TCDD

TOXICOLOGIE

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SPECIAL THEME

COVID-19 VACCINE SPECIAL

- HOW SAFE ARE VACCINES REALLY? AN OVERVIEW OF PAST AND PRESENT
- VACCINE SAFETY & THE SPOTTED HISTORY OF A SCIENTIFIC REVOLUTION
- THE “MONKEY VACCINE”: PLANET OF THE (J)APES?
- RARE EFFECTS OF VACCINES: IS IT WORTH IT?
- INTRAVACC AND LEIDEN UNIVERSITY DEVELOPED AN ANIMAL REPLACEMENT METHOD FOR VACCINES

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Colofon

Toxicologische Communicatie, Data en Documentatie

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Inhoud

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Editorial

There is no doubt that 2020 has been a year defined by COVID-19 and unlike any other that we have experienced in our lifetime. At the same time it was an opportunity to learn about the role that global pandemics have played in shaping the history of our healthcare systems. Most of us will likely remember 2020 as a year when we worked mostly from home, donned masks in public during infrequent outings, and advanced our digital collaboration skills to new levels. This unfortunately means that there are also no travel grant reports. To make up for this shortfall we have put together an exciting issue with a special theme about COVID-19 vaccines. Are vaccines safe? What do they contain, what are the side-effects and should we be concerned? With so many diverging opinions out on the internet we tried our best to separate fact from fiction.

And let's not forget, it's the end of the year so do join our Christmas competitions and who knows, you might be the lucky winner!

With the holidays around the corner, we wish everyone a safe celebration and as always do let us know what you think of this issue. If you have any topics you think would be interesting to cover in 2021 do drop us a line at redactie@toxicologie.nl

On behalf of the editorial team,

Barae Jomaa

Photo by Jess Bailey on Unsplash

News from the board

Welcome to the latest issue of TCDD, which is dedicated to COVID-19 vaccines, a very timely topic. Thanks to the TCDD team for yet another informative and entertaining issue, a wonderful testament to all their hard work. Looking back on this strange and challenging year, the prospects of a vaccine make me hopeful that we will return to a situation with more physical interaction with our colleagues, students and peers, something I miss very much!

In 2021, our NVT Annual Meeting will be held on June 9-10 2021, at Reehorst, Ede. Our organizing committee has been busy designing a hybrid virtual/face to face programme that can be adapted to whatever the situation is in June 2021. We have developed an exciting programme around the theme "The (r) evolution of toxicological models – how to address safety in target species." As in previous years, the first day will be specially tailored to our students and PhD candidates, while the second day (June 10) will be for all members of our society. Please save the dates!

Happy holidays, and all the best for a happy and healthy end to this strange year.

Here's to a fantastic 2021 and a safe vaccine!

Juliette Legler
President NVT

NVT 2021 Announcement

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

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

SECTIES RISICOBEOORDELING EN ARBEIDSTOXICOLOGIE

Vooraankondiging middagsymposium

Piekblootstelling

Op donderdag **18 maart 2021** organiseren de NVT secties risicobeoordeling en arbeidstoxicologie samen met de Contactgroep Gezondheid en Chemie (CGC) een voorjaarsbijeenkomst. Het onderwerp is “piekblootstelling”. Afhankelijk van de situatie op dat moment wordt de bijeenkomst fysiek (in Eindhoven) of digitaal georganiseerd.

Tijdens werkzaamheden kunnen er korte hoge blootstellingen aan schadelijke chemische stoffen plaatsvinden die gecorreleerd zijn aan bepaalde handelingen op bepaalde momenten. Deze piekblootstellingen kunnen acuut ernstige gezondheidsproblemen opleveren, maar ook gezondheidsproblemen op de lange termijn. Grenswaarden met een tijdgewogen gemiddelde concentratie van 15 minuten (TGG-15 minuten) kunnen helpen deze risico’s te herkennen, zodat gerichte preventieve maatregelen kunnen voorkomen dat die korte hoge blootstelling(en) plaatsvinden.

Dit klinkt makkelijker gezegd dan gedaan, want wat is precies een piekblootstelling en wanneer is zo’n grenswaarde nodig? Hoe meet je die pieken op de werkplek en hoe kun je het beste zo’n 15-minuten norm afleiden om het risico ervan te kunnen beheersen?

En bieden de 15-minuten normen voldoende bescherming of zijn daarnaast ook ‘absolute’ bovengrenzen nodig? Deze onderwerpen zullen aan bod komen bij deze bijeenkomst.

Zodra het definitieve programma bekend is wordt het op de website van de NVT gepubliceerd.

Noteer de datum alvast in uw agenda! ■

Datum: 18 maart 2021
Locatie: Eindhoven of digitaal

Bron: Djanko

RISK ASSESSMENT

Everything you always wanted to know about PFAS – Meeting Report

On the 5th of November, the Section on Risk Assessment organized a meeting with the intriguing title: Everything you always wanted to know about PFAS. This meeting was originally scheduled the 7th of April, 2020, but was postponed to November due to COVID. More than 90 participants attended this virtual meeting. **Fenneke Linker** from the Risk Assessment Section chaired the meeting.

INTRODUCTION

As a short introduction, Professor **Annemarie van Wezel**, University of Amsterdam, gave a general overview on PFAS. PFAS use is really wide-spread, in almost all industry branches and in many consumer products. OECD list contains >4700 PFAS substances of which only 107 substances are currently registered under REACH. PFAS are also called 'forever chemicals' because of their persistence. They are widespread, and are present in 99 of 100 environmental samples.

The main health effects are effects on the immune system, the liver, renal function and on thyroid hormone levels. Because of this heterogeneity, it is difficult to derive general health levels.

For humans, dietary intake is the main route of exposure.

In 2020 EFSA has proposed a single group Tolerable Weekly Intake (TWI) of 4.4 ng/kg bw per week for the sum of PFOA, PFNA, PFHxS, and PFOS. Europeans partly exceed this TWI.

Worldwide, PFAS is found in environmental organisms. Most reported PFAS concentrations in the environment are below their predicted no-effect concentration. However, our understanding of the toxicity is incomplete, due to lack of information on new PFAS, precursors, degradation products and mixture toxicity.

Annemarie illustrated that both in the Green Deal and in the EU Chemical Strategy, *essential use* and *benign by design* (or safe and sustainable) are important issues, that need to be further worked out. She advertised an EU project, PERFORCE, that started in January 2020, that is an innovative training network to train a new generation of innovative earlystage researchers, so that they will be able to face current and future challenges and to convert knowledge and ideas into products and services for economic and social benefit.

STATEMENT: The EFSA opinion for 4 PFAS should be summed to 4000+PFAS.

30 out of 90 people voted in favour.

A few remarks were made via the chat: what are the advantages /disadvantages of creating a single limit on all 4000+ PFAS when the group of chemicals is so diverse? An advantage would be a more inclusive risk assessment, but a disadvantage is that a lot of tox data has to be available.

Another question was whether it would be possible to use toxic equivalence like the TEQ for dioxins Instead of gathering all tox data, or are the adverse effects too different? Another participant referred to an RIVM paper on relative potency factors.

A third question was whether background levels only originate from pollution? The other sources are one of the big unknows. There are several activities related to pollution (e.g. at airports where fire fighter foams were used). Also, paper mills might have a relevant contribution, according to a recent exploratory study by RWS. Different investigations are going on to further map the sources.

STATEMENT: Research focus should be on possibilities how to replace PFAS by benign alternatives.
A majority, 60 of 90, raised their hand. It was also indicated that also non-chemical alternatives should be considered.

DETERMINATION OF PFAS LIMITS IN SOIL

Arjan Wintersen of the Dutch National Institute for Public Health and the Environment (RIVM) presented the determination of PFAS limits in soil, prepared together with his colleague Piet Otte. There are three building blocks used in setting Environmental Quality Criteria for soil: Human health risk limits, ecological risk limits (covering both direct and indirect (via food web) exposure) and "other" (risk) limits, which may be, e.g., background levels. RIVM is responsible for preparing science-based advisory limit value, the Ministry of Environment subsequently decides on the legal limit values.

Depending on the use of the soil, different criteria are developed. When used for agriculture or designated as "nature", a stricter limit value applies than for residential use; for industrial use the least strict value is applied.

At the moment, only two PFAS are significantly present in Dutch soil: PFOS at 1.4 µg/kg dry soil and PFOA at 1.9 µg/kg (95th percentiles). Higher concentrations are found in top soil than in subsoil and predominantly in built areas, not in rural areas or areas designated as nature. For PFOA, there is a clear link with its source, Nemours in Dordrecht, as its concentration decreases exponentially with the distance from the plant. There are no indications that other PFAS - like GenX - are structurally present in Dutch soil.

The current soil standards addressing human health effects were based on Tolerable Daily Intakes (TDI's) derived by the RIVM some three to five years ago. They vary between 6-21 ng/kg bodyweight/day for PFOS, PFOA and GenX. These are well above the current background values in soil. However, this year EFSA has derived a Tolerable Weekly Intake (TWI) of 4.4 ng/kg bodyweight for the sum of PFOS, PFOA, PFNA & PFHxS, which corresponds to 0.63 ng/kg bodyweight/day. Point of Departure was a Benchmark Dose Level (BMDL) of 17.5 ng/mL in blood serum of breastfed children, associated with a reduced immune response.

Ecological risk limits were based on the relative number of species affected at certain soil concentrations of PFOS, PFOA or GenX, either directly or indirectly via the food web. Due to the biocumulative properties of PFAS, the indirect limit values are up to nearly two orders of magnitude lower, and thus determine the limit to be used. These are still above the background values, but only less than one order of magnitude.

Arjen concluded by summing up what we still do not know, e.g. the transfer and accumulation of PFAS from soil to crops and farm animals. After his presentation quite a number of questions were asked, e.g.:

- **Are there other sources than man-made PFAS in the soil background levels?**
  Unknown, but RIVM will look into this issue

- **What about levels in groundwater?**
  Nation-wide Research is on-going, will be published beginning of next year

- **Has intake of PFAS via supermarket bought food been taken into account in PFAS exposure calculations?**
  No, that is not in the RIVM model (valid for any substance exposure via the environment)

To conclude Arjen put a **statement** to the vote: "The PFAS that we measure in the environment are only the top of the iceberg." It was supported by 40 of the 80 odd attendants of the symposium. Arjan himself left the answer open and stated PFOS and PFOA are the main PFAS in soil, but that it might be different for other compartments, depending on the mobility and the affinity of the PFAS (for components in the compartment concerned).

POLICY CONSEQUENCES

Marije Schouwstra, policy coordinator at the Ministry of Infrastructure and Water management (IenW) introduced us to 50 years of soil policy. In soil policy there is a balance between protection of the soil and the use for economic and social purposes. The basic principles are prevention and remediation. The approach in policy was that all contamination should be eliminated; remediated sites should be fit for all possible future functions. With PFAS a new kind of pollution was introduced: omnipresent despite a prevention policy. Such a wide dispersive use was not addressed in the policy.

Within the soil policy, according to the Standstill principle it has to be prevented that cleaner sites are polluted as well; if you want to transport soil, you have to be sure that you do not contaminate another site. You need a risk-based limit value (risicogrenswaarde) to be able to set a norm, and that takes time.

Marije shared a few lessons learned: Communication in extremely important. The Framework was experienced as tightening the rules. And our regulations have to be adapted to diffuse pollution: there is a need for development of a new methodology to cope with diffuse emerging contaminants.

STATEMENT: I make a conscious choice and try to buy products without PFAS.

30 out of the 90 participants raised their hand. As a consumer it is hard to know if products contain PFAS. But for some products, like rain coats and cooking utensils, you can buy PFAS-free products. It might be indicated on the label. But for a large number of products, it is impossible to make a well-informed choice.

STATEMENT: We have to phase-out all PFAS, also in essential uses.

Only 15 participants of the 90 raised their hand.

STATEMENT: before introducing new substances in production processes, you should proof its non-toxic and non -persistence character.

The majority of the participants agreed: 54 of 90

FROM SOIL TO (DRINKING) WATER

Frederic Béen from the KWR Water Research Institute presented the analytical methods available for determining PFAS in drinking water as well as ways to remove them from drinking water. At the EU-level, two limit values have been set for PFAS, established in December 2019: 0.1 µg/L for the sum of the 20 most important PFAS and 0.5 µg/L for the sum of the 4700 known PFAS. The latter value is not yet in vigour, awaiting the development of a suitable analytical method by the EU over the next three years. The new TWI for four PFAS developed by EFSA has not yet been used to derive a drinking water limit, but **preliminary** calculations using a simplistic approach led to a value of about 4 ng/L.

Frederic presented the following analytical methods:

1. Total organic/extractable fluorine methods: these are useful for rapid screening, yet not ideal for testing drinking water as their Limit of Detection (LoD) is 0.5 µg/L.

2. Total oxidizable precursors assay (TOPA): only useable for known PFAS, requires further validation and standardization, needs to be adapted to accommodate emerging PFAS as well.

3. Broad screening methods: do not need reference standards, will also identify unknowns, but mainly qualitative although more quantitative applications are being developed based on machine learning.

4. Comprehensive workflows: including a step-wise combination of available analytical methods to analyse water quality in the Netherlands and develop a monitoring programme targeted at locally important PFAS, a research project of KWR in collaboration with WFSR, RIWA, Water Boards and Dutch drinking water companies.

PFAS are extremely persistent and difficult to remove from drinking water. There is a well-developed method (Granular Activated Carbon (GAC)), that works well for long-chain PFAS but is less effective for the short-chain ones. For the latter PFAS various technologies are in development, but not ready yet.

After his presentation a number of questions were asked, e.g.:

- **How do you avoid cross-contamination during sampling (e.g. when the sampler wears a PFAS-treated rain coat)?**
  This is above all an issue in the lab, as many equipment used contain PFAS. Therefore, you have to be careful and make ample use of appropriate blanks

- **Should we also use bio-assays to analyse for PFAS?**
  Yes, indeed.

- **Instead of removing PFAS from drinking water, shouldn't we try to remove it somewhere else (probably meaning at the source)?**
  This discussion is on-going, but there is no decision yet.

FROM WATER TO LIVESTOCK TO CONSUMERS

Jacqueline Steenbergen-Biesterbos from the Netherlands Food and Consumer Product Safety Authority (NVWA) presented their study, in which NVWA investigated whether there is a possible risk for human health due to exposure to PFOA and GenX in food. In 2017 and 2018 PFOA and GenX were found in soil and water due to air deposition of these substances, in Dordrecht and Helmond. Livestock might be exposed if polluted soil,

grass or water is consumed. Subsequently, consumers might be exposed via the consumption of products of animal origin. Dietary exposure of children and adults was determined by measuring PFOA and GenX levels in various food items and using consumption data from the Dutch National Food Consumption survey.

The exposure of children and adults to PFOA and GenX via the consumption of cow's milk, meat (cow/sheep), cheese, yoghurt, egg and eel does not pose a risk for human health.

Despite the fact that the exposure of children and adults to PFOA via the consumption of carp exceeds the provisional EFSA-TDI of 0.8 ng/kg body weight per day, the risk for human health is expected to be low. A TDI is a health-based guidance value based on long term exposure. The carp was caught in a fishing pond in the close vicinity of a factory in Helmond. Fish from this pond will probably only, on occasion, be eaten by specific consumers (sport fishermen) leading to short term exposure. Furthermore, the risk assessment of carp was based on one fish and this fish does not provide an overview of the PFOA distribution in fish from the fishing pond.

Based on a comparison with the provisional EFSA-TDI of 0.8 ng/kg body weight per day, the exposure of children and adults to PFOA via the consumption of sheep's milk might pose a risk to human health. The risk assessment for sheep's milk is based on experimental transfer data from two sheep that do not show the same kinetics. Compared to dairy cows, the transfer of PFOA to milk in sheep is higher than one might expect. Therefore, no firm conclusion about the human health risk can be drawn. The full report can be found via https://www.nvwa.nl/documenten/consument/eten-drinken-roken/overige-voedselveiligheid/risicobeoordelingen/advies-van-buro-over-de-chemische-stoffen-pfoa-en-genx-in-voedsel.

Krista Bouma from the NVWA stated that for the risk assessment of PFAS in food contact materials (FCM), paper and paperboard are the main concern since PFAS in water and grease repellent coatings of these materials are present as monomers and not as a polymer, meaning they may more easily migrate to the food contained in them. However, data are needed on migration into food (instead of data on food simulants) in order to perform a more precise risk assessment. The NVWA has developed an analytical screening method that they can use on paper and paperboard to identify PFAS's present. 46 samples (paper and paperboard intended for hot and/or fatty contact) were screened. Significant amounts of PFCA's C13 and C14 were found, other PFAS's (PFOA, PFOS, GenX, fluorotelomers) were either not detectable or present in negligible amounts. Further development is also dependent on developments in legislation (maximum residue levels in food versus or migration limits). Further research is carried out by WFSR, PFAS will be determined in easy and fast-food, packaged in paper/paperboard. If significant amounts of PFAS are detected in the food, then also the food contact material will be investigated to establish if this was the source of the PFAS. The report is expected in Q1 of 2021.

STATEMENT: a risk assessment based on exposure via food is not sufficient. Other exposure sources/routes should also be taken into account.
A majority, 50 of 90 participants, raised their hand and agreed with this statement.

STATEMENT: Should PFASes also be banned from non-stick polymeric coatings?
Of the 90 participants, 42 agreed.

Fenneke Linker closed the meeting with a final statement: I gained new insights today. The virtual hand of 65 of the of 90 participants was raised! The slides of the presentations will be made available in the Risk Assessment section of the NVT website. ■

Source: NOS

ARBEIDSTOXICOLOGIE

Door: Jeroen Terwoert,
Specialist Arbeidshygiëne,
Inspectie SZW

Arbeidstoxicologie van de circulaire economie

Korte impressie van het online middagsymposium van de Sectie Arbeidstoxicologie van de NVT en de Contactgroep Gezondheid en Chemie, 8 oktober 2020.

Het schaars worden van grondstoffen, klimaatverandering en vervuiling leiden tot pogingen de economie te verduurzamen. Verduurzaming is een breed begrip. Het omvat onder meer: 1) energietransitie, ofwel de omschakeling naar vernieuwbare of oneindige vormen van energie, 2) de inzet van biobased grondstoffen in de chemie, 3) duurzamer bouwen en 4) het streven naar een 'circulaire economie' ("waste is food"). 'Groen' is niet per definitie ook veilig en gezond voor werknemers. Het Europese Agentschap voor Veiligheid & Gezondheid op het Werk heeft een inventarisatie laten uitvoeren van de mogelijke gevolgen van 'green jobs' voor de veiligheid en gezondheid van werknemers. Voorbeelden zijn de blootstelling aan indium tinoxide in de productie van zonnepanelen, epoxyharsen in de productie van windmolenbladen, organisch stof en endotoxinen bij de verwerking van biobased grondstoffen, zware metalen in de recycling van elektronica, vliegas in de wegenbouw, en aan PAK uit rubberkorrels afkomstig van gerecyclede autobanden. Hebben de voorvechters van vergroening en de innovatieve bedrijven voldoende aandacht voor blootstelling aan stoffen?

GOEDBEDOELDE KRINGLOPEN

Susanne Waaijers van het RIVM gaf een overzicht van de ontwikkelingen richting een circulaire economie. Circulariteit houdt het streven in naar minder gebruik, meer hergebruik en een gesloten keten met zo min mogelijk afval. Een consequentie van de goedbedoelde nieuwe kringlopen kan zijn dat er onbedoeld nieuwe blootstellingen ontstaan. Bij de circulaire economie komen veel nieuwe technologieën kijken, zoals chemische recycling, en worden nieuwe materialen gebruikt, zoals afvalproducten. Susanne lichtte haar verhaal nader toe aan de hand van de casus van plastic producten.

Egon Schreven lichtte toe waar hij zoal mee te dealen heeft als veiligheidskundige bij afval- en energiebedrijf Twence. Grondstoffenproductie- en terugwinning uit afval, en energieproductie bij verbranding en vergisting leiden tot vele potentiële blootstellingen. Voorbeelden zijn (hout)stof, kwarts, biologische agentia, zware metalen (o.a. lood, cadmium en kwik), vluchtige organische verbindingen, koolmonoxide en dieselmotorenemissies. Bij de risicobeoordeling gebruikt men luchtmetingen, veegmonsters, schattingen met modellen en biomonitoring.

SAFE & SUSTAINABLE BY DESIGN

Jolanda Willems (PreventPartner & GGD) besprak een casus over het toepassen van secundaire grondstoffen in de bouw en infrastructuur. Bij het betreffende bedrijf worden vervuilde grond, slib, afval en bodemas gereinigd en vindt recycling plaats van minerale reststromen tot secundaire grondstoffen. In het bedrijf ontstonden zorgen over de hoge frequentie van het kortdurend ziekteverzuim bij een groep medewerkers, waarbij infectieziekten een rol leken te spelen. Men zag met name een klachtentoename als "riool kolk gemalen vuil" werd bijgemengd. Bovendien leken de klachten te zijn begonnen sinds er bodemas werd bijgevoegd aan de productiestroom. Diverse micro-organismen, endotoxinen en basische aerosolen werden

TERUG NAAR INHOUD

als risicofactoren geïdentificeerd. Na het treffen van maatregelen worden geen gezondheidsklachten meer gerapporteerd en is het kortdurend ziekteverzuim niet meer verhoogd.

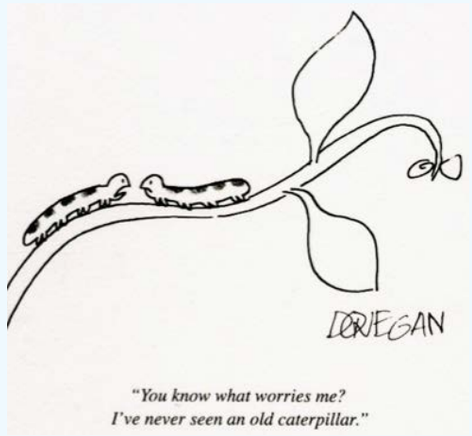
Annette Wilschut, toxicoloog bij DSM vertelde tenslotte over o.m. het streven naar 'safe en sustainable by design' producten. Eén van de grote uitdagingen bij herbruikbare producten is om die weer terug te krijgen, en te zorgen dat de producten 'onderweg' niet vervuilen. DSM probeert ook in te zetten op meer biobased productieprocessen, waarbij wel concurrentie met de voedselketen wordt voorkomen. Hoewel DSM zo min mogelijk gebruik wil maken van zorgwekkende stoffen, is er soms geen alternatief; dan probeert men het product op andere duurzame aspecten goed te laten scoren.

Een uitgebreider verslag van deze bijeenkomst verschijnt binnenkort in het Tijdschrift voor Toegepaste Arbowetenschap. De presentaties zijn te vinden de website van NVvA, onder de CGC. ■

TERATOLOGY AND REPRODUCTIVE TOXICOLOGY SECTION

By: Kirsten van Dycke, Sjors Schulpen, Josianne Theuns-van Vliet and Manon Beekhuijzen

Annual meeting addresses "Obesity and Reproduction"



On the 26th of November the Teratology and Reproductive Toxicology NVT section held their annual meeting with the topic "Obesity and Reproduction". Due to the current situation, this meeting was by webinar instead of face-to-face. We therefore decided to take this as an advantage and send our invitation also to the ETS (European Teratology Society) members which boosted the number of participants.

There were three presentations that together discussed the impact of obesity on the complete reproduction cycle, and a presentation on the use of experimental animal models in obesity research.

Annemieke Hoek (University Medical Center Groningen) presented on obesity and fertility, Rebecca Painter (AMC Amsterdam) presented on obesity in pregnancy, and Lenie van Rossem (EMC Rotterdam) presented on maternal obesity and life course health. It was concluded that obesity causes many issues in respect of fertility, pregnancy and postnatal development. As globally the number of people with obesity still rises, it becomes increasingly important to improve their lifestyle. A large multicenter study with obese subfertile women was recently performed in the Netherlands in which it was investigated whether a 6-months structured lifestyle program could improve fertility treatment outcome. Unfortunately, it was concluded that 6 months was too short to have an impact on live birth rates and TTP (time to pregnancy). However, it did lead to more spontaneous pregnancies and less fertility treatments.

Torsten Plösch (University Medical Center Groningen) presented on obesity and experimental animal studies with a focus on the role of epigenetics. He nicely explained epigenetics by showing the difference between caterpillars and butterflies; they both have the same genetic code, but by appearance they are completely different. He focused on the influence of the early fetal and neonatal environment on the health of the offspring at adult age in the rat. They investigated how disturbances in maternal-fetal nutrient supply during pregnancy and early postnatal nutrition later influence metabolic regulation, and found that the epigenome can be modified by nutritional components or lack of those components in the maternal diet. This results in changed gene expressions of key metabolic regulators which ultimately induces long-term metabolic changes. ■

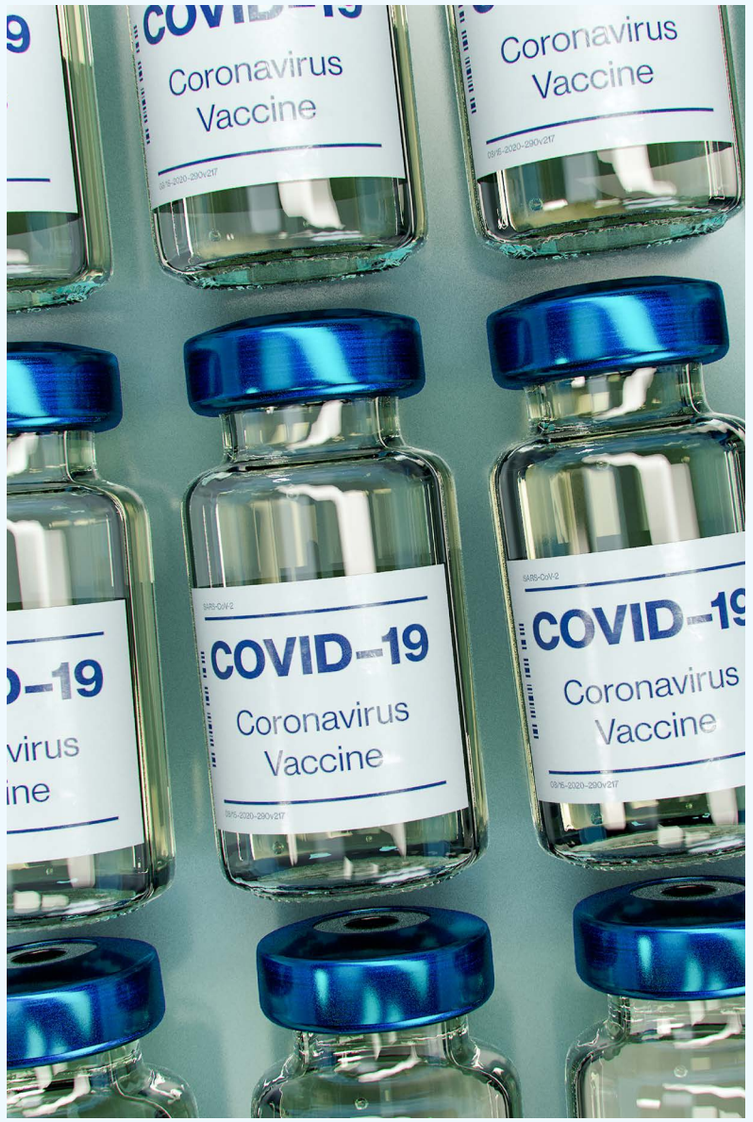
SECTION PHARMACEUTICAL TOXICOLOGY

How safe are vaccines really?

An overview of past and present

By Damiën van Berlo, Jacoba van Zanten, Yolanda Ponstein, Lambert Creuwels, Sylvia Le Dévédec and Daan Touw

The World Health Organization (WHO) defines vaccination as "the administration of agent-specific, but safe, antigenic components that in vaccinated individuals can induce protective immunity against the corresponding infectious agent (WHO, 2019)". Vaccines are biological preparations that can either be used as a prophylactic agent (protecting against possible future infection) or as a therapeutic agent (as treatment of a disease that has already manifested). The general public associates the former application with "vaccination", the latter application is mainly used against cancer and will not be considered further in this special.



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Prophylactic vaccines come in five main forms: 1) Attenuated/weakened virus vaccine that is still able to replicate within a host; 2) Inactivated virus vaccine, incapable of replication; 3) Subunit vaccines that contain fragment of the virus; such fragments, i.e. antigens, are recognized by our immune system; 4) RNA vaccines transfect a coding sequence (mRNA) into human cells, which is translated into a "fragment of the pathogen": when presented on the cell surface this triggers the desired immune response; 5) vector vaccines that consist of an inactivated existing virus (often an adenovirus, such as the virus causing the common cold) that carries RNA or DNA from a virus of interest (such as the SARS-CoV-2 virus that causes COVID-19).

Attenuated or weakened vaccines are similar to the natural infection and mostly create a strong and long-lasting immune response. A virus is often attenuated by culturing it for extended periods under suboptimal conditions or by introducing it into a species in which it does not replicate well. Examples are vaccines developed for measles, mumps and chickenpox. Vaccines based on inactivated viruses use the "killed" (by physical agents or chemical agents such as formaldehyde) version of the virus that causes the disease. Some influenza vaccines are produced by this procedure. Subunit vaccines do not contain live components of the virus but antigenic parts of the pathogen. A well-known example of a subunit vaccine is the hepatitis B vaccine which contains Hepatitis B surface antigens. More recent examples of subunit vaccines are the mRNA vaccines such as those currently developed against SARS-CoV-2 by Pfizer/BioNTech and Moderna; these are listed on the European Medicines Agency (EMA) website, along with other medicines targeted at

COVID-19 for which the EMA has provided advice (EMA; see references section).

Some vaccines also contain an adjuvant to boost the immune response. Some live attenuated or weakened vaccines contain "naturally occurring" adjuvants (immunostimulants with adjuvant behavior) which help the body to produce an effective immune response: examples are bacterial products such as flagellin, porin and bacterial DNA (Pérez et al., 2012). However, for vaccines that only contain parts of the pathogen (e.g., proteins), an adjuvant is added to stimulate immunity. Adjuvanted vaccines can cause more local side effects like redness and swelling and more systemic reactions like fever or body aches. Aluminium salts have been used for decades as an adjuvant. In later years oil-in-water emulsions are used as well, and also synthetic forms of DNA that mimic bacterial material. Finally, stabilizers can be used to maintain vaccine effectiveness after manufacturing.

The first modern vaccine was pioneered by Edward Jenner, a British physician and scientist who also coined the term "vaccine" in 1798. He showed that the relatively mild cowpox virus could induce immunity against the dangerous smallpox virus; this discovery is reflected by the term vaccine, which is derived from the Latin word for cow: vacca. Smallpox was a devastating and lethal disease, killed around 30% of those infected (this number was even higher for neonates). Among survivors, extensive body scarring occurred frequently and many were left blind. Smallpox is considered to have been around for millennia: a smallpox-like rash was found in Egyptian mummies, centuries before AD and symptoms similar to those caused by smallpox were already described in ancient texts (CDC, 2017). In the 20th century alone, around 300 million were estimated to have died from the disease. Through great efforts by the WHO, which launched a massive worldwide vaccination program, smallpox was completely eradicated in the late 1970s. The number of lives saved by the smallpox vaccine is enormous: the medical significance of the invention of this vaccine cannot be overstated. The timeline for smallpox elimination in the world is shown in the figure below.

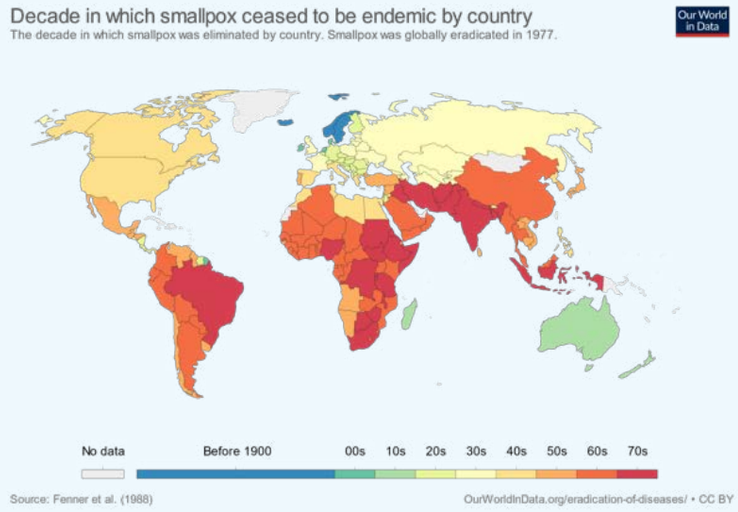

Figure 1. Geographical timeline of smallpox eradication (Fenner et al., 1988)

Since then, vaccines have been developed and applied for many different diseases such as measles, mumps, rubella, hepatitis A, human papilloma virus-induced cancer, tetanus, polio (with some side notes: see further on) and diphtheria with great medical success (Amanna and Slifka, 2020).

The impact of vaccination during the period 2011-2020 was assessed for ten different diseases (i.e., hepatitis B, yellow fever, Haemophilus influenzae type B, Streptococcus pneumoniae, rotavirus, Neisseria meningitidis serogroup A, Japanese encephalitis, human papillomavirus, measles, and rubella) using mathematical modelling. The main conclusion was that the vaccines developed to target these antigens saved more than 23 million lives in 73 countries (all are members of the Global Alliance for Vaccines and Immunizations) (Lee et al., 2013). The WHO estimates that vaccines currently prevent 2–3 million deaths a year (WHO, 2019). Many of the lives that were (and are being) saved are children. When the number of quality-adjusted life years (QALYs) were to be assessed, this would sketch a picture that is even more in favor of vaccination. There is a strong consensus among scientists and healthcare professionals that vaccines contribute tremendously to public health.

Despite of this huge health benefit, more and more people appear to be questioning the importance of vaccines.
In recent years, there was a lot of media attention in the Netherlands regarding the human papillomavirus (HPV) vaccination campaign; a disappointingly low percentage of the girls aged 13 to 16 who were invited to be vaccinated against HPV virus (this invitation is sent since 2009) responded to the invitation by taking the vaccine. This is despite the following facts (source: CBG-MEB and Arbyn et al., 2018):

- 80-90% of sexually active people are infected with HPV at some point in their lives;
- In 1% of women HPV infection leads to cervical cancer or a pre-stage thereof (HPV also causes other cancers but this is less common);

- Every year, 700 women are diagnosed with cervical cancer;
- The Gardasil and Cervarix vaccines against HPV only cause mild side effects.

Thus, at first sight, vaccination seems the sensible thing to do. Unfortunately, only 45% of the invited girls took the vaccine in the first round, while the Dutch Health Council expected 85%. In other countries, the picture was similar (e.g., Stokley et al. 2014). The WHO has listed vaccine hesitancy (also called anti-vaccination or anti-vax) as one of the top 10 global health threats (WHO, 2019). Anti-vax sentiments lead to 1.5 million deaths per year worldwide (WHO, 2019); when this is compared to the 2-3 million lives that are saved by vaccination each year (WHO, 2019), this is clearly cause for concern. In a recent Ipsos survey 27.000 adults originating from 27 countries were questioned on their opinion on COVID-19 vaccination. Overall, 1 out of 4 individuals would not take the vaccine, mainly because they worry about its side effects (56% of the vaccination opponents) and to a lesser degree because they question its effectiveness (29%). Especially in France, Hungary, Poland and Russia the attitude towards COVID-19 vaccination is negative (Ipsos report, 2020).

Is there a basis for the concern about vaccine safety that leads to vaccine hesitancy? At first glance there is not, because before a vaccine is introduced onto the market, extensive safety tests are required. The procedure a vaccine goes through before it reaches the market is shown in **figure 2** (taken from the EMA website):

During this process, the vaccine producer needs to comply with quality standards such as Good Manufacturing Practice (e.g., for production), Good Laboratory Practice (e.g., for pre-clinical studies), Good Clinical Practice (for the clinical trial phase) and Good Pharmacovigilance Practice (general drug safety). In the Netherlands, vaccine safety is evaluated by the Medicines Evaluation Board (CBG-MEB).

The clinical study phases in particular are an extremely important factor for vaccine safety. The aims and procedures of the different phases of the regulatory clinical study procedure is shown in **figure 3**, taken from the US Center for Disease Control and Prevention website (US CDC; European regulations are highly similar; please note that for the phase III clinical trials for COVID-19 vaccines often tens of thousands of volunteers are included, e.g. 30,000 for the "Oxford vaccine", 60,000 for vaccine developed by Janssen Vaccines).

It should be noted that not all subgroups present in the general population (i.e., pregnant women, the elderly, people with underlying disease) are easily included in the clinical trial phases shown above because participants are enrolled on a voluntary basis.

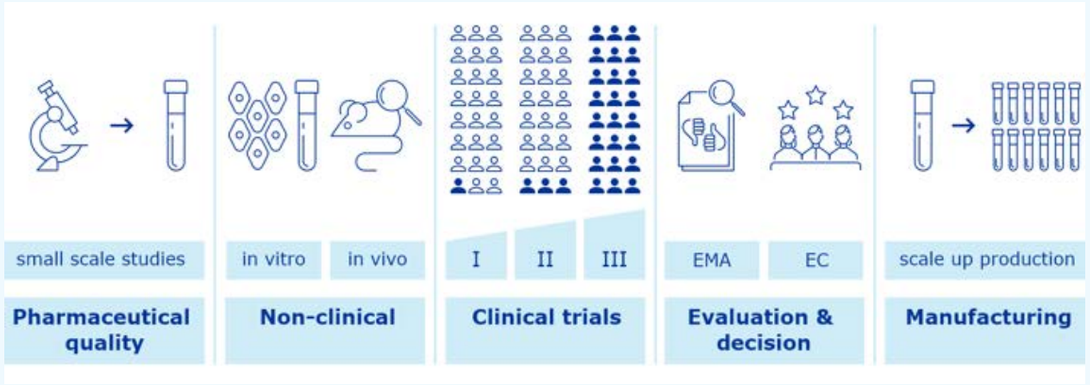

Figure 2. Vaccine development process (source: EMA)

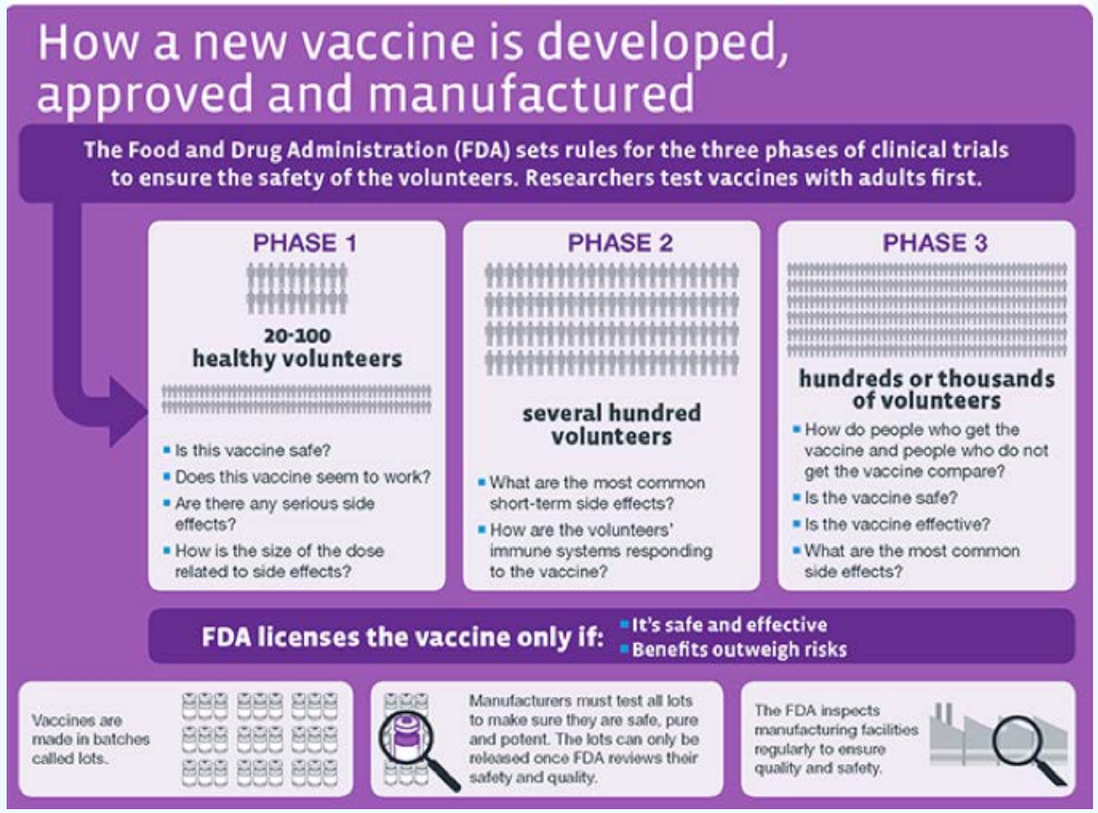

Figure 3. Vaccine testing (source: US CDC)

Requirements for inactivated or attenuated vaccines are laid down in specific guidelines of the WHO. Subunit vaccines that are produced using prokaryotic or eukaryotic cell lines, or by recombinant DNA techniques must be manufactured according to Good Manufacturing Practices (GMP). GMP guidelines have been established to protect the public against harmful medicines and against medicines with adverse side-effects. The main goal of GMP is to ensure that the manufactured product has good batch-to-batch consistency resulting in a high-quality product; the guidelines cover guidance for production and testing. A quality system should be in place to develop and maintain a control strategy during all manufacturing stages. The vaccine products are tested for process-related impurities like host cell proteins, host cell DNA, and medium components. Microbiological quality is assessed by testing for bacterial or viral impurities. Vaccines consisting of recombinant viral vectors are tested for the presence of replicating competent virus.

Safety testing doesn't stop when a vaccine is released onto the market: each produced batch is tested for effectiveness, purity and sterility. The effects of a recommended and accepted vaccine are continuously monitored in what is often called phase IV of clinical development: if for instance rare adverse health effects arise (even in a large phase III clinical trial very rare effects can be missed, although the chance is small; e.g. for a trial with 30,000 volunteers such as performed with the Oxford vaccine, there is a 95% chance of picking up a rare effect occurring in only 1 of 10,000 individuals; Amery, 1999) or effects are seen in a specific subpopulation that was not part of the phase III clinical trial, appropriate measures can be taken. The most drastic example is withdrawal from the market, other options include updating the product information ("bijsluiter": for the general public) and the summary of product characteristic (SmPC: for the healthcare professional). In the Netherlands the Lareb (for "Landelijke Registratie Evaluatie Bijwerkingen") continuously monitors side effects and does signal detection on the collected data. Healthcare professionals as well as consumers can both report side effects to Lareb: the former group is obliged to do so, for the latter group this is on a voluntary basis. After a risk is identified, an evaluation of the risk-benefit balance is done to confirm that this is still positive; risk minimization measures can be applied to improve the balance if needed.

However, it is important to acknowledge the fact that there is not only "good" when considering the impact of vaccines on health. In many cases, a vaccine may cause adverse side effects. The smallpox vaccine induced severe health effects in 1-2% of vaccinated individuals while 0.0001% (one in a million) died (Belongia et al., 2003; Miller et al., 2015). Although "death by vaccine" is known to be very rare (much more so in the present-day world compared to the period in which the smallpox vaccine campaign was rolled out), mild side effects (fever, muscle pain etc.) can be common. When serious side effects do occur, the risk-benefit balance is thoroughly evaluated: clearly, for a pathogen that causes a less serious disease course (in terms of the chance of an infected person dying) such as COVID-19 (0.5-1% mortality among infected people, as estimated by the WHO), a specific chance of the vaccine causing serious health effects would be considered differently than for a much more serious disease such as smallpox (± 30% mortality among the infected). In general, it should be clear that nowadays serious adverse side effects are not accepted easily for vaccines, unless they offer tremendous health benefit. Historically, there have been several incidents where a vaccine caused unexpected adverse health effects; the most noteworthy are the following:

1. Oral Polio Vaccine itself could cause polio: a vaccine that can be administered orally is more practical than a vaccine that is injected intradermally or intramuscularly; as a result, compliance among the population is generally higher because the administration itself is less painful. For such reasons an oral polio vaccine (OPV; weakened/attenuated poliovirus) was developed simultaneously to an injected polio vaccine (IPV; inactivated virus). Unexpectedly, OPV was able to recombine into a form that caused polio itself. The chance of developing serious paralytic polio upon vaccination with OPV was 1 per 300.000 vaccinated children; the number of cases on average recorded per year was around 100 in the last decade. To put this into perspective: in 1988 there were 350.000 cases of naturally occurring polio, with ca. 1500-2000 of these cases paralytic and 88-175 deaths (WHO fact sheet, poliomyelitis). Since 2017, vaccine-induced polio cases occur more often than naturally occurring polio; this seems counterintuitive, but actually reflects the success of anti-polio vaccination campaigns (WHO; see **figure 4**).

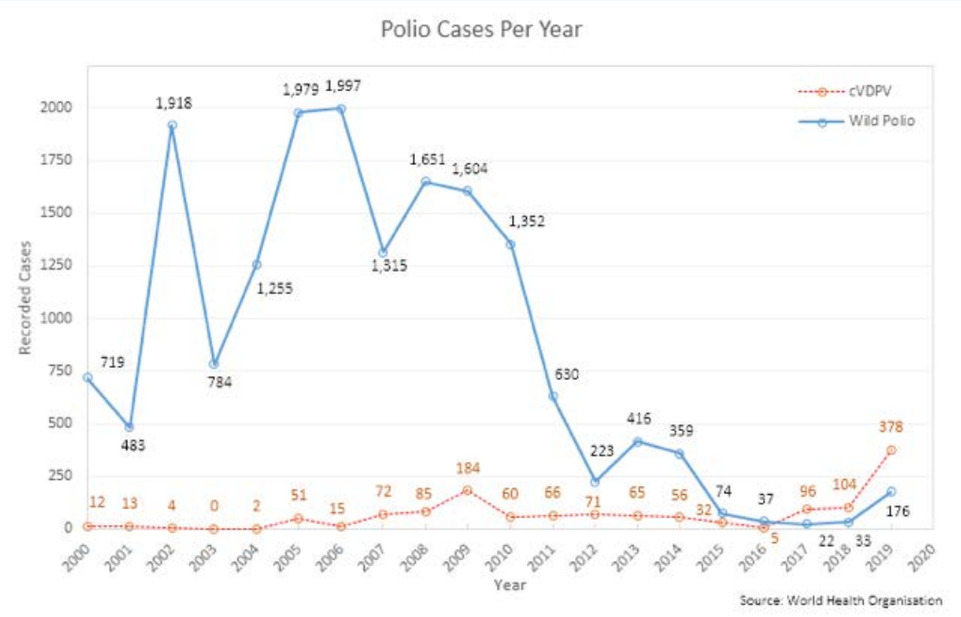

Figure 4. OPV-induced polio cases compared to naturally ("wild") occurring polio. Source: WHO.

Therefore, the WHO decided to change to an optimized vaccine formulation to try to reduce the incidence of vaccine-induced polio. Overall, the polio vaccination campaign is considered as extremely successful by healthcare professionals and researchers.

2. Millions of people were infected with polio virus or simian virus 40 because of incomplete virus inactivation in vaccine production;
   Regarding the injected polio vaccine (IPV), there was an incident in 1955 (the Cutter incident) where more than 200.000 children were inoculated with vaccine batches that were not properly inactivated (i.e., they were injected with a live polio virus): this caused 40.000 polio cases, 200 of whom were paralyzed to a certain degree while 10 children died (Fitzpatrick, 2006).

Another incident involving insufficient viral inactivation occurred between 1955 and 1963, when a significant percentage of polio vaccines was contaminated with simian virus 40 (SV40). This was due to the culture of the polio virus on kidney cell cultures that were derived from Rhesus monkeys (Garcea and Imperiale, 2003). Although the polio virus was chemically inactivated with formaldehyde, this was insufficient for complete inactivation of SV40. SV40 was later found to be very oncogenic in laboratory animals (especially rodents). Epidemiological evidence on a potential link between human cancer incidence and SV40 in polio vaccine is still inconclusive (Garcea and Imperiale, 2003).

3. Oral rotavirus vaccine caused serious intestinal complications: Intussusception is a serious and painful form of intestinal obstruction characterized by prolapse/folding of part of the intestine. This is visualized in **figure 5**.

After intussusception was observed in a number of children who had been vaccinated with tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV: also known as Rotashield), the association between both was investigated and confirmed (Murphy et al. 2001; Kramarz et al., 2001). Serious adverse health effects (including intussusception) were observed in 90-214 cases per million administered doses (Murphy et al. 2001; Kramarz et al., 2001). Rotashield was subsequently withdrawn from the market by the end of 1999 (it was introduced in August 1998) and was replaced by two vaccines with an improved safety profile (Rotarix® and RotaTeq®); none of these new vaccines was associated with intussusception at all (Patel et al., 2009).

4. More severe measles was found in children receiving an inactivated measles vaccine: In 1963 a second type of measles vaccine was introduced (next to a live vaccine), which was inactivated by formaldehyde. Successful immunisation by the new vaccine was initially high, but quickly receded within the 6 months post-vaccination. What was much more worrying, is that a new and severe type of measles occurred in children that were vaccinated with the new vaccine (Fulginiti et al. 1967; Rauh and Schmidt 1965). As a result, the vaccine was immediately withdrawn from the market.

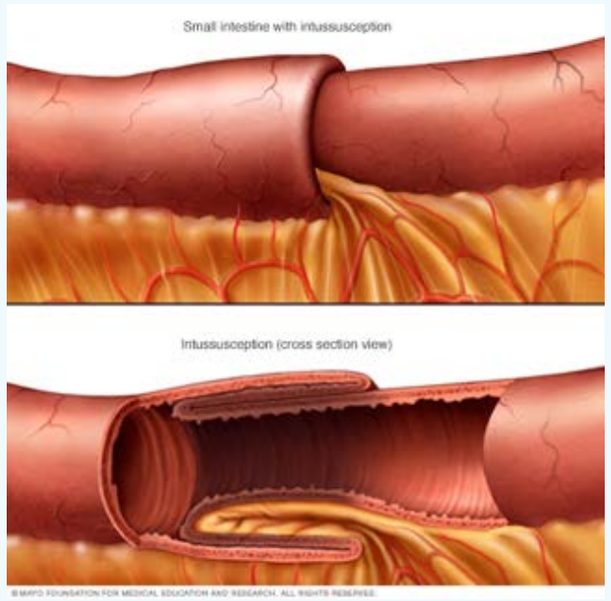

Figure 5. Intussusception (source: the Mayo Clinic)

5. Vaccine against respiratory syncytial virus worsened the course of RSV disease upon infection: The respiratory syncytial virus (RSV) is a known cause of lower respiratory infections in children and is estimated to be responsible for 66.000-199.000 infant (especially neonates) deaths, per year (Nair et al., 2010), worldwide. Because of the large disease burden associated with RSV infection, there is great interest to develop a vaccine. In the 60^{s}, a formaldehyde-inactivated RSV vaccine (FIRSV) was developed: unfortunately it did not confer protective immunity and worse, it caused more serious RSV disease progression in infected children (Kapikian et al., 1969).

6. High rate of side effect induction by Bordetella pertussis vaccine: Pertussis was a leading cause of childhood morbidity and mortality before the Second World War; in the 1940^{s} a whole-cell inactivated vaccine was implemented, which led to a massive improvement of disease burden and public health in general. However, the incidence of local and systemic adverse health effects was high (Cody et al., 1981); vaccination with the pertussis vaccine has been associated with encephalopathy, which is a form of permanent brain damage. Later on, this association was questioned (Shorvon and Berg 2008), but due to great public concern, replacement vaccines were developed.

Current perspective on vaccine safety

It is clear that vaccine safety is not something that should be taken lightly: there are differences in observed side effects between different vaccines. Nowadays the risk-benefit balance is carefully evaluated and monitored for each vaccine introduced onto the market. Historically, there have been several incidents with vaccines, some with serious consequences. But the attentive reader probably has noticed that nearly all of the incidents presented above occurred decades ago: especially in the 50s and 60s with exception of the proven link of rotavirus vaccine and intussusception in the late 90^{s} (i.e., the 3rd case presented above) and ongoing cases of vaccine-induced polio. It should be emphasized that in this period, pharmacovigilance and risk minimization were not as well developed as they are now.

So overall, should we doubt the overall safety of present-day vaccines? Absolutely not: much has changed since mid-20th century, vaccines are tested *in vitro*, in animals and subsequently in three clinical study phases, the last of which (phase III) involves testing in a large number of individuals, often thousands or tens of thousands (Weinberg et al., 2012). Such tests to be comply with stringent and robust quality standards such as GLP or GVP. If a vaccine is unsafe, this will be identified before it enters the market. It could be possible that a vaccine has very rare effects for which even a phase III clinical study is insufficient (because the groups are too small), or effects are observed in a very specific subpopulation that was under-represented in the phase III clinical study (e.g., elderly people, pregnant women, those with pre-existing disease). But even when unforeseen side effects occur, the health damage done is much smaller than the health benefit in by far most examples; this was true even for a vaccine associated with relatively serious and common side effects such as the Bordetella pertussis vaccine (see before). And importantly, since 2005 extensive regulations have been implemented to regulate and improve pharmacovigilance and risk minimization.

Vaccine development has moved to a state where we no longer mainly depend on live, weakened viruses. Newer forms of vaccines are no longer inactivated or attenuated viruses (processes that may in rare situations be defective, such as in the Cutter incident), but subunits which are not able of causing the disease against which they convey protection. Vaccines are produced in highly controlled (i.e., GMP) conditions, which involves extensive testing with quality characteristics covered by specifications.
If vaccines are safe, is the fear of potential side effects that is commonly seen within the anti-vax movement completely irrational? Probably not: a weakened, attenuated but replicating virus that is used as a vaccine might become active again and this effect is very difficult to predict. Long-term effects are often not very well known, but it must be stressed that this is true for most if not all new medicines that are developed and introduced onto the market. The immediate benefit of a vaccine for public health outweighs that of the additional knowledge that could be gained in a long-term study of many years to investigate long-term effects; in the meantime, patients may suffer or die that could have been saved.

However, serious concern should arise in the rare event that a vaccine is brought to a market prematurely, such as the Russian Sputnik V vaccine against COVID-19, that was approved by the Russian authorities before the phase III clinical study results were known. Fortunately, this is not an accepted practice in the Western world because

we are protected by our regulatory agencies such as the FDA, EMA and the CBG-MEB; such a vaccine would not be allowed onto Western markets before it is properly tested.

Conclusion

Present-day vaccines are very safe and the value of vaccines for public health can hardly be overstated. Incidents such as those that have occurred in the 1940s to 1960s are very rare nowadays because of extremely rigorous testing requirements and developments in vaccine technology; vaccines are no longer based only on weakened or inactivated whole viruses. If incidents occur (which happens rarely), they are much milder as well, because serious and common side effects will likely have been identified in the large phase III clinical study that is part of the standard regulatory testing procedure.
However, communication regarding vaccine safety, the main reason for scepsis among anti-vax groups, should be much improved if we are to increase positivity towards vaccination and confidence among the general public. Awareness regarding the importance of vaccines for public health should be increased: it is not that obvious to people that their health benefits from a disease that does not occur in their daily life (compared to for instance, a medicine that cures them of a certain disease).
If we want to beat infectious diseases to an extent where they no longer exist (such as smallpox), we can only achieve this together: by taking an available vaccine, not only to protect yourself, but also each other. ■

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Vaccine Safety & the Spotted History of a Scientific Revolution

From preservatives to contaminants, what are the potential safety concerns associated with vaccines?

By Barae Jomaa

Vaccines have never been without side effects and, for the foreseeable future, this is not about to change. The road to modern day vaccination programs is paved with efforts aimed at risk management. Variolation, a primitive predecessor to vaccination, involved the inoculation of a dried smallpox (variola) scab, which was shown to decrease smallpox mortality from 30% to 0.5-2%. This is thought to have worked by providing a lower count of the virus, likely alongside inactivated viral particles. Vaccination on the other hand originally used cowpox (variola vaccina), whose virus is thought to share a common ancestor with smallpox, to induce immunity. Smallpox vaccination is not without serious side effects, these include erythema and extensive lymphadenopathy or lymphadenitis[1], but in contrast with variolation, death occurs mostly in immune-suppressed individuals. It is Louis Pasteur who, in 1881, broadened the term vaccination to include any artificial induction of immunity against infectious disease. Variolation, which was first recorded in China in the 15th century, is not considered vaccination since it uses the same, mostly unmodified virus, and thus is not considered artificial. Modern vaccines are more complex and include, besides the immunizing agent, preservatives, adjuvants, stabilizers, residuals and, potentially, contaminants. In this article, we will cover these so-called excipients in more detail in order to gain a better understanding of the hazards involved. Hazards associated with the antigen itself will not be covered.

In The Cow-Pock—or—the Wonderful Effects of the New Inoculation! (1802):
James Gillray caricatured recipients of the vaccine developing cow-like appendages.

To begin with, it is worth mentioning that since vaccines are administered to healthy individuals and on a population level, regulators have a much lower bar in terms of determining what is an acceptable risk as compared to regular medicine. The fear of vaccines is often based on either exaggerated truths or correlations lacking causation and misinformation itself can thus create a threat to public safety. Clearly, once a vaccine has passed clinical trials and gained regulatory approval, the benefits have been deemed sufficiently great to justify any risk that may be involved. This is especially pertinent at a time when COVID-19 vaccines are about to be rolled out and a substantial number of individuals either believe the disease to be a hoax or have affiliations to political parties where such a view is embraced.

An overview of vaccine excipients and the hazards that may be associated with them follows hereafter. **Table 1** is a list from the US Centre of Disease Control and Prevention (CDC) that details the types of ingredients found in vaccines, their purpose and their most common source.

Preservatives

Bacteria or fungi can easily contaminate the vaccine medium and turn the cure into a poison. This is a good reason for adding preservatives and it is even often required in multi-dose vaccines. A striking example of what can go wrong is detailed in the book The Hazards of Immunization by Sir Graham S. Wilson[3]:

"In January 1928, in the early stages of an immunization campaign against diphtheria, Dr. Ewing George Thomson, Medical Officer of Health of Bundaberg, began the injection of children with toxin-antitoxin mixture. The material was taken from an India-rubber-capped bottle containing 10 mL of TAM. On the 17th, 20th, 21, and 24th January, Dr. Thomson injected subcutaneously a total of 21 children without ill effect. On the 27th a further 21 children were injected. Of these children eleven died on the 28th and one on the 29th."

The Royal Commission later found staphylococci to be the cause of the deaths: "...death resulted from an overwhelming toxaemia at the early stage of the invasion of the organism."

The most infamous preservative is Thiomersal (Thimerosal in the US), an ethylmercury compound. It can be toxic in cases of accidental exposure by ingestion, inhalation or contact with skin. However, besides rare allergic reactions, there is no indication of toxicity at the low doses present in vaccines. The real notoriety of this very effective preservative lies in an unproven link to autism[4]. According to the Dutch National Institute for Public Health and the Environment, "Thiomersal is not included in the vaccines that are used in the Dutch National Immunization Program. Thiomersal has never been included in vaccines used in the standard National Immunization Program." This program includes vaccination against twelve diseases: Diphteria, whooping cough, tetanus, polio, Hib disease, hepatitis B, pneumococcal disease, mumps, measles, rubella, meningococcal disease and HPV. According to the RIVM, Thiomersal is not and never has been in the annual flu vaccines though it was in the swine flu vaccine in 2009[5].

Adjuvants

Aluminum salts including aluminum hydroxide, aluminum phosphate and aluminum potassium sulfate are some of the most common adjuvants. They are present in DKTP (Diphtheria, whooping cough/kinkhoest, tetanus, poliomyelitis)-Haemophilus influenzae type b (Hib)-hepatitis B, DKTP, DTP (diphtheria, Tetanus and poliomyelitis), Pneumococal, HPV and Hepatitis B vaccines.

Type of Ingredient	Example(s)	Purpose	Most common source found...
Preservatives	Thimerosal (only in multi-dose vials of flu vaccine)*	To prevent contamination	From eating foods such as certain kinds of fish, mercury (which thimerosal contains) gets into the body
Adjuvants	Aluminum salts	To help boost the body's response to the vaccine	From drinking water, infant formula, or use of health products such as antacids, buffered aspirin, and antiperspirants
Stabilizers	Sugars, gelatin	To keep the vaccine effective after manufactured.	From eating food such as Jell-O® and resides in body naturally
Residual cell culture materials	Egg protein^	To grow enough of the virus or bacteria to make the vaccine	From eating foods containing eggs
Residual inactivating ingredients	Formaldehyde†	To kill viruses or inactivate toxins during the manufacturing process	Resides in body naturally (more in body than vaccines). Also found automobile exhaust, and household furnishing such as carpets and upholstery.
Residual antibiotics	Neomycin	To prevent contamination by bacteria during the vaccine manufacturing process	Antibiotics that people are most likely to be allergic to — like penicillin — aren't used in vaccines

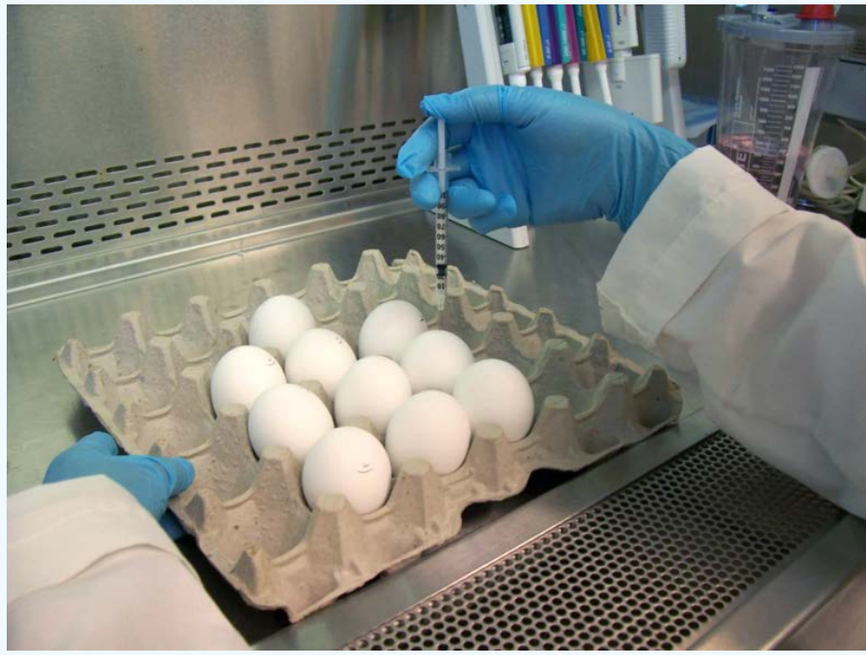
Table 1: Components in today's vaccines improve effectiveness, shelf-life and residuals[2]

These aluminum salts stimulate the immune system and as an added benefit, they also stabilize vaccines by helping to prevent the precipitation of proteins. While aluminum has been shown to be a neurotoxicant in animal tests, the RIVM has published an extensive review that casts doubt about the human relevance of these studies. Moreover, the level of exposure is for most subpopulations below the health-based limit value. The exception is children aged 0–6 months and 1–2 years, a subpopulations for which the aggregate exposure may exceed the Health Based Guidance Value (HBGV). The review concludes "the injected aluminium that is in the readily bioavailable Al3+ form will not add significantly to the aggregate exposure from all other sources of 0–1-year-old infants. There is some uncertainty around the kinetic behaviour of the part of the injected aluminium that is in particulate form, and whether and how this form influences the hazard profile of aluminium. However, aluminium-adjuvanted vaccines have a long history of use, and the uncertainty on the pharmacokinetics is offset by the many clinical trials and epidemiological studies supporting the safety of these vaccines."[6]

Stabilizers

Stabilizers prevent degradation and therefore ensure that the virus can be manufactured, transported and stored without affecting the stability of the vaccine. Such vaccine stabilizers can include 2-phenoxy-ethanol, gelatin, human/bovine serum albumin, lactose, monosodium glutamate (MSG) or sucrose.

The three HPV vaccines registered in the Netherlands are Gardasil, Gardasil 9 and Cervarix. The Gardasil vaccines contain polysorbate 80 as a stabilizer. While it might have been circulated over the internet that polysorbate 80 can lead to infertility based on an article by Little and Ward[7]. Namely, they state that injected polysorbate 80 is "known to cause similar ovarian damage to injected diethylstilboestrol in baby rats at 4mg dosages." A rebuttal followed highlighting that this figure "should not be considered a cause for concern, as 0.8mg of Polysorbate 80 (the cumulative dose over 12 years) is >90000 times lower than the acute exposure dose (based on rat intravenous LD50 of 1790mg/kg5) for a 41kg 12-year-old girl or >6700 times lower for a 3kg infant. The animal study, cited by Little and Ward, examining Polysorbate 80 toxicity on neonatal rats (over 4days) gave doses equivalent to 550–5500 times higher than the entire exposure a human child gets by the age of 12."[8]



Growing viruses: An FDA laboratory worker injects an influenza virus into an egg, where it will grow before being harvested—one of the many complex steps involved in creating a traditional flu vaccine. Image crerdit: U.S. Food and Drug Administration (FDA)

Residuals

Viruses and bacteria are replicated in cell cultures or in incubated chicken eggs. Egg proteins can therefore be found in, for example, most flu vaccines, which could be of concern to individuals with chicken egg protein allergy. Nonetheless, according to the Dutch National Institute for Public Health and the Environment, vaccines included in the National Immunization Program are not grown in incubated chicken eggs and therefore do not have any egg proteins[9].

What about the risk from cell lines? Mainly, they can contain residual antibiotics. Relevant to the Dutch National Immunization program, Vaxelis DKTP - Hib – HepB and Revaxis DTP vaccines "may contain traces of neomycin, streptomycin or polymixin B," whereas the MMRVaxpro BMR vaccine may contain traces of neomycin. "In rare cases children are allergic to neomycin, streptomycin or polymyxin. This must be reported by the parents to the nurse or doctor before the vaccination is given. It is then determined in consultation whether a vaccination is justified"[9].

Formaldehyde, a suspected carcinogen, is another potentially toxic residual that is found in vaccines. It is used during the manufacture of the diphtheria and tetanus vaccines to detoxify toxins and in the manufacture of the poliovirus and hepatitis B vaccines to inactivate viral antigens. While most of the formaldehyde is later removed from the vaccine prior to distribution, residual quantities will remain. The Children's Hospital of Philadelphia has

contrasted the dose of formaldehyde coming from vaccines with the amount naturally occurring in our bodies. "The average quantity of formaldehyde to which a young infant could be exposed to in the first two years of life may be as high as 0.7 – 0.8 mg." They go on to say that "all humans have detectable quantities of natural formaldehyde in their circulation (about 2.5 ug of formaldehyde per ml of blood). Assuming an average weight of a 2-month-old of 5 kg and an average blood volume of 85 ml per kg, the total quantity of formaldehyde found in an infant's circulation would be about 1.1 mg, a value about 1,500 times more than the amount an infant would be exposed to in any individual vaccine."[10]

Contaminants

One of the first recorded vaccine contaminations occurred in 1955 when more than 250 individuals contracted polio instead of being immunized against it. As it turns out, the vaccine was contaminated with live viruses which even led to many cases of paralysis. Polio's woes did not stop there since from 1955 to 1963 as much as a third of the polio vaccines were contaminated with simian virus 40 (SV40). It is a little known fact that the virus for the vaccine was grown in monkey kidney cell cultures that were rife with SV40. While polio caused paralysis, SV40 is a potent proven animal carcinogen and suspected human carcinogen[11–13]. Up to 30 million people have been exposure to SV40 as a result of the polio vaccine in the US alone with the Institute of Medicine finding that "the biological evidence is of moderate strength that SV40 exposure from the polio vaccine is related to SV40 infection in humans"[12]. A meta-analysis of 1,793 cancer patients concluded that there is "significant excess risk of SV40 associated with human primary brain cancers, primary bone cancers, malignant mesothelioma, and non-Hodgkin's lymphoma."[12]
In 2010 porcine circovirus (PCV) was found as a contaminant in Rotarix and RotaTeq rotavirus vaccines though PCV does not cause disease in humans[14].
A list of culture media and excipients for common vaccines, compiled from CDC and FDA data is available here: https://en.wikipedia.org/wiki/List_of_vaccine_ingredients

Summary

Taking a vaccine is not without any risk but few things in life are without risk. Regulators have learned many lessons from historical safety incidents and take great care before declaring a vaccine safe for widespread use. The Moderna COVID-19 vaccine is said to have been developed in just one weekend and its design completed by the 13th of January, 2020[15]. With 1.6 million deaths so far from COVID-19 and world economies driven to a quasi-standstill, regulators did not buckle under political pressure and made sure to only give approval after all the safety data and satisfactory results from clinical studies were in. This does not guarantee that there won't be any incidents; the Pfizer/BioNTech vaccine is already causing allergic reactions in individuals with a history of significant allergic reactions. A history of allergies should be reported to the nurse or doctor before the vaccination is given in order to determine whether a vaccination is justified.
As we have covered in this article, vaccines contain preservatives, adjuvants, stabilizers and residuals that are deemed as safe at their use level. In rare cases that have occurred sporadically over the past century, there have been unwanted vaccine contaminants. Such cases have been recorded in public records[14] and have served as foundational elements for further research and, ultimately, the improvement of our safety standards. ■

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The "monkey vaccine": Planet of the (J)Apes?

By Damiën van Berlo

In 1963, the famous science fiction novel La Planète des Singes (The Planet of the Apes) was published. Its author Pierre Boulle (who also wrote the Bridge over the river Kwai), described a grim future where primitive humans were ruled as slaves by much more advanced ape-like beings. Based on this classic novel a series of original movies (five in total) was released from the late sixties to mid-seventies. In the last decade, the book setting was revisited and three movie remakes were created. The story was greatly modified and now took place on a more or less present-day Earth. In The Rise of the Planet of the Apes (2011), a viral-based drug against Alzheimer's disease ("ALZ-112") is tested in various monkeys and apes. This particular drug is intended to help repair the diseased and damaged brain. In apes however, it greatly stimulates brain development, leading to much enhanced intelligence. The fan is hit by a foul-smelling substance when the gaseous successor to ALZ-112 induces life-threatening side effects in humans, infects a researcher during tests and a pandemic is born. This leads to the near-extinction of humanity, with remaining survivors battling the now highly intelligent apes for world domination.

This is where we arrive at the current situation, where society is plagued by the SARS-CoV-2 virus that causes COVID-19. Massive efforts have been undertaken by researchers and pharmaceutical companies to create a much-needed vaccine; more than 100 different vaccines are in development. Several of those are in an advanced stage of development (stage III clinical trial at least in progress), including the "Oxford vaccine" created by Oxford University in collaboration with AstraZeneca and vaccines created by pharmaceutical companies Pfizer, Moderna, Novavax and Janssen Vaccines.

The first vaccine that was approved by national authorities however (in this case the Russian Ministry of Health), was not among the examples above; it was "Gam-COVID-Vac" with the trade name "Sputnik V", developed by the Russian research institute Gamaleya. This approval has been criticized as a publicity stunt because the crucial phase III clinical trial was not yet performed. Thus, its approval seems highly premature and one should be extremely cautious with "Sputnik V". In parallel with the approval of "Sputnik V", a series of bewildering communications appeared on the internet, apparently of Russian origin; the Oxford university vaccine was displayed as a "monkey vaccine" that was suggested to turn people into monkeys. The presence of this message on Russian mainstream news media that are run by the Russian government strongly suggests that it has been directed; the campaign appears to be targeted at Brazil and India, where Russia is marketing Sputnik V.

As crazy as it sounds and looks, is there some truth to it somewhere? Is the Oxford University/AstraZeneca vaccine a "monkey vaccine", does it transfer ape DNA and does it pose a risk? Is there some historical context that is of interest?

What is interesting to mention, is that certain US polio vaccines that were used to inoculate children were contaminated with a monkey virus from 1955 to 1963: the culprit was simian virus 40 (SV40). This was due to culture of the polio virus on cells that were isolated from

the kidneys of Rhesus monkeys; whereas polio virus was effectively inactivated by formaldehyde treatment during vaccine production, SV40 proved to be more robust. SV40 is known to be highly oncogenic in rodents; it is still unknown whether infection with SV40 has caused cancer in humans (Garcea and Imperiale, 2003). It is very well possible that this incident inspired the writer responsible for the story of Rise of the Planet of the Apes. Also, the inventors of the "monkey vaccine" campaign may have tried to target residual public fear caused by this historical incident.

Let's look at what we know about the Oxford University/ AstraZeneca vaccine: it's a so-called vector vaccine, which means that an existing virus (often an adenovirus, e.g., the virus causing the common cold) is modified and loses its harmful activity; RNA or DNA from a virus of interest (in this case SARS-CoV-2) is incorporated within the vector so the immune system is activated and builds defenses against this virus of interest.

Interestingly, the vector used is a chimpanzee adenovirus against the common cold; however, it has been inactivated and serves as nothing else than as a means of transport. The adenovirus itself is not part of the chimpanzee and when humans are infected, the virus does not transfect ape DNA. It is not produced in or with use of chimpanzees, which are not monkeys by the way: they are apes. Many vaccines have been developed using the same or a highly similar chimpanzee- or human-derived virus as vector (the human immune system does not "see" the human or ape origin of such adenoviruses, they "look" the same), including the Russian Sputnik V. Also, humans share around 96-99% genetic similarity with chimpanzees (depending on whether insertions and deletions are taken into account; Chimpanzee Sequencing: Analysis Consortium, 2005). Because of our similarities to the ape (some humans are a bit more similar to apes in their behavior than others; these are called "adolescent males") has inspired famous zoologist Desmond Morris to write his classic book "the Naked Ape" (highly recommended!). Although the reduction of a human to a hairless ape sounds like a bald statement to me (maybe even bold), it's probably not that far from the naked truth.

Talking about truth, is there any truth at all to the "monkey vaccine" campaign? Basically there is not; I would consider it as bananas (= slang for "crazy"), as I am sure most of you do. ■

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Rare effects of vaccines: Is it worth it?

By Héloïse Proquin

Rolling out a new vaccine always raises questions. Usually more than with a new pharmaceutical product. Why this difference? Mostly because of one article published in the Lancet in 1998 by Wakefield et al. (1) that investigates the link between the MMR (Measles, Mumps, and Rubella) vaccine and development of autism. Additionally, a few years later, Wakefield alleged that the vaccine was not properly tested before being put into use (2). Consequently, this was seized by the media, igniting public fear and confusion over the safety of the vaccine (3). It took 6 years for the Lancet to say that they should have never published this paper, and 12 years to retract it. Furthermore, Wakefield was struck from the medical register in Great Britain and may no longer practice medicine there.

Created in 1976, this historic photograph depicted an elderly female as she was receiving a vaccination by a public health clinician during the nationwide Swine Flu vaccination campaign, which began October 1, 1976.

Photo by CDC on Unsplash

But what are the rare effects of vaccines? In this article, the example of the flu vaccine will be taken because it is a vaccine that is made every year, which should also be the case for the corona vaccine. In general, serious side effects from vaccines are extremely rare. For example, if 1 million doses of a vaccine are given, 1 to 2 people may have a severe allergic reaction (4). According to the CDC, these occurrences are not more than any other medicine given (5). In the case of the flu vaccine, serious adverse events are rare and one of them is the Guillain-Barré syndrome which occurs in about 1 in 1 million (6). It consists of a rare condition in which a person's immune system attacks the peripheral nerves by diminishing or leading to the loss of deep-tendon reflexes (7). Symptoms typically last a few weeks and hospitalisation is needed. However, with close monitoring and treatments, this disease can, even in the most severe cases, result in a full recovery.

All adverse effects of vaccines in the USA, for example, are recorded in the Vaccine Adverse Events Reporting Systems (VAERS) of the U.S. Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). During the period from January 1991 and December 2001, 128,717 case reports described adverse events (such as fever, injection-site edema, rash, agitation, chest pain, vomiting, including paralysis and death). From these case reports, 14.2% of all reports received were serious adverse events including deaths (1.4–2.3%), and life-threatening illness (1.4–2.8%) (8)(9). The highest rates of reported adverse events were for rotavirus and DTP vaccines, and the lowest rates were for influenza and hepatitis B vaccines. However, after investigation of the clinical and epidemiological data, VAERS demonstrated strong evidence that vaccines were not the cause of these serious outcomes.

From an economic and human health perspective, vaccination has been the cheapest and most effective measure to prevent the transmission of infectious disease starting with the smallpox vaccine. Smallpox was one of the most devastating diseases in the history of humankind, but after implementing a worldwide mass vaccination program, the disease was certified by the World Health Organization (WHO) as being globally eradicated in 1980 (10). Since then, many vaccines have been developed and modelling the vaccine impact in the 2009 US birth cohort showed that vaccination would prevent around 42,000 deaths and 20 million cases of disease and save $13.5 billion in direct health care costs and $68.8 billion in societal costs (11).

In our current situation, having no vaccine is costing already billions in healthcare costs and more billions in societal costs. The European Union is planning to give Euro 750 billion between 2021-2027 to various countries in order to help alleviate the financial crisis. This figure corresponds to the GDP of South Africa in 2019 (12). At the time of writing, almost 65 million were tested positive and 1.5 million people died from COVID-19. The related costs are still difficult to assess.

Rare effects of vaccines are as common as for any other medicine that people take on daily basis. The human and economic impact of all the diseases which can now be avoided with a vaccine are much more important than the rare effects of vaccines. We are now in a part of a society that does not need to fear that its children will one day succumb to these deadly diseases. ■

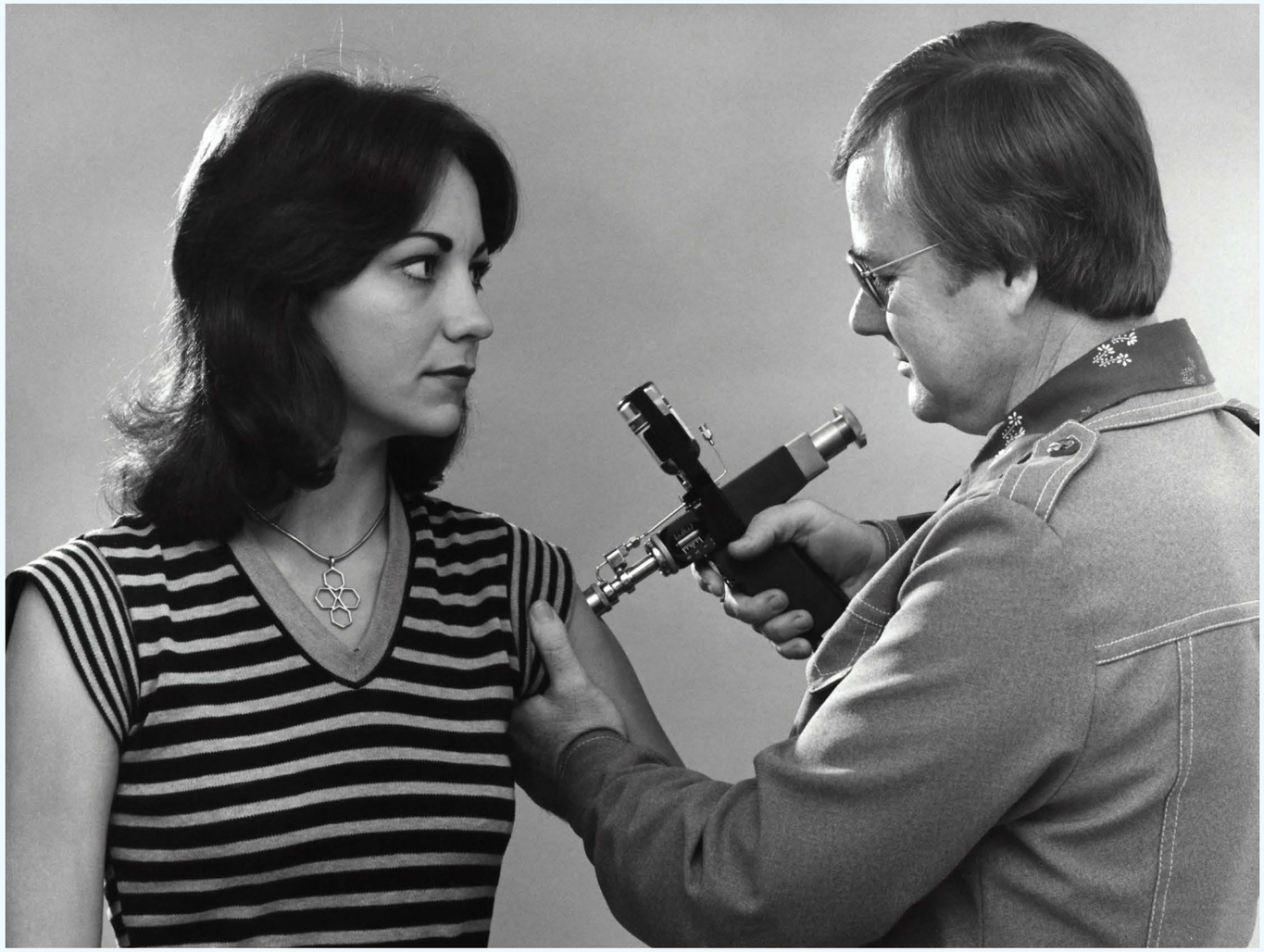

Photo by CDC on Unsplash

Created in 1976, this historic photograph showed an adult female receiving a vaccination that was administered by a public health clinician, by way of a jet injector, also known as a "Ped-O-Jet®", during the nationwide Swine Flu vaccination campaign, which began October 1, 1976.

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Intravacc and Leiden University developed an animal replacement method for vaccines

Press release
by Intravacc

Dutch, Bilthoven based, Intravacc, a global leader in translational research and development of viral and bacterial vaccines, announced the publication of a study in Scientific Reports on alternatives to the use of laboratory animals in vaccine quality control, last July 2020. The study was conducted together with Leiden Academic Center for Drug Research (LACDR) at Leiden University.

A great number of laboratory animals are still being used all over the world for the quality control of vaccines. This also applies for tetanus and diphtheria vaccines, both consisting of bacterial toxins inactivated by formaldehyde. This inactivation largely determines the quality of these vaccines.

Researchers from Intravacc and LACDR have been searching for a test that reduces the use of laboratory animals.

To this end, a small but important step in the way vaccines work was reproduced in a test tube. Inactivated model vaccines were treated with an enzyme that plays an important role in the first steps of the immune response. The enzyme, cathepsin S (CS), breaks down vaccines and pathogens into fragments that are recognised by immune cells. The inactivation step with formaldehyde affects the rate of breakdown by CS. It was assumed that the breakdown of inactivated vaccines would be slowed down by CS, but the opposite was the case.
It became apparent that it is possible to accurately and sensitively measure vaccine inactivation by quantifying the formation of vaccine fragments during breakdown by CS. This is remarkable as formaldehyde chemically alters vaccines in dozens of places, resulting in a heterogeneous protein mixture that is difficult to analyse.

This means that it may be possible to replace animal testing in the future for vaccines using this inactivation, such as diphtheria and tetanus toxoids. As these vaccines are effective and inexpensive, they will not be easily replaced by ‘modern’ products.

Dr. Jan Groen, CEO of Intravacc, says:
“As a result of the Covid-19 pandemic, some 400 therapies and vaccines against this virus are currently being developed worldwide. This affects the number of laboratory animals used in studies. Intravacc considers limiting the need for animal testing to be particularly important and plays an important role in the development of alternatives for this vaccine-related research. This study shows the progress we are making on this front.”

About animal testing alternatives
In routine vaccine production, animal testing is still regularly used to ensure the safety and efficacy of vaccines. Animal testing is inaccurate, expensive and raises ethical concerns. In 1959, Russell and Burch published their Principles of Humane Experimental Technique, which laid the foundation for the Reduction, Refinement and Replacement of animal experiments (the 3R Principle). This has led to more thoughtful and responsible use of laboratory animals worldwide for the release of medicines and vaccines. Non-animal methods have been accepted by regulators and intensive development, validation and harmonisation of 3R methods is still ongoing. The Dutch Ministry of Agriculture, Nature and Food Quality fosters 3R research in the Netherlands

About Intravacc
Intravacc, based in Bilthoven, the Netherlands, a global leader in translational research and the development of viral and bacterial vaccines. As an established independent R&D organization with many years of experience in the development and optimization of vaccines and vaccine technologies, Intravacc has transferred its technology all over the globe, including oral polio vaccines, measles vaccines, and DPT, Hib and influenza vaccines. Intravacc offers a wide range of expertise to independently develop vaccines from lead concept to clinical phase I/II

studies for partners worldwide such as academia, public health organizations (WHO, BMGF) and biotech and pharmaceutical companies. Intravacc also has its own proprietary vaccine platform, and established state-of-the-art research and (GMP) production facilities. Its aim is to substantially reduce development risks and costs of new vaccines in order to contribute to global health and equity in access to vaccines worldwide

To learn more, visit www.intravacc.nl

About the Leiden Academic Center for Drug Research
Developing new drugs is a complex process in which many parties work together. The researchers at the Leiden Academic Centre for Drug Research (LACDR) are committed to develop new and optimized drugs that are more effective and easier to manufacture. Their work covers the entire development and production of a drug, from molecule to pharmacy. The institute combines knowledge from various disciplines: chemistry, biology, computer science, physics and mathematics. To get the right result the eventual drug, the researchers from Leiden share their fundamental knowledge with partners such as the Leiden University Medical Centre, companies at the Leiden Bio- Science Park, and numerous other Dutch and international institutes and companies. ■

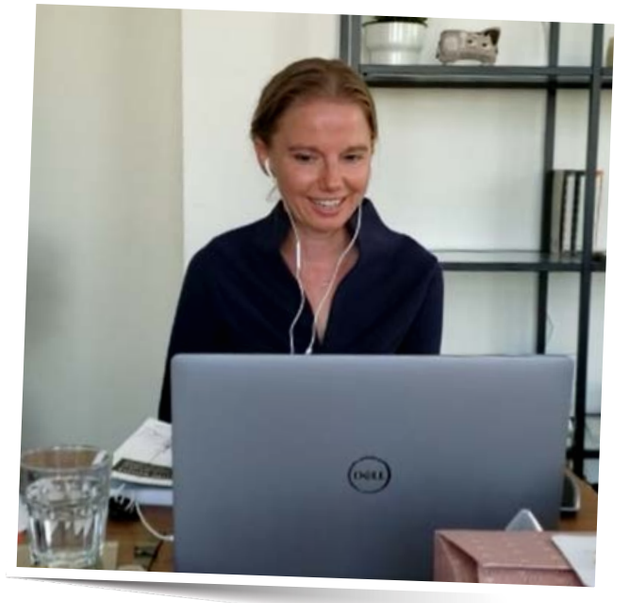
Paper: Michiels, J.M.; Meiring, H.D.; Jiskoot, W.; Kersten, G.F.A. & Metz, B. Formaldehyde treatment of proteins enhances proteolytic degradation by the endo-lysosomal protease cathepsin S. Sci Rep 10, 11535 (2020). https://doi.org/10.1038/s41598-020-68248-z

Universiteit Leiden

Intravacc.
Innovating vaccines

Exciting Models:

Exploring the applicability of human neuronal cell models for *in vitro* neurotoxicity screening and seizure liability assessment.



By Anke Tukker

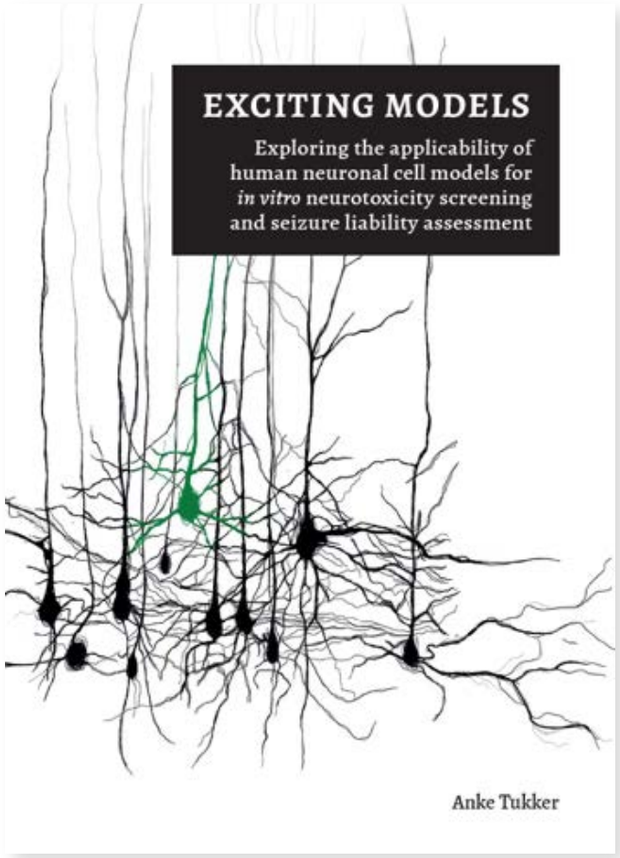
On October 6th 2020, I defended my thesis entitled: "Exciting Models: Exploring the applicability of human neuronal cell models for ***in vitro*** neurotoxicity screening and seizure liability assessment." I performed my PhD research under supervision of Dr. Remco Westerink and Prof. Juliette Legler in the Neurotoxicology Research Group at the Institute for Risk Assessment Sciences at Utrecht University.

Worldwide more and more people depend on medication for the treatment of mental or neurodegenerative disorders. This strongly increases the demand for drugs affecting the central nervous system (CNS). Because these drugs have to cross the blood-brain barrier to reach their targets, they pose an increased risk for adverse side effects in the CNS. One of the most severe nervous system related side effects is a seizure. Seizures can be live threatening events. During a seizure, neurons fire in a hyper-synchronous and hyper–active manner, resulting in over-excited neuronal networks. Currently, the potential of a drug to cause seizures is investigated late in the drug developmental process using either *in vivo* or ex vivo models. This animal research is expensive, time consuming and ethically debated. Also, when it comes to seizure liability assessment, outcomes of aforementioned experiments on animal models are not always predictive for human risk. There is thus a clear need for alternative test strategies. Preferably, these strategies should make use of human cells to circumvent inter-species translation. The recent introduction of human induced pluripotent stem cell (hiPSC)-derived neurons provides new opportunities. For my PhD research, I investigated the potential of hiPSC-derived neurons for *in vitro* seizure liability assessment as an alternative for the current *in vivo* and ex vivo test strategies.

In my research I showed that mono-cultures of mainly excitatory (glutamatergic) excitatory neurons form active neuronal networks. Activity of networks was measured using micro-electrode arrays (MEAs). These arrays allow for non-invasive measurements of local field potentials over time. Since measurements can take place in a sterile environment, the MEA technique is very suitable for following the development of neuronal networks over time. The creation of co-cultures through the addition of astrocytes changed the activity pattern of the networks and more bursting and network bursting occurred. This also resulted in network structures more closely resembling the *in vivo* brain. Adding more inhibitory (GABAergic) neurons to these co-cultures enhanced the synchronicity of the networks. I also found that the way networks cultured on MEAs react to exposure to known seizurogenic and non-seizurogenic compounds is greatly influenced by network composition. After testing different models with different ratios of neurons to astrocytes and excitatory to inhibitory neurons, one model was chosen for further testing. This decision was made based on ease of culture, reproducibility and resemblance to the human brain ratios. The selected hiPSC-model could be modulated with seizurogenic compounds, such as picrotoxin, pentylenetetrazole and amoxapine as well as with non-seizurogenic compounds such as phenytoin. Simultaneously with the selected hiPSC-derived neuronal model, primary rodent cortical cultures were exposed to

the same compounds. This rodent culture is the current gold standard for MEA experiments. The obtained data showed that the human cultures performed just as well, or even outperformed the rodent-based model. The outcome of my PhD research thus shows that hiPSC-derived neuronal co-cultures can trigger a paradigm shift in *in vitro* neurotoxicological research and seizure liability assessment towards animal-free testing in the future.
The defense of my thesis was supposed to take place in April. However, due to the pandemic I postponed it till October, hoping that I could defend in person in the Academy building in Utrecht. However, even though that was possible, I had moved in this time to the United States to start my new position as postdoctoral researcher in the laboratory of Prof. Aaron Bowman at Purdue University. With all the travel restrictions that were and are in place, I was unable to come to the Netherlands and my defense took place from my new living room in Lafayette, Indiana. It was a special experience to move to another country and defend during the pandemic, an experience that I will not easily forget.

My thesis is available online and can be found here:
https://figshare.com/s/7d813d62159fcbe58c94 ■



REGISTRATIE CIE

Inschrijving register

Voorletters	Achternaam	Datum inschrijving	Datum afloop registratie
A.	Abdelkhaliq	12-10-20	12-10-25
K.Z.H.	Caris-Bergs	12-10-20	12-10-25
S.	Suriguga	12-10-20	12-10-25
P.	Vangrieken	12-10-20	12-10-25
T.	van der Lugt	12-10-20	12-10-25

Inschrijving TiO

Voorletters	Achternaam	Opleider	Datum inschrijving
M.G.G.	Sturkenboom	Prof.dr. J. Touw	06-11-20
L.S.	Gerber	Prof.dr. M. van den Berg	06-11-20
N.M.	Ruijter	Prof.dr.ir. I.M.C.M. Rietjens	06-11-20
W.	Bil	Dr. E.D. Kroese	06-11-20
J.	Wang	Prof.dr.ir. I.M.C.M. Rietjens	06-11-20

AIO toxafette - Wouter van de Hoef

By Wouter van de Hoef, PhD candidate, Utrecht University, Institute for Risk Assessment Sciences (IRAS)

1. Can you introduce yourself?

Hi, my name is Wouter van de Hoef and I am from the beautiful town of Veenendaal, not too far from Utrecht. I did both my bachelor's and master's at Utrecht University. I first finished my degree in Biomedical Sciences, then worked for a year after which I continued my master's in Toxicology and Environmental Health. I started my PhD at the Institute for Risk Assessment Sciences in September 2019. The coming years I will be working on the project "an integrative study on farming exposures", under the supervision of dr. Inge Wouters, dr. Wietske Dohmen and prof. Dick Heederik.

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

Livestock farms have both positive and negative health effects on their environment. For instance, the incidence of some allergies (like asthma) is lower in agricultural areas compared to urban areas. On the other hand, emissions of organic dust, endotoxins and ammonia from livestock farms have a negative health effect on farmers and local residents.

Endotoxins are building blocks of the outer membrane of gram-negative bacteria such as E. coli. Endotoxins are often attached to organic dust known and are known to be strong modulators of our immune system. Inhalation of organic dust containing endotoxins can produce inflammation of lung tissue. Acute exposure to organic dusts can make you cough, cause shortness of breath and increase mucus production. Chronic exposure might lead to a reduction in lung function. People are increasingly concerned about the consequences of environmental pollution derived from farming environments in relation to their health.

The aim of my PhD is to integrate farming exposure studies from occupational and environmental sciences. I will try to develop an environmental monitoring system to determine farming exposures both indoors and outdoors. In addition, I will study microbial flow from animals to humans, spatial distribution patterns of pathogens and resistant microorganisms, and their transmission routes.

3. What was your motivation to start as a PhD student?

My motivation to apply for a PhD position really materialized while doing my internships at IRAS and TNO. I really enjoyed setting up a study, going into the field, collecting data, and analyzing data. After my master's I was looking for a position that would fit both my interests as well as my background. When I heard about this position opening up it instantly felt like a match. Another motivator was that I feel a strong affinity with the subject matter. I grew up on a farm, my grandparents were farmers and some of my family members are still farmers.

4. Why did you choose a subject in toxicology?

I chose this subject because toxicology really fascinates me. I am very interested in how compounds are taken up, broken down and how they affect the human body. In addition, the field of toxicology and environmental health is very diverse and multidisciplinary. Many projects in these fields have a lot societal impact.

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

I think the future of our research topic looks very bright. The Netherlands is one of the world's largest agricultural producers in the world. In addition, the Netherlands is also one of the strongest agricultural innovators. But even though our way of farming is top notch, problems will arise in a small country when many farms are located close to residential areas and nature. This also means in terms of research there is ample opportunity and a driving force for farms to keep lowering emissions both indoors and outdoors.

I really hope with our research we can be part of the solution on how to reduce farming emissions. I also think it is an exciting time to do a PhD in this field, to see livestock farming making a transition from conventional intensive farming to more sustainable alternatives.

6. Does the project meet your expectations, why or why not?

Yes it does, I feel both my internships during my masters were as good a preparation I could wish for. I am also very happy with my supervisors and colleagues. I am convinced that good supervision can really make or break your PhD. I could not have expected at the start of 2020 that I would be unable to perform field work for well over 3 months, but luckily, we had already started field work and we received an extension to continue our project. In short, my PhD feels like a more professional continuation of my master's.

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

1. Exercise, sleep and eat healthy
2. Don't compare yourself to other PhD candidates
3. Don't be afraid to ask questions and to ask for advice

8. Do you consider research communication as an important aspect of your PhD and why so? If yes, to what kind of audience?

Yes, I think research communication is a vital part of doing research. We are not performing research in a vacuum, just to be enjoyed by our academic peers. Often stakeholders, research participants and other interested parties are not familiar with the ins and outs of our research fields. This means we have to think and communicate differently to effectively convey our research results into a language, format and context that everyone can understand.

On a personal note, this year we collected personal exposure measurements from farmers on pig farms in order to study the association of working tasks and farming characteristics on dust and endotoxin exposures. At the start of 2021 I will also report back my findings to participating farmers. One of my main goals is to clearly explain the research results to my audience.

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

Now that we are (mostly, if not completely) working from home it may too often feel like work and our personal life are more intertwined than before. That is why I chose to not setup my home office in the living room or any other space I like to relax. To balance my PhD with my personal life I like to spend time with my fiancée, friends, family, doing fitness and going outdoors. During your PhD you have periods where you make long hours and periods you can slow down a little, but so far, I don't feel I really have to choose between one or the other.

10. What goals do you have regarding your career after your PhD? Would this be inside or outside academia, and why? Would you consider going abroad?

Some of my colleagues at IRAS are able to get a job as a postdoc, and others find a job at a research institute or a university (abroad). To be honest, I have not been giving much thought about the next job after my PhD. I will be aiming for a job where I can be involved with research. More importantly, I want to develop new skills during my PhD in order to be well-prepared for life after a PhD. As of now, I am not considering going abroad, but you never know.

11. Please answer the question from the last toxafette PhD-candidate: What is the best motivation for you to continue if something does not go the way you planned or imagined it?

I am both stubborn and perfectionistic, traits that do come in handy when something small is not going my way. I can easily work hours or even skip a meal if a line of code is not handling my data the way it should be. In the long run both during your career and in relationships things will always go differently than you had anticipated, but that is okay, as long as you can keep seeing things in perspective. Mistakes are easily made and often not the end of the world.

https://www.pigbusiness.nl/artikel/363344-onderzoek-naar-blootstelling-stof-en-endotoxinen-bij-varkenshouder-jaap-kreuger/

TERUG NAAR INHOUD

Borstvoedingsthee nu ook afgeraden voor zwangere vrouwen

Er bestond al een advies aan zwangere vrouwen van om maximaal twee koppen venkel- en anijsthee per dag te drinken en aan vrouwen die borstvoeding geven om het helemaal niet te nemen. Nu raadt de beroepsorganisatie van verloskundigen KNOV het drinken van borstvoedingsthee helemaal af voor zwangeren en vrouwen die borstvoeding geven. Het advies van KNOV is gebaseerd op een advies dat Bureau Risicobeoordeling & onderzoek (BuRO) schreef over de gezondheidsrisico's van borstvoedingsthee.

Door Jacqueline Steenbergen – Biesterbos, Coördinerend Specialistisch Adviseur Chemische Veiligheid, Nederlandse Voedsel en Warenautoriteit (NVWA)

Borstvoedingsthee is speciaal bestemd voor vrouwen die borstvoeding (gaan) geven. De theeën zijn vaak voorzien van gezondheidsclaims over bevordering van de moedermelkproductie en verbetering van moedermelk. In de regel bevatten deze theeën venkel, anijs en karwij. De exacte samenstelling van deze theeën is niet bekend.

Photo by Wes Hicks on Unsplash

BuRO heeft onderzocht of de consumptie van thee met venkel en anijs door vrouwen die borstvoeding geven een gevaar is voor de gezondheid van de baby. BuRO heeft literatuuronderzoek uitgevoerd en het RIVM/WFSR Front Office Voedsel- en Productveiligheid (FO) gevraagd om een risicobeoordeling uit te voeren. Het literatuuronderzoek en de risicobeoordeling vormen samen de basis voor het advies van BuRO. De FO risicobeoordeling is uitgevoerd voor de belangrijkste stoffen in anijs, venkel en karwij, namelijk estragol, trans-anethol en d-carvon. Er kunnen ook andere stoffen voorkomen in borstvoedingsthee.

Gezien de vele onzekerheden met betrekking tot de inname en effecten van estragol (een genotoxisch carcinogene stof), uit moedermelk van een moeder die vanaf het eind van de zwangerschap en gedurende de borstvoedingsperiode vier koppen borstvoedingsthee met anijs, venkel en/of karwij drinkt, concludeert BuRO dat een gezondheidsrisico van estragol voor baby's gevoed met deze moedermelk niet volledig kan worden uitgesloten en moet worden afgeraden. De gezondheidsrisico's van trans-anethol en d-carvon zijn voor baby's verwaarloosbaar.

Voor meer detail kan het volledige BuRO-advies worden nagelezen, zie hiervoor https://www.nvwa.nl/documenten/consument/eten-drinken-roken/overige-voedselveiligheid/risicobeoordelingen/advies-van-buro-over-gezondheidsrisico%E2%80%99s-borstvoedingsthee.

Kankerverwekkende stoffen in paracetamol

Het lijkt steeds vaker in de media voorbij te komen. Meldingen van kankerverwekkende stoffen in geneesmiddelen. In Juli 2020 brachten zowel Zembla en het NRC het nieuws dat er in de paracetamol die in Nederland vrij te verkrijgen is, een kankerverwekkende stof is gevonden. Nadat deze partijen monsters hadden laten analyseren, bleek de paracetamol, met grondstoffen afkomstig van het Chinese Anqiu Lu'an Pharmaceutical, 4-chlooraniline (PCA) te bevatten.

Door Carolien Schophuizen

Het nieuws van de vervuilde paracetamol wordt breed opgepikt door de media, zeker nadat er in het voorjaar een ware run op paracetamol geweest is, tijdens de eerste COVID-19 golf. Veel Nederlanders maken zich ernstige zorgen naar aanleiding van dit bericht. Maar het college ter beoordeling van geneesmiddelen (CBG) gaf aan dat de veiligheid van het product nooit in het geding is geweest[1]. De onzuiverheden bleven namelijk ruim onder de toegestane grenzen voor geneesmiddelen.

De basis voor de onrust ligt bij het bestaan van verschillende grenswaarden voor geneesmiddelen en voor voedsel. De oorzaak van deze verschillen tussen deze grenswaarden staat beschreven in het onderzoeksrapport wat, op verzoek van de minister van Gezondheidszorg en Sport, is opgesteld door het CBG en de Inspectie Gezondheidszorg en Jeugd (IGJ)[2].

Voor geneesmiddelen worden de limieten bepaald door de ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use)[3]. Voor voedingsmiddelen adviseert de EFSA (European Food Safety Authority) de Europese Commissie over de limieten[4]. Zowel de EFSA als het ICH gebruiken hun eigen berekeningsmethoden om het maximaal toelaatbaar risico te bepalen. De EFSA gebruikt de BMDL10-methode. Dit is een standaardmethode die wordt gebruikt door voedseltoxicologen. Voor geneesmiddelen wordt de TD50-methode toegepast. Beide methoden gaan uit van hetzelfde risico-principe, namelijk het risico dat één extra persoon op 100.000 kanker zal ontwikkelen in het geval van levenslange dagelijkse blootstelling aan de concentratie in kwestie. Maar er zijn verschillen in welke onderzoeken door de EFSA en het ICH zijn gebruikt als basis voor de berekening, en ook in de interpretatie.

Om de carcinogeniteit van PCA te onderzoeken zijn verschillende dierstudies uitgevoerd[5]. De twee meest belangrijke zijn een 103 weken durend onderzoek in ratten en een 103 weken durend onderzoek in muizen. In de studie met ratten ontwikkelde zich tumoren in de bijnier en de milt, terwijl in de studie met muizen, tumoren ontwikkelden in de lever. Het ICH nam de muizenstudie als basis voor de berekeningen (omdat volgens de WHO de milttumoren in ratten zijn geassocieerd met een niet-genotoxisch mechanisme)[3], terwijl de EFSA uitging van de rattenstudie (omdat ze het genotoxisch mechanisme niet konden uitsluiten)[4]. Omdat de studie bij ratten tumoren zag ontstaan bij lagere doseringen, berekende de EFSA een lagere ondergrens.

In onderzoeksrapport van het CBG en de het IGJ wordt geconcludeerd dat de verschillende limieten gesteld door verschillende Europese instanties verwarring kunnen veroorzaken. Maar ze stellen ook dat het bepalen van limieten gebeurt in een dynamisch werkveld, waar door het gebruik van verschillende rekenmethoden, uitgangspunten en wetenschappelijke inzichten kan leiden tot verschillen. Er wordt in het rapport bevestigd dat de gebruikte en gevolgde methoden door de ICH goed onderbouwd zijn, zijn gebaseerd op een actuele wetenschappelijke basis en ook geaccepteerd worden door andere instanties (ECHA en WHO). ■

References

1 CBG-MEB. Veiligheid paracetamol staat niet ter discussie. Nieuwsbericht.09-07-2020.22:30
2 MEB/IGJ. Report on paracetamol and PCA. 26-08-2020
3 ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. 03-02-2018 EMA/CHMP/ICH/83812/2013
4 EFSA. Peer review on the review of the approval of the active substance diflubenzuron regarding the metabolite PCA. 2015
5 ECHA. 4-chloroaniline.2020

TERUG NAAR INHOUD

Christmas Photo Competition

End of 2020 is near
But there's something wrong with this year
It's quite undesirous
We need an update, this year contains a virus

As we could not be side by side
Team meetings turned into pyjama parties
We also discovered a new countryside
Test places created by the authorities

We never had so much time for ourselves
Time to finally hang these new shelves
Six months later nothing begun
But these new camera filters are really fun

All in all, it was a year to remember
And it's time for our last moment of fun together
A contest starting in a shopping centre
During a cold night of December

A fairy wanted to play with a family member
And pulled a joke on her brother and sister
Life, she gave to all a Christmas sweater
But they decided to take over

They came all over the place
And conquer the world up to the hyperspace
You will try to picture them on the spot
Without you getting caught

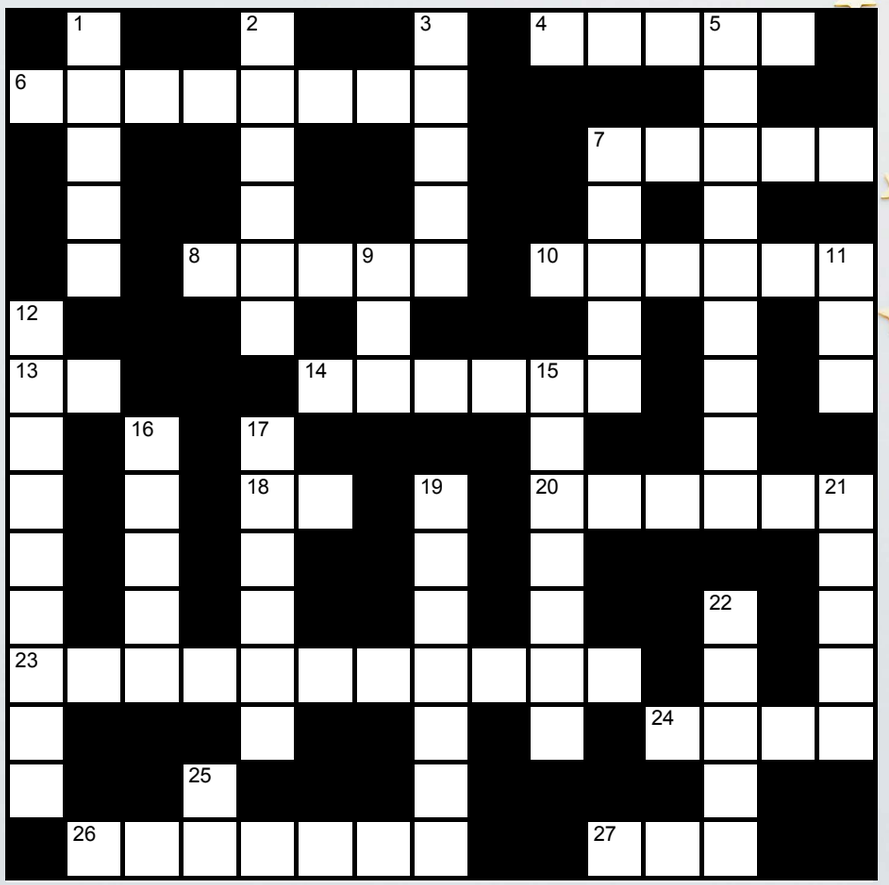
The best proof of their existence
Will get a price with social distance

If you haven't guessed it, we're looking for funny photos you have made of Christmas sweaters! To win a special gift and have some fun along the way, submit your photo to redactie@toxicologie.nl with the subject **Christmas Photo Competition**.

Christmas Puzzle

Dit jaar weer een ouderwetse kruiswoordpuzzel. Maak kans op een mooie prijs én eeuwige roem. Stuur je oplossing naar de redactie van de TCDD via redactie@toxicologie.nl onder vermelding van "uitslag kerstpuzzel 2020".

This year an old school crossword puzzel. You can win a nice gift and eternal glory! Send your solution to the TCDD redaction via redactie@toxicologie.nl using the subject "uitslag kerstpuzzel 2020".



ACROSS

4 It tells you when the New Year begins (5)
6 At ____ the clock strikes twelve (8)
7 A big celebratory meal (5)
8 New Yorkers celebrate in ____ Square (5)
10 What Spaniards eat as the clock strikes twelve (6)
13 How did you see ____ the New Year? (2)
14 I'm determined to lose ____ this year (6)
18 I usually stay ____ until 12 (2)
20 I'm planning to ____ smoking (4,2)
23 14, 20 and 27 across, and 25 down are examples of New Year ____ (11)
24 Used to represent the New Year in cartoons (4)
26/7D New Year's Day (7,5)
27 I'm joining the gym to get ____ (3)

DOWN

1 5 down is a ____ drink (5)
2 16 down are used to ____ the New Year (4,2)
3 What do the ____ hold for 2021? (5)
5 Traditional drink for celebrating the New Year (9)
7 See 26 across
9 December 31st is New Year's ____ (3)
11 Polite way of drinking 5 down (3)
12 They explode and light up the sky (9)
15 Scottish New Year celebrations (7)
16 They go dingdong (5)
17 Another name for 5 down (6)
19 New Year's Day is a ____ in many countries (7)
21 Would you like to come to our New Year's ____? (5)
22 Drink to (the New Year, for example) (5)
25 I'm cutting down ____ alcohol (2

TERUG NAAR INHOUD

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