is de luchtconcentratie waarbij volgens inschattingen van de Gezondheidsraad het aantal

werkenden dat schadelijke effecten ondervindt beperkt blijft. Het rapport van de Gezondheidsraad vindt u hier. Bedrijven die denken dat de invoering van de advieswaarde niet haalbaar is, wordt gevraagd aan te geven welk blootstellingsniveau wel realiseerbaar kan zijn en op welke termijn. Komen er geen bezwaren, dan gaat de SER ervan uit dat de voorgestelde gezondheidskundige advieswaarde kan worden ingevoerd.

Richtlijn voor onderzoek en rapportageformat

Hieronder staat de brief aan de brancheorganisaties, een richtlijn voor branches en bedrijven voor onderzoek naar de haalbaarheid van een voorgestelde grenswaarde en het rapportageformat voor bedrijven waarin stapsgewijs wordt aangegeven welke gegevens er door bedrijven dienen te worden aangeleverd. Royal HaskoningDHV ondersteunt de brancheorganisaties bij dit proces, met onder andere een online vraag- en antwoordsessie op donderdag 28 mei a.s. van 10.00 tot 11.00. Via het e-mail adres: haalbaarheidstoets.isocyanaten.wps@nl.rhdhv.com kunt u zich opgeven voor deze sessie en tevens ook vragen stellen.

[Brief aan de brancheorganisaties \(pdf\)](#)

[Richtlijn voor onderzoek naar haalbaarheid van een voorgestelde grenswaarde \(pdf\)](#)

[Rapportageformat haalbaarheidsonderzoek door bedrijven \(pdf\)](#)

Joep van den Berckenprijs

De Joep van den Berckenprijs Commissie, bestaande uit Martijn Rooseboom, Marjorie van Duursen, Jacqueline van Engelen, Theo de Kok en Henk van Loveren (voorzitter) heeft na bestudering van de ontvangen nominaties besloten de prijs voor het beste proefschrift in 2019 toe te kennen aan Carin Lunenburg, voor haar thesis "Personalised medicine of fluoropyrimidines using DPYD pharmacogenetics".

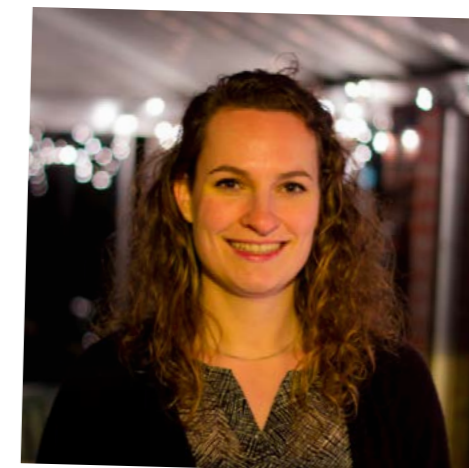
De commissie was van oordeel dat het een zeer relevant onderzoek voor een aanzienlijk probleem in de kliniek betreft, namelijk het ontdekken van diagnostische markers van het DPYD gen d.m.v. DPYD genotypering.

Dit gen codeert voor het enzym dihydropyrimidine dehydrogenase dat betrokken is bij de afbraak van fluoropyrimidines. Dit is met name van belang om de ernstige, potentieel dodelijke, toxiciteit door fluoropyrimidines te mitigeren door de dosis 'personalised' aan te passen bij de behandeling voor o.a. borst-, maag- en darmkanker.

Het onderzoek combineert op excellente wijze fundamenteel toxicologisch onderzoek met de klinische praktijk en heeft geleid tot een grote set aan publicaties in internationale vakbladen waaronder Lancet Oncology. De inzichten die uit dit onderzoek voortgekomen zijn hebben inmiddels al hun weg gevonden naar een aanpassing van de klinische behandelrichtlijnen.

Volgens de traditie wordt de Joep van den Bercken laureaat uitgenodigd om tijdens de jaarvergadering van de NVT het onderzoek waarop het proefschrift is gebaseerd te presenteren. Helaas is dit jaar de jaarvergadering afgelast. Carin zal wel dit jaar de prijs in ontvangst nemen, en zal in 2021 alsnog worden uitgenodigd haar werk te presenteren.

De commissie en het bestuur van de NVT feliciteren hierbij Carin van harte met de prijs. ■



REGISTRATIE CIE

Inschrijving register

Voorletters	Achternaam	Datum inschrijving	Datum afloop registratie
D.	van der Merwe	07-01-2020	07-01-2025
L.C.P.	Borra	17-02-2020	17-02-2025
L.C.P.	Kamelia	19-02-2020	19-02-2025
A.	Zwartsen	24-02-2020	24-02-2025

Inschrijving TiO

Voorletters	Achternaam	Opleider	Datum inschrijving
F.	Widjaja	Prof.dr.ir. I.M.C.M. Rietjens	17-02-2020
M.H.	Rietdijk	Prof.dr.ir. I.M.C.M. Rietjens	17-02-2020
Q.	Ren	Prof.dr.ir. I.M.C.M. Rietjens	17-02-2020
A.D.	Simons	Prof.dr. A.J. Murk	17-02-2020

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

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