TCDD

TOXICOLOGIE

NUMMER 3
OKTOBER 2019

SPECIAL THEME:

ARTIFICIAL INTELLIGENCE

- MACHINE LEARNING AND AI IN TOXICOLOGY-INTRODUCTION ON ARTIFICIAL INTELLIGENCE
- APPLICATION OF AI-BASED METHODS IN TOXICOLOGY, PHARMACOLOGY AND HEALTHCARE
- TACKLING LITERATURE INFORMATION OVERLOAD TO UNRAVEL TOXICOLOGICAL NETWORKS
- AN INTERVIEW WITH PROF. EVELO: USING ARTIFICIAL INTELLIGENCE IN TOXICOLOGY

NEDERLANDSE VERENIGING VOOR TOXICOLOGIE

Colofon

Toxicologische Communicatie, Data en Documentatie

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Bestuursvergaderingen 2019
25 november

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Het lidmaatschap wordt automatisch verlengd tenzij de NVT-ledenadministratie vóór 1 december van het lopende jaar schriftelijk of per e-mail een opzegging heeft ontvangen. Hiervan ontvangt u een bevestiging.

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TCDD
TOXICOLOGIE

Inhoud

TERUG NAAR INHOUD

Even voorstellen: Jasper Woutersen

Als nieuwe redactielid voor de TCDD wil ik mij graag even voorstellen. Ik ben Jasper Woutersen, 28 jaar en sinds 2 jaar werkzaam bij Charles River Laboratories. Bij Charles River ben ik werkzaam als Studie Leider voor *in vitro* en genetisch toxicologie studies. Hierin ben ik onder meer betrokken bij *in vitro* huid sensibilisatie studies, *in vitro* fototoxiciteit studies en *in vivo* Comet en Micronucleus studies bij ratten en muizen. Daarnaast ben ik betrokken bij het opzetten en valideren van nieuwe studies binnen Charles River. Buiten mijn passie in de toxicologie heb ik nog veel dingen waar ik enthousiast over word. In mijn privéleven zijn mijn vriendin en ik veel bezig met het milieu en duurzaamheid waardoor ik dit ook graag in mijn werk meer wil doortrekken. Daarom ben ik recent begonnen met een Master Milieuwetenschappen om mij meer in de milieu toxicologie te ontwikkelen en ik hoop uiteindelijk een stap te kunnen maken in de richting van Milieu- en ecotoxicologie. Ik wil de redactie dan ook met een milieu/ecologische blik verbreden. Daarnaast vind ik de relatie en interactie die wij, als toxicologen, met de gemeenschap hebben erg fascinerend en dit hoop ik ook terug te kunnen laten komen in mijn redactie werk. Ik heb een hele brede interesse en ik vind het daarom heel erg leuk om in iets nieuws te duiken, ik ben dan ook head first in de artificial intelligence of machine learning gedoken.

Namens de redactie,

Jasper Woutersen

How things have changed? *Computer programs to replace animal testing, already covered in TCDD #3 from 1989!*

Nieuws van het bestuur

I'm very excited to write my first 'News from the Board' in my new position as President of NVT! At this moment I am enjoying the EUROTOX meeting in sunny Helsinki, where I just attended my first Business Council meeting with representatives from the various Societies of Toxicology throughout Europe. Congratulations to Professor Theo de Kok, who was elected EUROTOX Executive Committee Member. This position complements his role as Chair of the Local Organising Committee of the joint IUTOX-EUROTOX ICT meeting organised by NVT in Maastricht in 2022. Also considering the recent election of Professor Henk van Loveren to the Board of Directors of IUTOX, we will be well represented at ICT2022!

But to tell you to the truth, I'm not thinking much about 2022 myself.. my head is still full of great memories of our successful 40th Anniversary meeting of NVT only a few months ago. Thanks to all those who participated in the meeting, including the section representatives who organized the sessions, the 25 invited speakers, the 230 delegates, and in particular, our excellent PhD organizing committee. Congratulations to the prize winners as well! We also launched our new online re-registration system at the meeting. Be sure to read the reports on these two exciting days of science and networking further on this issue of TCDD. We have already started organizing next year's meeting of NVT in June 2020; the precise dates will follow soon.

So what are my plans in the coming years as President of NVT? I believe my main mandate is to strengthen toxicology science and education by promoting NVT outreach activities and collaboration within the Netherlands and beyond. Suggestions and feedback from members are always welcome! The NVT Board has recently provided input into a research project initiated by EUROTOX, a mapping initiative to inventory toxicology research and teaching in Europe in order to provide a better understanding of the current state of toxicology training in Europe, as well as an up-to-date picture of the profession. The results of this inventory will be important to substantiate - or negate - anecdotal evidence that suggests that career opportunities in Toxicology as well as student numbers have declined in recent years, and will help us prioritize our actions in the future.

Those of you who attended my inaugural lecture last year know that the role of toxicology in 'One Health' (the integration of human, animal and environmental health) is a priority in my career, a theme that I will extend into my NVT activities by promoting the activities of all of our sections and welcoming new initiatives for interdisciplinary collaboration. For now, I'll take some time to learn the responsibilities of my new role, relying on the excellent guidance of past president Henk van Loveren as well as Minne Heringa and all our dedicated Board members in the transition, including our new Secretaris Nicole Nijhuis who recently succeeded Milou Dingemans. Thanks to you all! And to refer to my inaugural lecture one more time: the future of toxicology is bright!

On behalf of the Board,

Juliette Legler
President

SECTIE RISICOBEOORDELING

INVITATION - Autumn symposium:

‘Responsible research and the use of epidemiology studies in norm setting’

Date: 1 October 2019 (13.00 – 17.00 h)
Location: RIVM, Antonie van Leeuwenhoeklaan 9
Bilthoven

In 9 out of 10 cases health-based guidance values are derived based on animal studies. However, human data are preferred, which in practice boils down to using epidemiological data for the derivation of health-based guidance values. As epidemiological studies are not designed for norm setting and present various methodological difficulties, the quality of the data is not always considered sufficient to actually derive a health-based guidance value.

This autumn symposium will discuss the (conditions for) use of epidemiological data when deriving a health-based guidance value.

PRELIMINARY PROGRAM:

13.00 – 13.20	Registration
13.20 – 13.30	Welcome
13.30 – 13.55	Prof. dr. Lex Bouter (VU Amsterdam) “Research integrity, replicablility and transparency”
13.55 – 14.20	Dr. Gerard Swaen (Maastricht University) “Health-based guidance values based on epidemiological data”
14.20 – 14.50	Coffee break
14.50 – 15.15	Dr. Marco Zeilmaker (RIVM) “Deriving health-based guidance values using epidemiological research, some examples”
15.15 – 16.15	Discussion
16.15 – 16.30	Wrap-up and closure
16.30 – 17.00	Drinks

You can register for this meeting by sending an email to vspsecretariaat@rivm.nl. Please report “Registration NVT autumn symposium – 1 October” in the title of the email and report your name and affiliation in the email itself. ■

Prof. dr. Lex Bouter (VU Amsterdam)

Dr. Gerard Swaen (Maastricht University)

SECTIE ARBEIDSTOXICOLOGIE

Verslag symposium Dieselmotoremissie: op weg naar een grenswaarde

In maart 2019 heeft de Gezondheidsraad een gezondheidskundige advieswaarde voor dieselmotoremissie gepubliceerd, als basis voor het vaststellen van een wettelijke grenswaarde. Recent heeft ook de Duitse overheid een voorstel gedaan voor een grenswaarde voor dieselmotoremissie (DME).
Klik hier voor meer informatie.

Report NVT Annual meeting 2019

This year's annual meeting of the Netherlands Society of Toxicology was held on June 12 and 13 at the ReeHorst in Ede. This year's meeting was the jubilee meeting with the theme "Innovation through integration: celebrating 40 years of Toxicology".

This two-day event was attended by almost 230 participants: professionals, PhD candidates and students from academia, industry and governmental organisations. The conference was opened by Prof. Dr. Henk van Loveren, and featured a special guest appearance by Prof. Dr. Jan Koeman, one of the founding fathers of our Society! Afterwards, the scientific meeting was kicked off by the interesting keynote lecture from Dr. Russell Thomas from the EPA, USA. During his lecture entitled "Coming to Terms with the State of the Science in Toxicology and Defining a Path for the Future", he showed how new technologies such as High-Throughput Assays are quickly developing and how existing challenges of *in vitro* systems (e.g. measuring 'cellular pathology', incorporating metabolism and exposure routes) can be addressed. This excellent lecture set high standards for the rest of the day.

After a short break, the day's program was continued with the first parallel session: "Application of IVIVE and PBPK modelling in risk assessment" and "Microbiome: the forgotten population in toxicology". All parallel sessions were organised in collaboration with two or more NVT sections which resulted in varied and interesting topics and speakers. Each parallel session was closed by pitch presentations of posters related to the topic of the parallel session.
After lunch, the first poster session took place. In total over 60 posters were presented during the NVT, which covered a broad range of topics. In the afternoon parallel session, a session about "New advances in exposure assessment" was held in parallel with the PhD platform presentations, where final year PhD candidates could present their work. Anne Zwartsen (IRAS, UU), Lenny Kamelia (WUR), Giada Carta (VU) and Hanna Dusza (IRAS, UU) were selected to present their work during this session, which they did with great enthusiasm. Finally, the program of the first day was closed by Ruben Mersch, who gave a very interesting presentation about "The science of science communication". He shared some valuable lessons in a humoristic though also confrontational way about the communication of scientific data and its impact. Glyphosate was used as a practical example, which was afterwards discussed by experts from industry, academia and governmental organizations.

The sessions of the first day provided sufficient input for discussions during the drinks and dinner. The 'Speed dining' dinner provided an opportunity for networking and getting to know new people in the field. Afterwards the summer-themed party with live music from the band called "EAR" was a festive way to celebrate the 40 years of the NVT!

Russell Thomas during his Keynote lecture

The band made the party to a great success!

The second day started off with the business meeting, in which Prof. Dr. Juliette Legler was officially appointed as President of the NVT. After the business meeting, she opened the second day of the conference and ➜

introduced the second keynote lecture given by Spinoza prize winner Dr. John van der Oost (WUR) about "CRISPR-Cas – from biology to applications". This highly interesting lecture provided insights into this relatively new technique and additionally he shared some possible applications of CRISPR-Cas that can be of interest for toxicology. After this lecture, the parallel sessions "Big data in toxicology: what's hidden in it?" and "Intuitive toxicology: expert vs public risk appraisal" took place. Before the lunch break, the Joep van den Bercken Award 2019 was awarded to Dr. Shalenie den Braver-Sewradj who presented her thesis about "Inter-individual variation in hepatic drug metabolism".

After the lunch, it was time for the last poster session and afterwards for the final parallel sessions: "Developing *in vitro* based alternatives to animal testing" and "Safety assessment of nanomaterials: integrating grouping and testing". The NVT annual meeting 2019 was finalised by the "Grande finale" starring Prof. Dr. Bas Blaauboer (IRAS, UU) and Dr. Ignacio Miro Estruch (WUR), who presented and discussed their views on several toxicology-related topics and statements. The meeting was closed with the award ceremony, where the PhD platform presentation prize was awarded to Hanna Dusza (IRAS, UU), the PhD poster prize to Christy Tulen (UM), the student poster prize to Annemijne van den Berg (IRAS, UU) and the public poster prize to Philippe Vangrieken (UM). Special mention to Marjo den Broeder (IRAS, UU), who was awarded the Science Slam trophy, for the creative ode to the zebrafish she recited during the Grande Finale.

Overall, the committee looks back on a great meeting, which was also very well received according to the evaluation forms, with an overall grade of 8.7! The committee would like to express their gratitude once more to everyone directly and indirectly involved in organizing and participating in this meeting, which made it a big success!

Next year's Annual Meeting will be organised by NVT board members Juliette Legler, Suzanne Heemskerk, Martijn Rooseboom, and Peter Theunissen. The PhD organizing committee consists of Gina Mennen, Christy Tulen, Charlotte Hoogstraten, Lennart van Melis and Victoria de Leeuw.

Stay tuned for the date and place of next year's Annual Meeting! Any input or ideas for the Annual Meeting can be e-mailed to nvtmeeting@gmail.com. ■

The committee looks back to a great meeting! From left to right: Juliette Legler, Lukas Wijaya, Suzanne Heemskerk, Katja van Dongen, Cormac Murphy, Megan Houweling, Menno Grouls, Victoria de Leeuw, Martijn Rooseboom, Peter Theunissen.

Ruben Mersch and the discussion panel during the session "The science of science communication"

During the meeting there was plenty of time for networking

Please start using the Xaurum PE Online system for tracking your progress and status towards re-registration as toxicologists!

By: Rob Stierum

Dear colleagues,

As presented during the NVT 2018 Annual Meeting, NVT has implemented, together with KNCV, responsible for the administrative handling of reregistration requests, and Xaurum PE, PE Online. This, based upon the hard work also by of Paul Scheepers, at that time from the RT, Frans Koeman from KNCV and a smaller test team involving Peter Theunissen and Martijn van Velthoven.

PE Online is a new electronic system for submitting information on your receiving and sending activities, needed for reregistration. Easy to use, even from mobile devices.

Accessible via:
https://www.pe-online.org/SPE001_PR_Inloggen.aspx?taalID=&CalendarPopUp=&css=&profgrTo=&role=&scrn=&username=

To make an account, use your e-mail address known at/ used for your communication with KNCV

Below, there is also a link to the NVT 2018 Annual Meeting presentation, with instructions how to start using the system.

https://drive.google.com/open?id=1Hv9heXkiDdslXbh5TfvmnFtaBNLjPJFO

It is intuitive to use. The layout of the system may change a bit while we go, but start using it, as by 1-1-2024 it is mandatory to use the system and new credit system for sending/receiving, and replacing paper work for re-registration)! (it is wise to keep records of your certificates of attendance/publications in your own possession as well, in case)

Provide feedback to Frans Koeman at regnvt@kncv.nl as this can help to further refinements of the system. ■

Rules and Requirements applicable to the registration of Toxicologists in The Netherlands

Prepared by:
Concilium Toxicologicum
Effective as of: June 2019.

Professionals in the area of toxicology can have their professional skills registered in a national registry of toxicologists, if they meet specific requirements on education and experience.

The Concilium Toxicologicum (CT) of the Netherlands Society of Toxicology (NVT) decides by Decree which requirements apply to the Registration and to the Renewal of Registration of Toxicologists as well as the attainment targets of the training program required for Registration. These Rules and Requirements of the NVT are formulated by the CT in consultation with the Registration Committee Toxicology (RT) of the NVT and are detailed below in the "Decrees" of the CT. The requirements for Registration by the NVT are sufficient for and recognized by EUROTOX for registration as a European Recognized Toxicologist (ERT).

Requirements have been formulated for the Admission of the Candidate Toxicologist, for the Appointment as Supervisor, for the Training Faculty, for Registration as a board-certified Toxicologist, and for Renewal of Registration. All requests for Admission, Appointment, and (Renewal of) Registration are judged by the Registration Committee Toxicology (RT) of the NVT.

DECREE 1. REQUIREMENTS FOR REGISTRATION AS SUPERVISOR

The Supervisor proposes the personal training plan together with the Candidate, chairs the Training Faculty (at least 2 members), and assists in the process of Registration. The NVT aims to have Supervisors at all Dutch institutions at which toxicology is taught.

Supervisors will be nominated by the Executive Board of the NVT. Requests to register a Supervisor must be submitted to and will be approved by the Registration Committee Toxicology (RT) of the NVT according to the criteria listed below. Supervisors are subsequently appointed by the Executive Board of the NVT.

All Supervisors must have a PhD degree and have been registered by the NVT as a Toxicologist for at least five years. The expertise of a Supervisor must cover at least two distinct subfields of toxicology. Examples of subfields are listed under Degree 4.

Supervisors based in toxicological research, affiliated to a university or a similar institution, must be employed in the field of toxicology for more than 70% of the time (at least 0.7 fte). They must have a chair at a Dutch university as professor. Moreover, they need to have more than 5 years of experience in supervising PhD students.

Supervisors in the field of applied toxicology need to have extensive (at least 10 years) experience in the field of applied toxicological research and/or consultancy. They must have broad experience in supervision of toxicological research in an applied environment. They are experienced in research management and/or in supervising toxicologists who (mainly) work in non-academic settings such as industry and consultancy.

Supervisors (being already Registered Toxicologists, ERT) are appointed for a period of five years by the executive board of the NVT. For Renewal of Registration as Supervisor, the same criteria apply as defined for Renewal of Registration as a Toxicologist, with the additional requirement that a Supervisor in the five years preceding Renewal must have mentored at least two Candidate Toxicologists. Deviations from this requirement have to be well motivated and approved by the executive board. ➜

The executive board of the NVT will be responsible for checking these criteria prior to renewal and to maintain a list of Supervisors including the term for which they have been appointed.

DECREE 2. ADMISSION CRITERIA FOR THE CANDIDATE TOXICOLOGIST

Candidates have to find a Supervisor at the start of the professional training track. A request to be admitted as a Candidate Toxicologist must be submitted to and will be judged by the Registration Committee Toxicology (RT) of the NVT.

The NVT keeps a record of Toxicologists, who are registered by NVT as Supervisor (see Decree 1). NVT and Koninklijke Nederlandse Chemische Vereniging (KNCV, the entity that handles the registration administration of the NVT) will do this within the limits of the General Data Protection Regulation (EU) 2016/679 ("GDPR"). The Supervisor proposes the personal training plan together with the Candidate, chairs the Training Faculty, and assists in the process of Registration.

The Candidate Toxicologist has successfully completed his/her education at a recognized academic university (scientific education)). A master's degree (MSc) in a medical, biological, veterinary, biochemical or pharmaceutical field provides the most suitable background for the training program. Deficiencies in basic knowledge in anatomy, histology, physiology, cell biology and chemistry (biochemistry, organic chemistry, analytical chemistry) will require supplementation advised by the Supervisor; this will then become part of the personal training plan.

REQUIREMENTS FOR SUPERVISORS (DECREE 2) AND TRAINING FACULTY (DECREE 3).

Requirement regarding	Supervisor from research field	Supervisor from applied field
1. Period of registration as ERT by NVT	>5 years	>5 years
2. Appointment	>70% in toxicological field	>70% in toxicological field
3. Tasks	leading role regarding toxicology	leading role regarding toxicology
4. Expertise/experience	Appointed professorship	≥10 years of experience in toxicology
5. Level/title	Full professor	PhD
7. Training Faculty*	Supervisor + at least 1 board certified toxicologists (>5 years of registration)	Supervisor + at least 1 board certified toxicologists (>5 years of registration)
8. Renewal of registration	every 5 year + preceding 5 year having mentored >2 candidate toxicologists	every 5 year + preceding 5 year having supervised >2 candidate toxicologists

* See **Decree 3**: the Supervisor may be the same person as the PhD Supervisor (promotor)

DECREE 3. REQUIREMENTS FOR (MEMBERS OF) THE TRAINING FACULTY

Requirements for the Chair of the Training Faculty (the Supervisor) are described in Decree 1.
All other Members of the Training Faculty:

- must be a NVT-registered Toxicologist for at least five years;
- preferable work in a (sub)field of toxicology that is closely related to the field in which the Candidate receives practical training;
- must be able to judge the Candidate's performance and whether the Candidate meets the requirements for Registration;
- must have experience in leading working groups;
- are allowed to give (un)solicited advice regarding the training plan.

The chair shall not have a direct professional relationship with the candidate (e.g. manager). This does not apply to the promoter of a PhD student.

DECREE 4. REQUIREMENTS FOR REGISTRATION AS TOXICOLOGIST

Requests for Registration must be submitted to and will be judged by the Registration Committee Toxicology (RT) of the NVT.

The Toxicologist must have the following knowledge and competences:

1. A general overview of the entire field of toxicology. In the Netherlands this is offered by the curriculum of the Postgraduate Education in Toxicology (PET) and consists of: ➜

A. Compulsory/mandatory courses

1. General Toxicology
2. Molecular Toxicology
3. Cell Toxicology
4. Pathobiology
5. Organ Toxicology
6. Introduction Laboratory Animal Science
7. Epidemiology
8. Ecotoxicology
9. Risk Assessment

B. Optional courses

A selection of at least three of the following courses:

1. Medical and Forensic Toxicology
2. Occupational Toxicology
3. Food Toxicology
4. Immunotoxicology
5. Reproductive Toxicology
6. Mutagenesis and Carcinogenesis
7. Toxicogenomics
8. Risk Communication
9. Legal and Regulatory Toxicology
10. Neurotoxicology

Information regarding the content, duration, schedule, and other details of the courses offered by the Postgraduate Education in Toxicology can be found on the website of the PET (http://www.toxcourses.nl/). Having successfully completed a course that is accredited by EUROTOX may be used to demonstrate the toxicological knowledge.

2. The Toxicologist must also have a proven research experience with a toxicological focus with a minimum duration of four years, and a minimum of four publications in internationally recognised scientific peer-reviewed journals as well as a PhD degree.

The Registration will be valid for a period of five years. Renewal of Registration should be requested as stated in **Decree 5**.

DECREE 5. RENEWAL OF REGISTRATION

Requests for Renewal of Registration must be submitted to and will be judged by the Registration Committee Toxicology (RT) of the NVT. Request based on a complete dossier that can be assessed by the RT should be submitted at least 3 months before the Registration expires.

For Renewal of Registration the professional activities of the Toxicologist must provide evidence of current activities in the field of toxicology. In addition, the RT uses a system of quantitative requirements (credits) appreciating both “sending” and “receiving” activities (see Re-registration) on the procedure and requirements of Renewal of Registration).

When requirements for the Renewal of Registration are not met, the RT has the option to make the Renewal conditional.

The renewed Registration will be valid for a period of five years, after which one can again apply for Renewal.

Additional information

Forms for admission and (renewal of) registration can be downloaded from the NVT website https://toxicologie.nl

The administration of the registration procedure is taken care by the office of the KNCV. The address of the Registration Committee Toxicology is:

Registration Committee Toxicology
c/o Koninklijke Nederlandse Chemische Vereniging
Frans Koeman
P.O. Box 249
2260 AE Leidschendam
Phone: 070-3378790
e-mail address: regnvt@kncv.nl

Machine Learning and AI in Toxicology
Introduction on Artificial Intelligence

By: Jasper Woutersen and Damiën van Berlo

As you may have noticed, the theme of this TCDD issue is Artificial Intelligence (AI) and the related terms Machine Learning and Deep Learning. AI in biomedical and information science is steaming hot; but what is it exactly and can it be of value for Toxicology? To start with the last question: the answer is a resounding YES! You can read more about possible applications relevant for Toxicology in a different article in this TCDD.

This introduction is all about the first question: you will all have heard of AI, it has been a common theme for Hollywood Science Fiction movies for a long time.

Just think of the *Terminator* series where the AI Skynet fights humanity for survival and world domination. Spielberg's *AI*, where the AI takes the form of a harmless-looking little boy. The excellent *Ex Machina* by Alex Garland, where an AI is more human than its developers expected. Or the iconic HAL in Stanley Kubrick's *2001: A Space Odyssey*, that apologizes while killing the spaceship crew. And there are many more examples; *Star Wars, Star Trek, Tron, Blade Runner* etc.

The emphasis in the movies has been on the risks of developing an advanced AI, that could become a bit too human for our own good. A vision which also has been propagated by tech guru Elon Musk, the mind behind Tesla, Space X and the Boring Company, who called AI "humanity's biggest existential threat" and compared it to "summoning the demon". This sounds extreme, but leading science minds such as the late Stephen Hawking have expressed similar views.

Another emphasis in the movies is on the moral/ethical dilemma caused by the existence of an AI entity and its rights as an intelligent being. Nowadays advanced

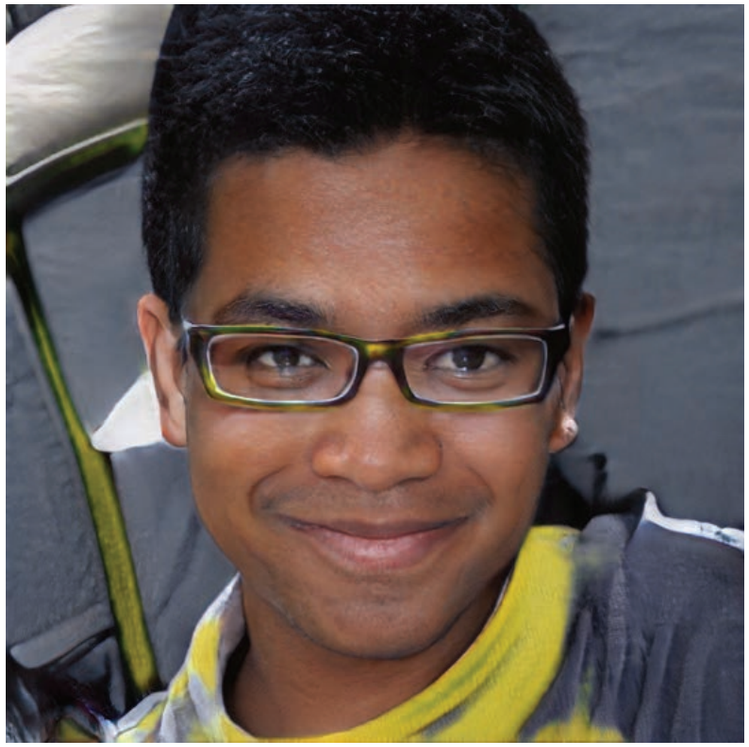
children's toys are available such as Sony's Aibo robot and the Nao robot produced by Aldebaran Robotics, that are capable of simulating emotions to increase bonding with children. Is it really so different, a computer displaying what appear to be emotions such as anger and ➜

affection guided by small electric currents, from our own brain? Which, after all, is “hard-wired” into our bodies via neurons that propagate electric signals?

Back to the science: how does this relate to the academic discipline Artificial Intelligence, founded in 1956, that might benefit data science and Toxicology? Well, first of all, computer software and “smart” algorithms are currently far removed from what most people generally consider as “intelligent”, i.e. a human. Actually, the definition of AI is not unambiguous. If one would ask experts in the computer sciences field about the term AI, they will usually tell you that it is a term mostly used by the media. The media embrace exaggeration because it attracts attention; AI is an effective attention-grabber, and for the media, attention equals income.

Intelligence in itself is difficult to define; similarly, AI can be defined broadly, so that even simple statistical models are part of the definition; this is often referred to as “weak AI”. But it can also be defined narrowly, so that only self-learning robots with capabilities so advanced that they appear self-aware are part of the definition. The latter can be considered as “strong AI”; in this context it is interesting to mention that in 2015, a Nao robot has passed a self-awareness test performed in the US Ransselaer Polytechnic Institute, for the first time in robot history.

In general, the term AI can be defined as the ability of a computer or machine to mimic human-like cognitive functions. This usually relates to learning and problem solving. Applications of AI in present-day society include autonomously operating cars, understanding human speech and playing complex strategy games such as



chess or Go. With success; IBM’s Deep Blue was the first chess computer to be able to beat a world champion in chess (Kasparov) in 1997; advanced speech recognition systems are part of Apple’s Siri and Amazon’s Alexa and great advancements towards the self-driving car have been made, with companies such as Tesla and Mercedes leading the pack.

So how does an AI work? An AI often uses algorithms; a set of instructions that a machine or computer can execute. These algorithms are constructed by programmers; some AIs can even write their own algorithms. Most AIs analyze their surroundings and take actions to achieve a pre-set or induced (by reward-punishment) goal; failed attempts provide information that will increase the success chance. This is the “experience” or “learning” component; the more experience and thus information an AI accumulates (or you insert into the AI), the more efficient it becomes. This fundamental aspect of AI is called “Machine Learning”.

For example, if you would like to “teach” a computer to recognize faces on a picture you will train the computer using a dataset representing pictures with faces and then tell them these pictures show faces. Using Machine Learning, the computer will improve its own performance by continuously incorporating new data into the algorithm (or set of algorithms) the computer uses to recognize faces. ➜

An AI term that is strongly related to Machine Learning and often pops up in the scientific literature (and job openings because experts are highly sought after) is Deep Learning; here, there are multiple layers of algorithms, with each providing another interpretation of the data it's being fed. Such a network is called an artificial neural network. When going back to the previous example (picture recognition): there's an input, which is the picture, and an output, which is the estimation whether the picture shows a face yes or no, with the output being between 0 and 1 (0.8 being 80% certainty that there is a face in the picture). In between, there's a network of "neurons" which can all be more "on" or more "off". One of the neurons/algorithm layers in this network could, for example, assess the picture and tries to identify the eyes. How the information will pass through the neural network is not predefined, it is determined by the computer and will be optimized to predict the outcome (face in picture) in the best way possible.

One example are Convolution Neural Networks (CNNs), this algorithm simulates how vision works in animals and humans, by a set of overlapping windows that compare the image at different levels to a reference to make a decision. In contrast to a ML algorithm, the input are not numbers, but the image in itself, as the CNN will transform the image for the analysis as require.

So, how is this useful to us toxicologists? This will be discussed in the following article of this TCDD issue.

And you might be wondering who the people on the pictures are supposed to be and why they're included in this article... actually, we inserted them because they aren't people; they are all generated with the website This Person Does Not Exist, which uses AI and neural networks to generate pictures. A small parallel to the famous Turing test can be made: this test consists of a conversation with either a human or an AI: if you cannot tell whether your discussion partner was a real person, the AI passed the test. Could you distinguish the non-existing, AI-generated people from real people? ■






Application of AI-based methods in toxicology, pharmacology and healthcare

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Alasdair Irvine, MSc is a PhD student (Pharmacology Department, Utrecht University) with a background in data analysis;
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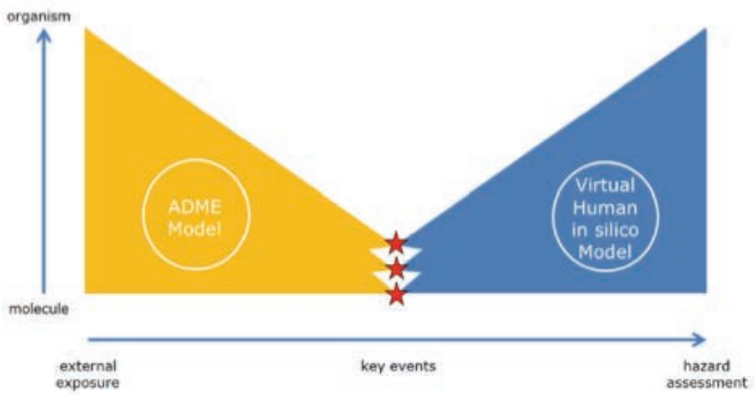
The smart machines are coming, and their arrival will affect society deeply. They will drive our cars, diagnose our diseases, fight our wars and take our jobs. And we cannot stop them. But why would we want to stop progress? We might as well make good use of it; this article will provide some examples of how toxicology, pharmacology and healthcare can benefit from AI-based methods. Please note that it is by no means intended as an exhaustive overview; there are many more potential applications, the sky is the limit.

[the authors recommend first reading the previous article "Introduction on Artificial Intelligence"]

Building a Virtual Human:

Recently, an interesting article by the RIVM on the virtual human in chemical safety assessment has been published in Current Opinion in Toxicology, providing an overview of AI-based methods that are or can be applied for toxicological purposes; this is highly recommended reading [1]. In a previous publication, Yvonne Staal et al. have described the construction of ontologies, networks of adverse outcome pathways (AOPs), and their use in computational models [2]. I.e. the ontology/AOP network would be fed into a computer model, which would predict toxicity of a compound of interest. The toxicological context of the Virtual Human concept described by Piersma et al. is outlined in the figure below:



From external exposure to hazard assessment at the organism level, via key events triggered at the molecular level. ADME (absorption, distribution, metabolism, excretion) represents compound kinetics; the Virtual Human *in silico* Model represents the adverse outcome pathway network.

To design and build the Virtual Human, machine learning and probably deep learning are extremely powerful tools; multiple layers of algorithms will probably have to be implemented for the complex modelling needed to bring the Virtual Human to life. In the next years you will probably hear or read a lot more on this.

An example of a similar approach is the Virtual Brain. The Virtual Brain is a composite designed by several scientists to simulate the intricate networks in the brain for application in prediction and modeling of complex tasks [3]. This tool is currently used to obtain a deeper understanding of the brain and to diagnose and treat several illnesses; e.g. to improve stroke therapy.

Machine Learning in Healthcare

As explained in the introduction to AI you can find earlier on in this TCDD issue, deep learning can be used to analyse images, for instance to identify faces. Instead of numerical data being fed into the system, the input consists of the images themselves. Using deep learning, the model will look for patterns in a training dataset and apply these for new cases.

This can be applied to improve the diagnosis of diseases based on physical traits; for instance, machine learning beat clinicians at diagnosing Turner syndrome based on facial features [4]; Turner syndrome is a genetic condition in which a female partly or completely misses an X ➜

chromosome. In a similar experiment, the diagnostic performance at diagnosing melanoma of an artificial neural network was superior to that of a group of 58 dermatologists [5].

The use of statistics and routine predictive modelling has become commonplace in healthcare practice, particularly in developed nations such as the United Kingdom and the Netherlands. Health care providers across Europe have been put under pressure to deal with increases in demand associated with shifting demographics and linked comorbidity [6]. In order to ensure that resources are allocated to in the most effective way, clinical practice has increasingly been informed by clinical prediction rules (CPRs) based on routinely collected patient data [7]. The use of models such as the Framingham risk score for cardiac health [8] proved the worth of predictive models to both clinicians and policymakers and there is continuous development of systems capable of aiding diagnosis and highlighting opportunities for clinicians to intervene earlier, and recommend lifestyle changes and pursue preventative measures rather than treat patients with (increasingly expensive) medication.

The use of such data in centralised electronic health records (EHRs) has led to the development of risk stratification models to help manage the demand. Providers such as the NHS have developed a population-derived algorithm to predict future emergency admissions in individuals 40 years or older. Using a database of 186,523 patients in the Tayside region (central Scotland) the model is known as PEONY (Probability of Emergency admissions Over the Next Year) it can be implemented at individual patient level as well as family practice level to target case management [9]. This allows for the identification of various risk factors including sex, age, and prescription of certain drug groups as per the BNF and primary care intervention of high risk individuals. Recently, such models have been augmented by the use of machine learning methods, namely a random forest classifier and a gradient boosting classifier. This led to substantially improved discrimination and calibration for predicting the risk of emergency admission [10]. The use of these machine learning methods allowed the addition of more variables from over 4 million patients and measurements across a larger timeframe (between 1985 to 2015) while remaining stable across a range of prediction time windows and when externally validated. Clearly, AI-based methods hold great promise for better diagnosis and to ensure that available healthcare facilities meet the demand of the patient population(s); we will probably see the day in the not too distant future when a physician is assisted by AI-connected imaging techniques for diagnosis. Because of the importance of a personal, empathic approach by clinicians (for which clinicians are nowadays trained), we won't see robo-doctors anytime soon.

Pattern recognition in large datasets of patient samples: This is another well-developed application of machine learning for biomedical purposes.

Machine learning techniques also allow us to find patterns in large datasets such as those produced by methods related to -omics (genomics, proteomics), where simple statistical analysis is not possible or suboptimal. These techniques extend to classification, modelling, feature importance, just to mention a few. Coupling these techniques with the modern advances in personalised medicine and omics-based measurements, we are able to discriminate, classify and find more intricate patterns in tissue samples obtained from individual patients. This offers unprecedented possibilities for the investigation of pathological mechanisms [11]. Globally, several efforts are being made to gather and share this data with repositories such as the Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA) to speed up scientific advances towards medicine.

For example, let us consider DNA methylation. DNA methylation can be measured in blood using different machines and it affects the expression of certain genes. In general, high methylation results in low gene expression and vice versa. DNA methylation patterns have been correlated to several diseases such as; rheumatoid arthritis, inflammatory bowel disease, Alzheimer's disease, different types of cancer, depression, etc.

If we consider DNA methylation data we will have around half a million variables, and using simple statistics it will be difficult to find patterns related to a disease given the amount of data. Nevertheless, the use of machine learning techniques allows us to find underlying patterns to serve as a basis to generate better understanding of the studied disease. An interesting example is the use of DNA methylation data to diagnose chronic fatigue syndrome (CFS) [12]. ➜

CFS patients suffer from extreme fatigue that can't be explained by an underlying medical condition, and therefore it is difficult to diagnose. In recent years, several studies using DNA methylation and Machine learning techniques have uncovered possible bio-markers to diagnose the disease by reducing thousands of variables to less than one hundred, facilitating diagnosis of the disease. This opens up the path to treatment.
Another example is the use of Machine learning techniques for finding candidate micro-RNA (miRNA) biomarkers for cancer. miRNAs are noncoding RNA molecules, with a critical role in the post-transcriptional regulation of gene expression. Current miRNA technology is able to measure more than four thousand different sequences. It is not easy to identify biomarkers from four thousand variables; the amount of data and noise from different platforms, patients and tissues make this a very complicated problem. Nevertheless, new studies have been able to discriminate important miRNAs related to cancer; these are even called oncomarkers. The possibility of measuring oncomarkers non-invasively is highly relevant for its prognosis, diagnosis and even possible therapies in the near future [13].

Predicting toxicity based on chemical structure:
Quantitative Structure-Activity Relationships (QSAR) approaches are commonly used in toxicology and pharmacology; they are obtained by screening databases and linking specific toxicological/pharmacological endpoints to the molecular structure of the compound. This has proven to be quite predictive for certain niche applications, such as small molecule mutagenicity [14].
During the last century, a massive amount of toxicological data has been generated and published. The implementation of regulations such as REACH has greatly accelerated the accumulation of data; databases produced by pharmaceutical companies are also worth mentioning. Data mining of such massive databases, delving deep into the data to find the "gold" in the form of new pathways, patterns and relationships, is a toxicological application that can be greatly facilitated by AI-based methods; artificial neural networks (ANN), self-learning computer models based on the biological neural network, are very useful for this purpose.
To illustrate the potential: a recent study used Machine learning of toxicological big data (database of 10 million chemical compounds) to investigate how Read-Across Structure Activity Relationships compares to reproduction of animal tests; under the conditions they used, the machine beat the repeat animal test [15].

Identifying the most predictive set of *in vitro* assays to replace an animal test:
The Netherlands is one of the pioneering nations when it comes to replacement of animal tests with animal-free alternatives; the government has communicated the national ambition to be world leader in the development of innovative *in vitro* tests by 2025.
Although a great number of high-potential *in vitro* tests have been developed and published, some of which are used to replace animal tests for the more basic endpoints (such as skin- or eye irritation), it is not realistic to replace the more complex regulatory safety tests (e.g. the OECD TG 451 carcinogenicity test, the OEC TG 443 extended one-generation reproduction toxicity study or the OECD TG 413 sub-chronic inhalation toxicity study) by a single *in vitro* test. A battery of tests would be needed, to cover the main endpoints relevant for a toxicological phenomenon; such endpoints are defined by working groups consisting of international experts in the field as AOPs. Still, many AOPs are probably needed to properly describe something like reproductive toxicity.
One of the most important aspect of an *in vitro* test (or any safety test) is its predictivity for the endpoint of interest in humans and similarly, the collective predictivity of a battery of tests. Where machine learning and deep learning would be extremely valuable, is in investigating which combination of *in vitro* tests results in the best predictivity of toxicity in humans. The aim would be to achieve a predictivity superior to that of the standard animal test that is mandatory for compliance with the regulations. This would be an extremely convincing argument to finally replace the animal test by *in vitro*/*in silico* methods.

The Virtual Pathologist:
(Toxicological) pathologists are rare and are becoming increasingly so because not enough pathologists are trained to compensate for those that have retired; this is a worrying development, because pathology is still the single most important endpoint for an overall toxicological assessment in animal (or patient) material. Apparently, young people are not interested in a life behind the microscope, even if it is extremely important for biomedical science.
Also, there is an incredible amount of stored tissue sections (or tissues in paraffin blocks from which new tissue sections can be cut) that often have excellent longevity and from which a massive amount of new ➜

information could be obtained. This extremely rich treasure trove is mostly neglected; tissue sections are collecting dust and the tissues mounted on them are slowly degenerating. One way to tackle these issues would be to develop an AI system; the Virtual Pathologist. When we would develop an automated system for the evaluation of microscopic tissue sections (or analyze databases of images made with advanced digital pathology systems such as Aperio Scanscope) and couple this to deep learning algorithms, we can access this treasure. We would need to feed the AI construct with a large amount of data that has been evaluated by human pathologists. E.g., build a collection of tissue section slides that represent "inflammation", or "fibrosis", or "necrosis" and let the Artificial Neural Network identify the characteristics of each of these toxicological processes. If the AI is nourished with sufficient information, it will become proficient at identifying pathology from tissue sections.

Conclusion:

There any many interesting applications for AI-based methods in toxicology and pharmacology; please note that the examples given here are just a sample. For the application of AI, the lifeblood of any successful system is the quality of the data used to train and evaluate it. Without high quality data, the engineering of any intelligent system is virtually impossible. Making quality data available, for instance by joining the Open Science initiative and by opening up databases that are presently locked (e.g. pharmaceutical data), would accelerate the application of AI-based methods and could increase the chances of being successful.

In our opinion, the field should embrace the future and open up to machine learning and AI. We will have to, if we want to remain a leading country in the toxicological and pharmacological fields. There is much future work to be done in our fields, but we can also learn a lot from the past; the wealth of available data (e.g. from – omics approaches) contains novel and extremely useful information.

Regardless of personal opinions and feelings on the matter, one thing is for sure: smart machines are here to stay. Or as one of those smart machines might say itself: I'll be back. ■

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Tackling literature information overload to unravel toxicological networks

At TNO, we develop and apply various data driven technologies to hazard, exposure and safety sciences, including exposure modelling, development of exposome data technologies, computational drug target safety assessment and immunology, PBPK modelling and systems toxicology.

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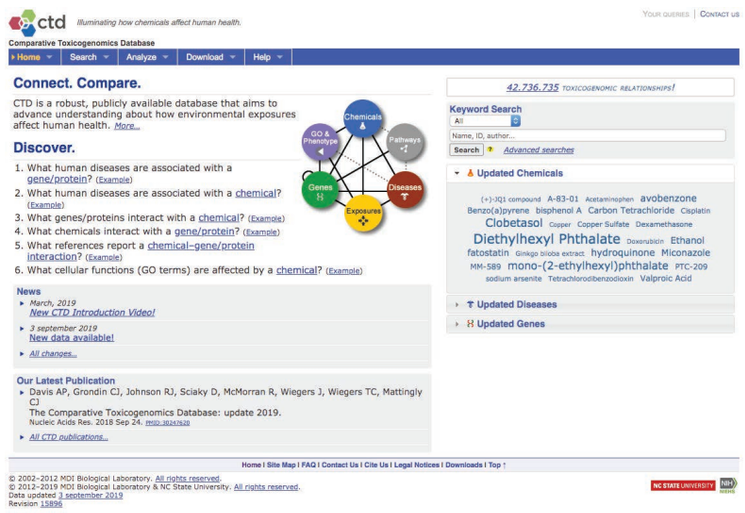
In today's information-saturated world, it is challenging to keep up with the scientific literature on potential hazards and toxicological mechanisms of interest which continues to grow at head-spinning speed and is scattered across thousands and thousands of scientific papers. We are developing automated approaches to assist in the interpretation of these.

In the past, valuable databases have been manually assembled from literature resources containing toxicological/biological networks that describe complex relationships among chemical-genes/proteins-disease that facilitate unravelling the molecular mechanisms in environmentally influenced diseases. For example, Comparative Toxicogenomics Database (CTD), a popular toxicological database that contains over 165,000 interactions that connect more than 6,400 chemicals to 3,900 phenotypes are manually curated from over 19,000 scientific articles (Davis, Allan Peter, et al. Toxicological Sciences 165.1 (2018): 145-156.) However, such a manual task of structuring data from less structured (meta) data sources is undoubtedly tedious and needs to be automated.



Text mining is a promising alternative to the mundane task of manual curation of scientific articles for knowledge discovery. Text mining is the computational process of grabbing novel information (knowledge discovery) from a collection of textual input. Novel information include hypothesis, associations, trends that are not explicitly confronted in the input text sources that are examined (Nisbet, Robert, John Elder, and Gary Miner. Handbook of statistical analysis and data mining applications. Academic Press, 2009.) Although text mining tools are largely available and serving diverse application domains, text mining tools suitable for discovery in a biological context are limited. (Howe, Doug, et al. Nature 455.7209 (2008): 47). As such, INDRA (Integrated network and Dynamical Reasoning Assembler), an automated software infrastructure that uses text mining and machine learning tools is one among the few text mining tools in the public-domain for bio-curation (Gyori, Benjamin M., et al. Molecular systems biology 13.11 (2017).

We recently introduced INDRA to extract and structure information from literature. The application of INDRA resulted in the generation of causal biological networks that can be the basis for several applications. ➜

INDRA
Integrated Network and Dynamical Reasoning Assembler

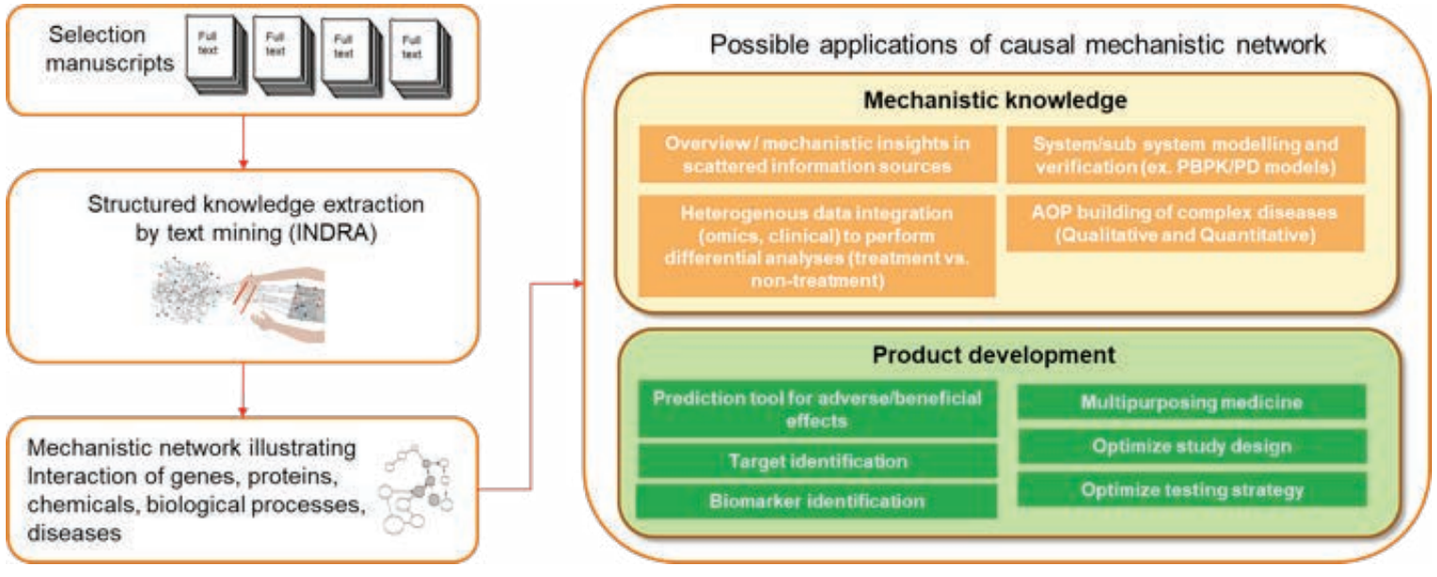


Fig.1 Workflow to generate causal mechanistic networks from full text manuscripts using the text mining tool INDRA and possible applications.

Fig. 1 illustrates work-flow and some applications of the INDRA text-mining tool. In short, selected manuscripts are processed to construct knowledge statements. These statements represent mechanistic relationships such as inhibition/activation or increase/decrease amount between biological agents such as chemicals, proteins/genes, protein-families, bioprocesses, and diseases. The biological agents are mapped, and categorized with ontological information (e.g. UniProt, HGNC, MESH, PubChem, CheBI, GO, FPLX, Pfam, InterPro, MIRBASE, and HMDB). Finally, the statements are assembled into a mechanistic networks for interpretation.

In the next sections we describe two use cases in which we applied the INDRA: i) biomolecular networks generation from scientific literature relevant to identify benzene carcinogen characteristics and ii) early-life immune networks generation to elucidate the dynamics of early life immune health development.

Biomolecular networks generation from scientific literature relevant to benzene carcinogen characteristics

INDRA was used to generate ab initio biomolecular networks from scientific articles, retrieved from PubMed queries relevant to benzene carcinogen characteristics. Fig. 2 is an overview of these networks. Within each network is embedded the causal relationships among the benzene, benzene metabolites, other chemicals, related genes/proteins, biological processes that features in one of more known key characteristics of carcinogens. Interestingly, the automated network assembly clearly describes direct associations between benzene, the creation of known metabolites such as phenol and hydroquinone, the involvement on known proteins e.g. CYP2E1, and relevant Gene Ontology Biological Processes related to intermediate endpoints such as DNA damage checkpoint.

Early-life immune networks to generate knowledge on the dynamics of early life immune health development

To be able to generate early-life immune networks a total of 2966 articles were selected using the literature databases of which 829 articles (451 original manuscripts, 378 reviews) were considered relevant after screening. This resulted in 249, 296, 344, 252, 287, and 215 articles classified into resp. the 1st, 2nd, 3rd trimester, birth, ➜

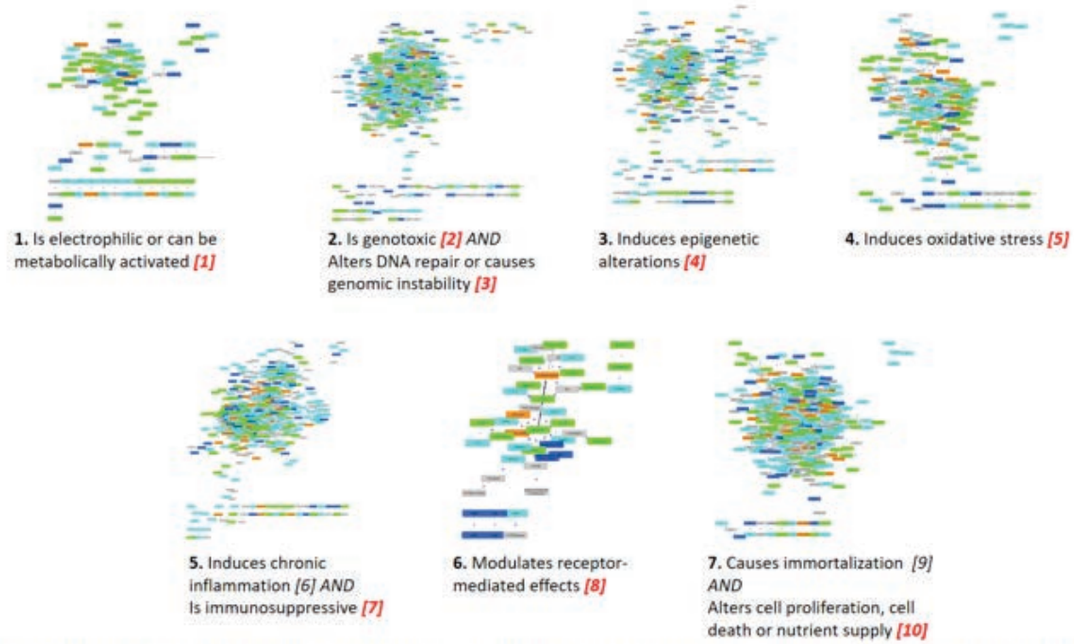


Fig.2 Overview of BDC-INDRA networks resulting from literature queries. Bold number refers to query number. Numbers between brackets refer to the 10 key characteristics. Numbers in red refer to those key characteristics involved by benzene.

newborn and infant period (some articles covered multiple periods). From these full text articles, INDRA extracted resp. 2101, 3234, 3654, 1568, 2917 and 1487 unique relationships between entities, resulting in 6 large causal early-life immune networks each covering a different early life period. As example, the early life immune network of infants (1-24 months of age) is depicted in fig. 3.

Conclusions

Here we describe work in progress on the application of a promising text mining/machine learning tool called INDRA, which extracts and structurally organizes relevant information from thousands of papers to understand causal relationships among chemicals, genes, proteins and processes in the toxicology domain. This tool when complemented with expert knowledge enables researchers to discover more information in an efficient way.

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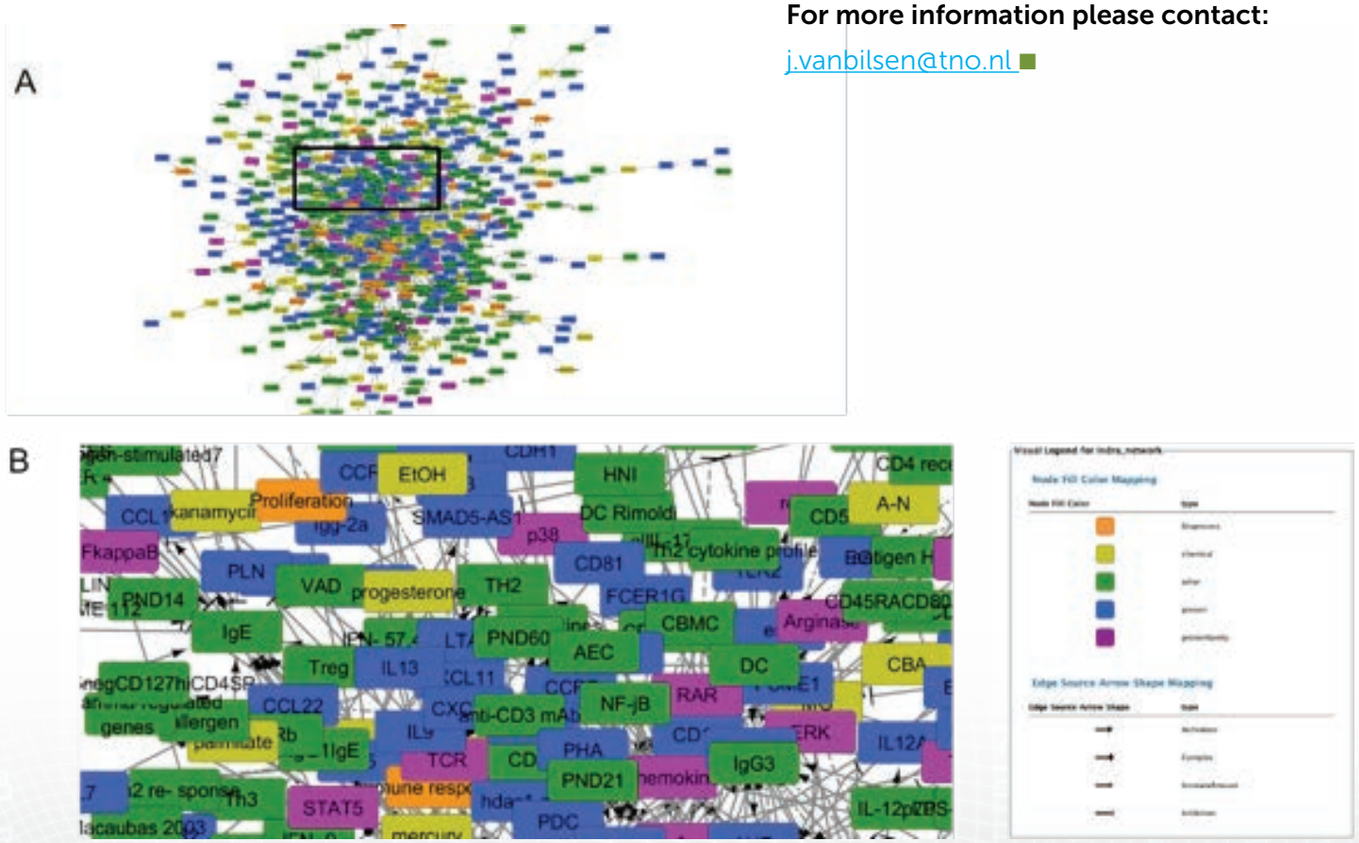


Fig. 3: Example of a literature-derived causal network generated by the text mining tool INDRA. A. Early life immune network for infant period (1-24 months) generated from 1487 full text manuscripts. B. Magnification of early life network for infant period (magnified area depicted by square in A)

An interview with Prof. Evelo:

using artificial intelligence in toxicology

Chris Evelo is Professor of Bioinformatics for integrative Systems Biology at Maastricht University. His main research interest is to integrate different bioinformatics approaches to allow real understanding of the data generated in large scale genomics experiments.

Chris Evelo

How did you get into the field of machine learning?

I have a background in toxicology and physiologically based kinetic modelling, and have worked in the field of occupational toxicology. Because of my knowledge on both biology and computers, I was asked to lead the department of bioinformatics at Maastricht University. At our department, we make use of microarray data and focus on the question how to analyze and understand omics data. This has led to the development of a pathway approach, instead of focusing on individual genes. The pathway analysis has evolved into big data analysis: the combination of a lot of measurements and a lot of knowledge. Before, omics techniques were mainly expensive microscopes that observed gene expression involved in inflammation, immune system and cell cycle without understanding the pattern. The field is now progressing towards single cell gene expression analysis using intensive sampling at different time points to capture dynamic processes. This technology provides the next step to observe patterns in gene expression. Machine learning is used to couple data, such measurement of genes and proteins, and find correlations.

What is needed for machine learning?

The main challenge is the interoperability problem. All data needs to be coupled and therefore improvement of data is needed. In automated text mining, a form of artificial intelligence, data coupling is being done for example by Google to read literature and by PubMed that uses Mesh terms. These annotations of articles help computers to perform automated literature searches. Another example is PubMed Central Europe, where text miners use automated text mining to search for specific proteins and diseases to find correlations. Identifiers such as UniProt (for protein sequences) are very helpful and can be recognized by both people and machines. The text mining field can be improved using available annotations and interoperability solutions. In addition, if you provide information to these AI systems about known correlations between genes and proteins, the predictions are greatly improved.

Can this automated text mining also be used for quantitative data?

There is no automated reading of quantitative data. There are some examples of tables and graphs being read by computers, such as QSAR tables that can be read if the tables are prepared according to the same structure. It would be interesting to provide researchers a layout for collecting data. Especially for graphs, it would help if all underlying data would be available and not only a figure. That would help to combine quantitative data and find quantitative correlations using AI. There is a lot to gain to structure data and procedures.

What is deep learning?

Machine learning includes deep learning, in which all ➜

data and all methods are put together and the computer gives an output. While in other machine learning techniques correlations are included, deep learning is AI without any predefined correlations. The difficulty of deep learning is that we cannot explain the result of the analysis anymore. How do you explain to a patient that a medicine will not be prescribed because the computer says so? We need understandable AI.
A way forward towards understandable AI is by using computational models that we understand and subsequently increase the number of combinations and complexity.

Would it be possible to use AI techniques to build a complex model based on human physiology, toxicology, epidemiology and clinical data to predict effects of substances?

There is a lot of epidemiology data and biomonitoring data available that we could use more in toxicology. This type of data could help to monitor the influence of exposures on health effects. This provides more relevant information compared to rodent data. In toxicology, however, we would like to prevent the occurrence of adverse health effects and not just monitor. Therefore, people are working on the development of virtual human models that can predict the health effects of exposures. Using these models, we would like to predict the human physiology better compared to animal data. For the development of a virtual human model, we need a combination of available *in silico* and *in vitro* models such as QSARs, PBPK, stem cells, human-on-a-chip. Combining existing computer models is currently being done.
We can learn from other disciplines. For example in cancer research, machine learning is effective as they are better in data sharing and solving interoperability issues.

What is the value of adverse outcome pathways (AOPs) in the development of models that predict human health effects better?

AOPs are the way forward to predict toxicology pathways. Especially the complexity of overlapping pathways is helpful in structuring available data and progress towards better prediction models. There is currently need for quantitative AOPs, which is hold back by organizations such as OECD because originally AOPs were thought to be general pathways and not substance-specific. We need international agreement that quantitative AOPs are the way forward.

Could you give an example of AI in toxicology?

Examples of machine learning in toxicology are QSARs and modeling of kinetics for substances that are similar to substances that we know. The challenge is to predict effects of substances that will be developed in the future and that are not similar to what we know. In the field of medicine, existing data (form databases, text mining etc.) is combined into large data/knowledge graphs using AI. Deep learning based knowledge graphs might help to understand the effects of new substances.
Another challenge is the validation of new AI approaches. Especially regarding deep learning, can we use techniques that we not fully understand for regulatory decisions; can we ban a substance if the computer says so?

What are the pitfalls of using machine learning in toxicology?

There are pitfalls of machine learning in any field. It is important to check which parameters the computer choses for its computational models. Do we understand the chosen parameters and do we agree with the assumptions? We need cooperation between toxicologists and specialized data analysts. AI is a whole new discipline that goes beyond linear models; it is not something a toxicologist can simply learn.

What would you hope the combination of toxicology and machine learning brings us in the future?

As mentioned before, I hope the combination of models provides a risk analysis of substances without animal testing. Animal models are not the best predictive models for the human situation, they are not ethical and expensive. Alternative models can be developed by combining AI, databases, text mining, existing knowledge on toxicology and human biology, existing models and new computational models.

What are the next steps we should take?

We need use cases to identify where it goes wrong. In my experience, it goes wrong in interoperability of data and models, we are combining data too fast. There is need for tools how to combine data, and this should be use case driven. Now, the biggest drive in data harmonization comes from a field that we do not understand yet, the research on nanomaterials. There are still a lot of questions and by making use of a lot of data we hope to get some answers. Nanomaterials are probably not the best use case for AI. We need a use case that is data rich, that ➜

we know and understand better to identify what is missing for understandable AI.

Is there need for education of toxicologists?

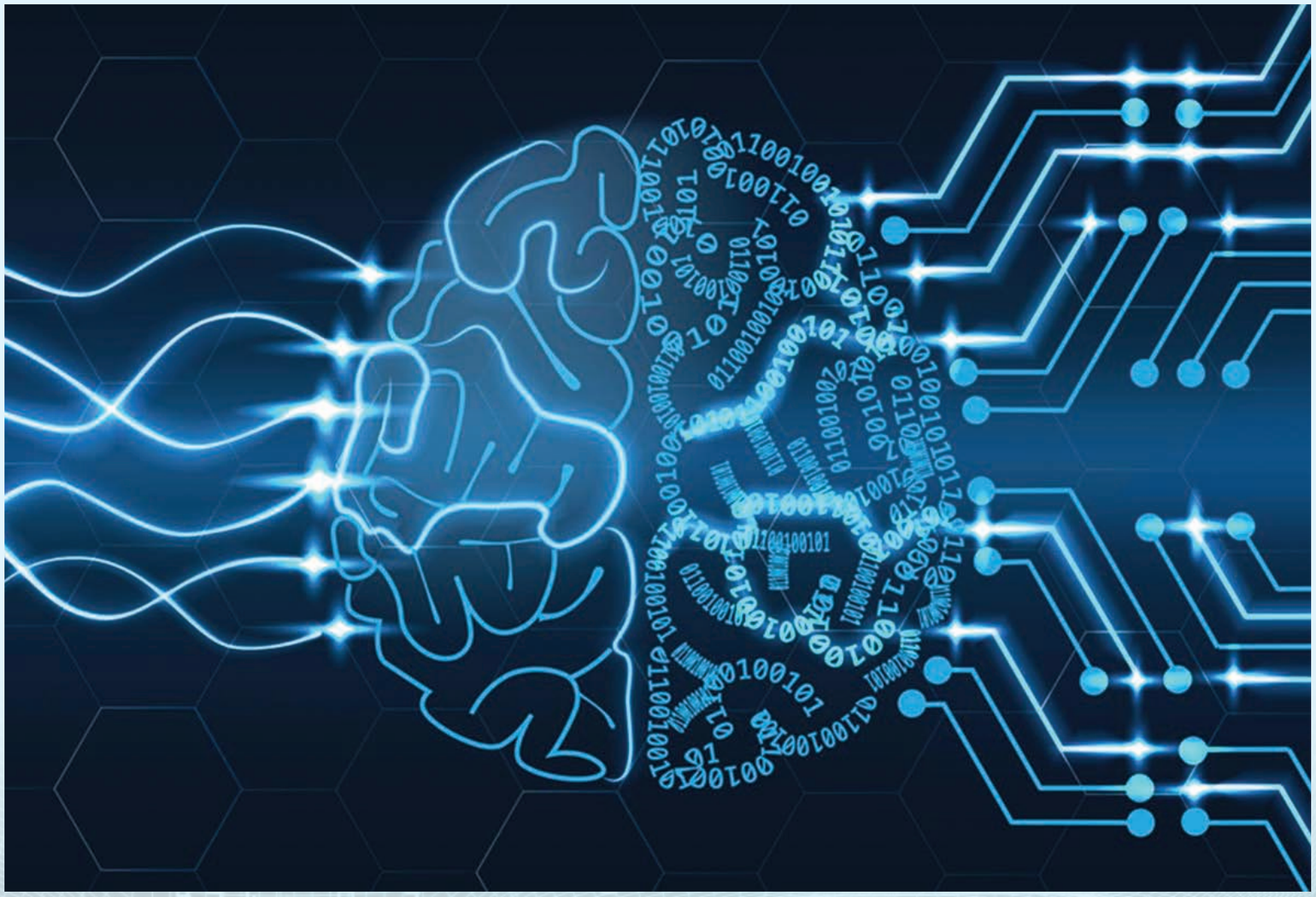
Yes, we need cooperation between disciplines. Data analysis is very complex, only some people are interested to focus on that. It is difficult to find generalists, such as doctors, that also focus on data analysis.
Learning to make a data management plan is necessary for successful projects. Universities and also EU projects provide some training, however these trainings are not as effective as they could be. An example is that researchers could be instructed to use other programs for data storage to increase interoperability: make it clear that Excel is not the only choice. Provide other tools to the researchers to store and share their data and evaluate their use.

What are you currently working on to progress the field of AI and toxicology?

There is a lot of attention for toxicology in the field of rare diseases induced by gene mutations. In this field, rare disease networks are built and these are being used as AOP to check effects of medicinal drugs. Within the European project for rare diseases and the EU tox risk project, we are currently working on the link between acetylation processes, epilepsy inhibitors, neurological disease and the treatment with clofibrate. Using AI, all existing data, tools and methods are combined to understand the mechanism behind the rare disease and its treatment.

What is your take home message?

Work in interdisciplinary teams to enhance use of AI in toxicology. It is all about combining existing data, tools and methods in the field of toxicology and data science to develop understandable AI for predicting health effects of substances. ■

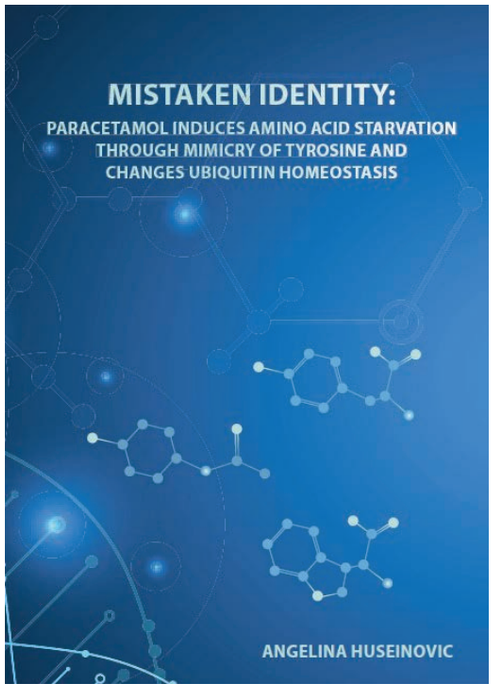


Mistaken identity: Paracetamol induces amino acid starvation through mimicry of tyrosine and changes ubiquitin homeostasis

My name is Angelina Huseinovic and I followed the MSc-program Biomolecular Sciences specializing in Biological Chemistry and Molecular Cell Biology at the Vrije Universiteit Amsterdam. I my PhD took place at the Division of Molecular and Computational Toxicology under supervision of Prof. Dr. Nico Vermeulen, Dr. Chris Vos and Dr. Jan Kooter. My PhD project was within the AIMMS institute and designed to bridge between two Divisions: Molecular Toxicology and Genetics. I defended my PhD thesis on May 24th 2019 and, currently, I am working as a postdoc on HPV-induced carcinogenesis at Cancer Center Amsterdam-VUmc at the Department of Pathology.

Motivation

Paracetamol is a widely used analgesic and antipyretic drug and generally considered safe at therapeutic concentrations. However, due to its hepatotoxic potential, and availability and presence in many medical formulations, it is worldwide a major cause of acute liver failure. The hepatotoxicity during overdose is mainly caused by the formation of toxic quinone-imine metabolite NAPQI through the action of CYP enzymes in the liver, which causes glutathione (GSH) depletion, mitochondrial damage and subsequent cell necrosis. Paracetamol toxicity can also occur following therapeutic doses and, besides hepatotoxicity, it can cause kidney damage and rare but severe skin reactions like the Steven-Johnson syndrome and toxic dermal necrolysis. In recent years, several large cohort epidemiological studies reported that prolonged maternal paracetamol use could interfere with normal development of newborns and increase the chance for ADHD, asthma, male infertility and autism symptoms later in children's life. Besides its analgesic and antipyretic properties, paracetamol has been shown to interfere with the psychological state by reducing feelings of empathy. Despite substantial evidence for the involvement of CYP-metabolism in paracetamol toxicity, not all toxic effects can be explained by the action of NAPQI and related processes. Several studies showed that paracetamol can be toxic before NAPQI formation and without GSH depletion. This NAPQI-independent toxicity is attributed to the parent compound and its mechanism still remains unknown.



The aim, methodology and results

The main objective of my PhD project was to study genes and pathways that are involved in paracetamol-induced toxicity notably due to the parent drug and unrelated to paracetamol metabolism. For this purpose we used baker's yeast Saccharomyces cerevisiae as the model organism because of the absence of oxidative paracetamol metabolizing enzymes, its simplicity, and high functional conservation with eukaryotic cells. The final goal was to translate the findings in yeast to humans.

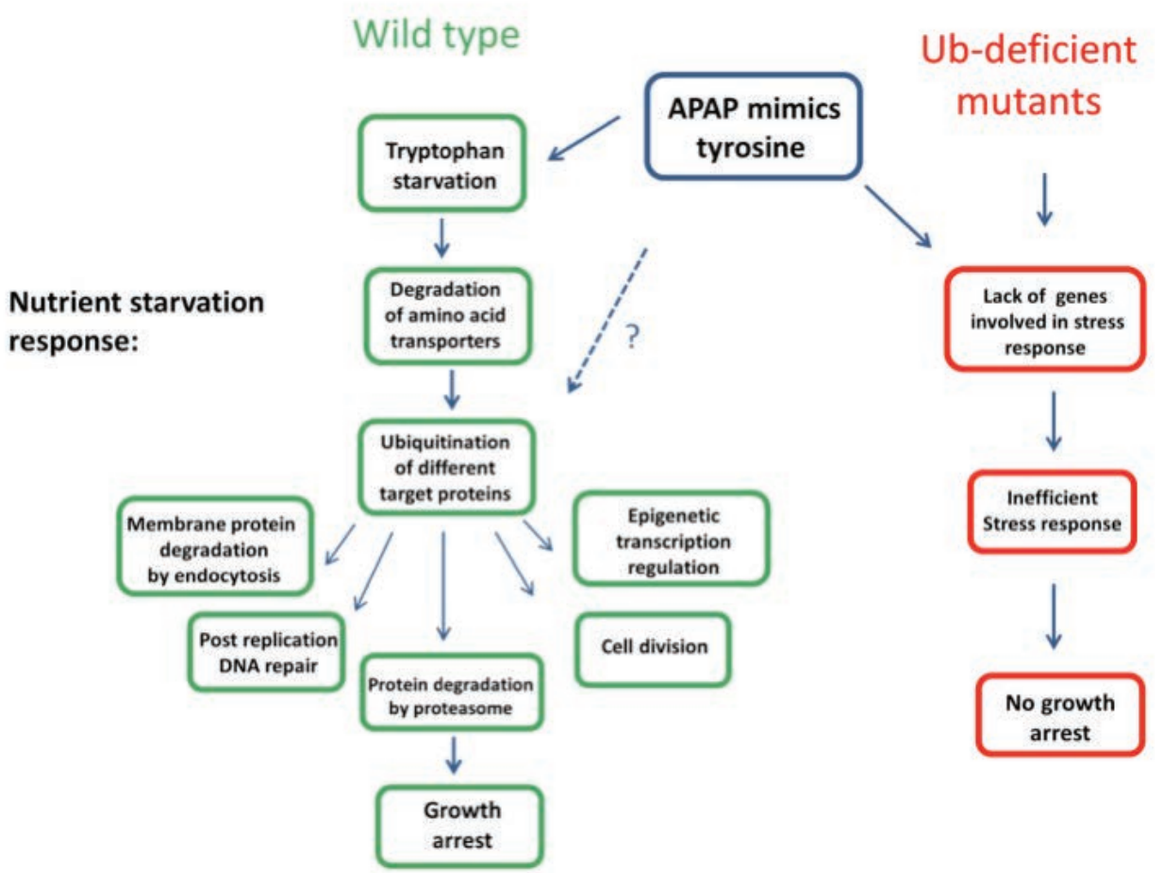
The availability of a genome-wide gene deletion strain library allowed us to screen for genes and pathways involved in paracetamol-induced toxic in a high-throughput fashion and to perform chemogenomic profiling by comparing the toxicity profile of ➜

paracetamol to other drugs, chemicals and amino acids. The genome-wide screen showed a connection between paracetamol-induced toxicity and ubiquitin levels in yeast. The stress response was mediated by processes regulated by ubiquitination, in particular processes necessary to achieve the nutrient starvation response, such as vacuolar degradation of membrane proteins and the RTG pathway. Chemogenomic profiling of different drugs, other chemicals and amino acids revealed a similarity in toxicity profiles between paracetamol and other drugs/chemicals that can cause nutrient starvation response and an almost identical profile similarity with the amino acid tyrosine, which was attributed to their chemical structure similarity. Follow-up experiments revealed further the importance of aromatic amino acids in paracetamol toxicity showing that paracetamol was causing inhibition of tryptophan uptake through mimicry of tyrosine. We also developed an HPLC-based method to measure intracellular concentrations of all amino acids and showed that paracetamol caused a decrease in intracellular concentrations of most essential amino acids in yeast and, importantly, also in human hepatoma cells indicating the relevance of these findings for humans.

Conclusion

In my thesis we have shown for the first time that unmetabolized paracetamol causes a disturbance of the ubiquitin homeostasis as well as amino acid starvation in yeast and human hepatoma cells with special attention to aromatic amino acids. The observed toxicity was CYP metabolism and by inference NAPQI-independent. This is an important step forward in the understanding of the mechanisms of adverse effects of paracetamol in humans. Amino acids are essential nutrients and precursors for biosynthesis of various bioactive compounds, i.e. neurotransmitters such as dopamine, serotonin, melatonin and others. Therefore, in order to fully assess the clinical relevance of the present findings, it remains essential to determine whether the parent paracetamol indeed causes altered and/or reduced amino acid levels in humans and, furthermore, what the consecutive effects are on short- and long-term toxicities of this widely used analgesic and antipyretic agent.

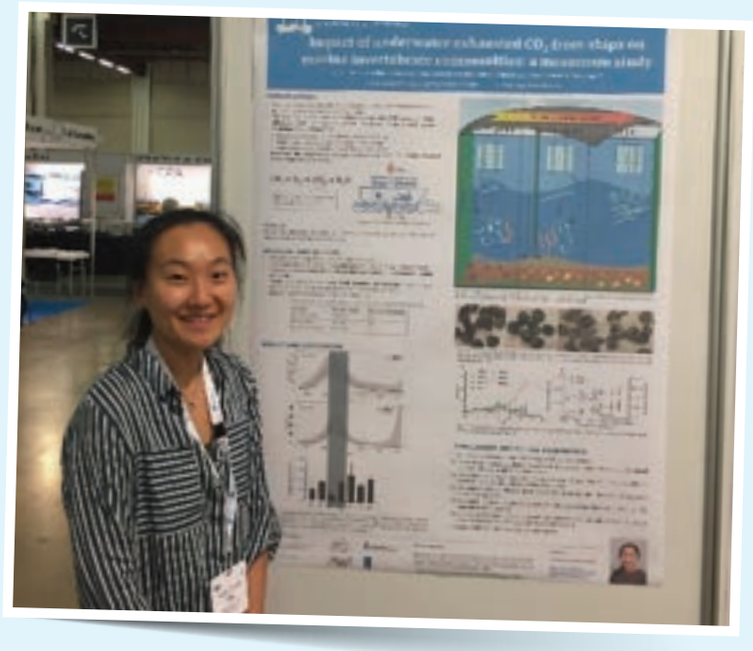
My thesis is available online via the link http://dare.ubvu.vu.nl/handle/1871/56029 ■



Model to illustrate the effect of paracetamol in yeast. Paracetamol disturbs uptake of tryptophan through mimicry of tyrosine. This leads to a nutrient starvation response and growth arrest.

A short conference report

By: Yuzhu Wei
Marine Animal Ecology group, Wageningen University, the Netherlands



From 26-30 May 2019, I participated in the five-day SETAC Europe 29th Annual Meeting, in Helsinki, Finland. This event brought together over 2000 scientists, assessors, regulators and managers from around 60 countries in environmental toxicology and chemistry.

There were workshops, presentation platforms, poster sessions and keynote talks in the annual meeting. It is educational and it covers a wide range of topics including the latest methodologies, research and regulations in Environmental toxicology and chemistry. For instance, I learned about the new efficient method of using pattern matching to scan literature to identify chemicals and microbial contamination in aquatic environments. Additionally, I heard about the novel study of using Potential (No) Effect Activity instead of Potential (No) Effect Concentration to better determine environmental risk of complex substances. Although a real mixture can be much more complex than the studied substances, it is exciting to see the potential of this method and the development of this method in the future. Furthermore, large amounts of presentations and posters were related with microplastics. It is interesting to see how this relatively new pollutant becomes a hot topic in Environmental Toxicology field and the possibilities to study it from so many different angels. Part of my PhD results were presented as a poster entitled "Impact of underwater exhausted CO2 from ships on marine invertebrate communities: a mesocosm study" on Tuesday (28th). It was exciting to experience that attenders are interested in this topic, although many of them do not focus on gas pollution in their own studies. Due to the variable of fields, our discussions extended from the impact of underwater exhaust gas to the impact of other exhaust gasses and the potential of applying those exhaust gasses to serve our daily life. Those discussions have brought me some new ideas about further research on my project. In addition, I am glad to receive feedback, like some attenders starting to rethink about gas pollution due to my presented topic. For example, to their knowledge, most available gas pollution studies are focussed on the impact towards human being. While some gas pollutions, in this case the exhaust gas from ships, may have significant impact on the ecosystems. It is important for us to understand those impacts on ecosystems, although it may not be directly related with humans.

Besides research sessions, this SETAC event also include some company exhibitions, which is very useful for a 3rd year PhD candidate like me. I was able to introduce myself to those companies, learn their business focus and the required skills of their future employees. It helped me find the focus of self-development in the coming year to have a better start of my career after my PhD.

I would definitely recommend others to visit at least one of the SETAC events. They are SETAC Africa, Asia/Pacific, Europe, Latin America and North America. The event offers a very high level of scientific sessions. It is a great place to meet people who share the common interest in environmental toxicology and chemistry. It is a professional and fun event to attend! ■

AIO toxafette - **Christy Tulen**

Introduce yourself and tell us something about your PhD project.

My name is Christy Tulen and currently I am in the 2nd year of my PhD project at the department of Pharmacology and Toxicology, Maastricht University. I did my Bachelor Nutrition and Health and Master Molecular Nutrition and Toxicology at Wageningen University. In February 2018, I started my PhD project which focusses on the mechanistic and causal involvement of aldehyde-induced mitochondrial dysfunction in chronic obstructive pulmonary disease (COPD) lung pathology. The aim is to unravel the link among exposure to aldehydes, mitochondrial dysfunction and development of COPD, which can form the mechanistic basis to regulate aldehydes in cigarette smoke and can provide insight in tobacco induced COPD pathogenesis. My project is a collaboration of the Department of Pharmacology and Toxicology (MUMC+, Maastricht, the Netherlands), the National Institute for Public Health and the Environment (RIVM, Bilthoven, the Netherlands) and the Netherlands Food and Consumer Product Safety Authority (NVWA, Utrecht, the Netherlands). During this PhD project, we will use both *in vitro* and *in vivo* exposure models in order to investigate our hypothesis.

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

The major challenge during my PhD project is to combine a variety of tasks, which requires a realistic planning, setting priorities and being flexible. Due to multiple responsibilities and deadlines, both related to scientific research (e.g. practical laboratory work), scientific communication (e.g. presenting, writing) and education (e.g. supervising tutor groups), it is important to have a tight, realistic planning by setting priorities. At the same time, a PhD-project requires to be flexible. In particular, in periods of cell culture experiments you never know exactly the planning of the week, because cell experiments do not like to be planned. The trick is to accept this. A new experiment that succeed in one go, is often too good to be true, so when the cells are not behaving as expected I remind myself: 'That is how the lab works'.

What did you expect from your PhD project?

I expected a PhD project to be a challenging job in which I can develop myself through various tasks and responsibilities. During the first year of my PhD, I already experienced the diversity of a PhD project. I like the combination of scientific research, laboratory work, presenting, writing, teaching and personal development of soft skills. In addition, I expected to work in an international environment and I was looking forward to collaborating in a multidisciplinary international team as part of the PhD project. I find it interesting and challenging to discuss topics from different points of view and in this way learn from each other. The importance of (inter-) national collaborations is something I already experienced during the first part of my PhD project. My PhD project is a collaboration between Maastricht University, RIVM and NVWA and various additional collaborations with (inter-) national research institutes and universities have already been initiated last year e.g. United States Environmental Protection Agency. Research is not about working solely on one specific topic, but is also about meeting researchers, discussing, learning from each other, get inspired and collaborate to bring the research project to the next level.

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

Research is all about making choices and setting priorities due to time, money and stakeholders involved in the project. However, if these resources are unlimited I would like to conduct more in-dept research into the causal effect of aldehydes present in tobacco products →

on mitochondrial dysfunction and the development of COPD in order to translate these fundamental research outcomes into tobacco product regulation and probably therapy applications for COPD treatment. Furthermore, I would like to use interesting and promising exposure models for further research in the field of inhalation toxicology such as air-liquid interface exposure of primary lung cells, precision-cut lung slices and lung-on-a-chip.

How do you combine your PhD-project with your personal life?

Of course, it is sometimes challenging to combine your PhD with your personal life, but I think it is all about a realistic planning and setting your priorities straight. I try to find a good balance between my PhD project and my personal life. Since my project includes periods of cell culture work, I am not as flexible as someone who performs data-analysis and can access or close the dataset from every place at every time of the day. During these experimental weeks, I am bound to the lab, which could include long lab days, and even it can happen that I need to come to check my cells during weekends. However, this is always just a certain period. Therefore, during experimental weeks and deadlines my priority is my PhD project, while during other periods I am more flexible. Nevertheless, I think this is inherent in trying to achieve a specific goal, which is in my case: promoting. Overall, I think it is important to have a good work-life balance to be able to be more focussed and productive during work hours and to really enjoy hobbies and spare time with family and friends.

What are your future career plans?

At the moment, I have no specific future career plans. I like the diversity of a PhD in which no day is the same. I am enthusiastic about scientific research due to my curiosity to elucidate molecular pathways underlying diseases and translate fundamental research outcomes into society applications. Besides, I like teaching and the interaction with students and I consider it as a challenge to communicate research findings in a clear, understandable and convincing way to a diverse audience both to scientific researchers as well as to the society. Nowadays, I am broadly interested and open for opportunities in academia, industry or research institutes. I will orientate myself during the coming 2.5 years and will consider what will be a challenging next step in my career. Let's see what the future will bring.

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

I am a member of the NVT society since the first year of my PhD. I expect from being a member to have the opportunity to get in contact and meet toxicologists from both academia and industry in order to expand my network. In addition, I expect that the meetings organized by the NVT provide the opportunity to gain more insight in the latest developments in the research field of toxicology and give a platform to present and discuss data with fellow researchers to inspire and learn from each other. This year, I will be part of the organizing committee of the NVT annual meeting 2020, which I expect to be a unique opportunity to broaden my network in the field of toxicology and develop personal soft skills. I am looking forward to the organization of the NVT annual meeting in 2020.

Answer to the question of the previous PhD-candidate: What is the most important lesson that you have learnt from your PhD journey until now?

The most important lesson I have learnt from the first 1.5 year of my PhD journey, is to enjoy the PhD journey including the ups and downs. Achieving the milestone of a PhD title is important, but I think the distance that you must travel including its ups and downs, fears and failures is even more important. The PhD journey of 4 years consists of different phases, which contribute to both professional and personal development. For example, when an experiment failed in which you invested a lot of time and effort, it feels like a failure and waste of time, energy and money. At these moments, it is the trick to keep positive, put things into perspective and realize that the most instructive moments are often the failures (i.e. the downs) because these situations require you to be critical at your project and skills which will contribute to improvement. Nevertheless, a PhD is also a fun and unique journey, which gives you the opportunity to have freedom and responsibility in determining the direction and planning of your PhD project, provides the chance to develop and improve scientific research skills and personal soft skills and facilitate the ability to travel, to broaden your network and meet inspiring researchers.

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

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

AIO toxafette - **Iris Schaap**

Introduce yourself and tell us something about your PhD project.

My name is Iris Schaap. I recently graduated and I am writing my own Ph.D. proposal in collaboration with Dr. Nynke Kramer and prof. Dr. Juliette Legler. My background is in Toxicology (MSc Toxicology and Environmental Health) and Fine Arts (Rietveld Academy Amsterdam), with a specific interest in the complex relationship between mankind and its surroundings. This formed the intrinsic motivation to formulate a question that I had into a research proposal: How and to what extent do anthropogenic stressors affect populations?

It is well known that anthropogenic influences have been affecting the natural balance between top predators and lower food chain species, in which a specific loss of large top predators is observed, including marine mammals. However, identifying a specific mechanism which explains the decline of high tropic species populations is challenging. Although the use of a framework in the form of adverse outcome pathway (AOPs) can support an effective translation of knowledge into endpoints, there is an urgent need for innovative scientific tools to understand the link between chemical mixture exposure and the adverse effect on the general health of organisms and population. Unfortunately, there is no established methodology how to connect effects seen at higher biological organization levels with sub-organismal dynamics, despite recent intensive efforts in AOP development. My research proposal aims to assess the impact of a myriad of stressors to (marine mammal) population health by integrating state-of-the-art modeling concepts, bioassays and generic-energetic AOP analysis.

Answer to the question of a previous PhD-candidate: How would you explain your research to someone with minimum science education?

Mankind has an important influence on the health of populations and ecosystems on earth. The effects of climate change and ocean acidification are often studied. Nevertheless, the role of chemical pollution remains unclear. To date, it is known that the accumulation of some chemicals can result in adverse health effects in organisms including marine mammals. Marine mammals are essential animals in marine food chains and can act as an indicator of human health due to i.e. dietary similarities. By applying innovative techniques, this project aims to better understand the relationship between chemical exposure and their adverse effect on the energy budget of marine mammals.

What are the major challenges that you have encountered in writing a research proposal?

Since I didn't have any experience in writing a research proposal, I found it quite challenging to translate an idea into numbers and figures, e.g. finance and planning. Nevertheless, this also helped me to narrow down the proposal and separate essential from less-essential parts.

What do/did you expect from writing a PhD proposal? Having no experience, also results in not having expectations. From the start, I was looking for a project that triggered my curiosity and would inspire me, which it did in every way.

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

I think I would like to expand the generic concept of the proposal a bit more by constructing an AOP network of 3-4 single AOPs with a specific focus on energy homeostasis. Each AOP can be seen as a biologically plausible and scientifically defensible chain of events that can lead to an energy disturbing effect. Nevertheless, as more energetic AOPs are described, systems of interconnected AOPs that share one or more key events will merge and form a network.

What are your future career plans?

I hope that my research proposal will be granted and that I can pursue my interest in understanding the complex as well as gentle relationship between mankind and the environment. If not, I will keep searching for option to still do so.

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

I do not, but it is on my to do list!

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

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

Verslag van MKMD On Tour, 27 mei te Utrecht

Door Marja Berendsen (ZonMw) en Damiën van Berlo (U-AIM, Universiteit Utrecht)

Meer Kennis met Minder Dieren (MKMD) is een programma van ZonMW gericht op innovaties die bijdragen aan het beantwoorden van wetenschappelijke vragen zonder dierproeven. Zie ook: https://www.zonmw.nl/nl/onderzoek-resultaten/fundamenteel-onderzoek/programmas/programma-detail/meer-kennis-met-minder-dieren/

Publiek-private samenwerking is essentieel als we de kwaliteit van proefdiervrij biomedisch onderzoek willen verbeteren. Maar hoe werkt zo'n publiek-private samenwerking? Wat is er nodig om er zeker van te zijn dat de samenwerking leidt tot succesvolle proefdiervrije innovaties? In de middag van 27 mei presenteerden drie 'Utrechtse' consortia hun projecten en ervaringen. De conclusie was dat er geen algemene succesformule bestaat voor samenwerking in consortia. Wel bleek dat er veel geleerd kan worden door ervaringen te delen. ZonMw en de Utrecht-Advanced *In vitro* Models (U-AIM) hub van de Universiteit Utrecht organiseerden deze tweede bijeenkomst van MKMD on Tour.

Jos Malda (hoogleraar Diergeneeskunde en teamleider van U-AIM) opende de middag met een korte introductie van U-AIM. Het belangrijkste doel van deze 'hub' waar expertise en kennis gebundeld wordt, is om het gebruik van proefdieren sterk te verminderen door de ontwikkeling van innovatieve dierproefvrije modellen te versnellen.

U-AIM creëert en faciliteert samenwerkingen tussen onderzoekers, studenten, wet- en regelgevers en de industrie om *in vitro* modellen verder te ontwikkelen, te valideren en te implementeren conform de belangen en wensen van deze stakeholders. Multidisciplinaire samenwerking en verbinding met stakeholders zijn daarbij essentieel. U-AIM heeft een brede focus; Jos Malda bevestigde op een vraag uit de zaal dat ook veranderingen in wet- en regelgeving de aandacht hebben en dat daarmee veel te winnen is.

Vl.n.r.: Nynke Kramer, Bas Blaauboer en Eveline van Rijswijk (moderator)

Menselijk restmateriaal voor onderzoek: een logisch idee maar lastig te organiseren

Met het project VitalTissue deden Evita van de Steeg (TNO en projectleider) en Martje Fentener van Vlissingen (Erasmus MC) veel ervaring op met het vormen van dit consortium en de samenwerking. In het consortium van VitalTissue werken verschillende organisaties uit het publieke en private domein, kennisinstellingen, (academische) ziekenhuizen, bedrijven en stichtingen samen om vitaal menselijk restmateriaal beschikbaar te maken voor onderzoekers.

Biomedisch onderzoek is namelijk nog in veel gevallen afhankelijk van diermodellen maar die hebben in veel gevallen een zeer beperkte voorspellende waarde voor toepassing bij mensen. Medicijnen die nauwelijks bijwerkingen gaven bij apen, bleken bij klinische testen op mensen levensbedreigende situaties op te leveren. Een oplossing hiervoor is het gebruik van vitaal menselijk weefsel dat na operaties in ziekenhuizen overblijft. Met dit materiaal kunnen biomedische wetenschappers onderzoek doen. De grote uitdaging is hoe dit materiaal onder de juiste voorwaarden en op tijd bij de juiste onderzoeker terecht komt. In het project Vital Tissue, dat gefinancierd wordt door de Stichting Proefdiervrij, de Samenwerkende Gezondheidsfondsen en ZonMw, onderzoeken Evita van de Steeg en haar team hoe dat gerealiseerd kan worden. ➜

VitalTissue is een groot consortium met bijna 20 partners die allemaal belang hebben bij dit project. Maar zoals Martje van Fenterener Vlissingen beaamde: “Het is een voor de hand liggend idee maar heel erg moeilijk om te organiseren.” Met alle partners moet overeenstemming bereikt worden over het regelen van toestemming van de patiënt, opslag en beheer van data, het prepareren en bewaren van het materiaal en het transport. En allerlei juridische en ethische aspecten moeten hierin meegenomen worden. De uitkomst van het project Vital Tissue zal een advies zijn met opties voor specificaties van de samples, logistiek, voorwaarden voor het bewaren en beheer van informatie.

De kracht van kleine consortia

Het project Risk-IT bestaat uit een relatief klein consortium waarin de partners samenwerken om betere en proefdiervrije methoden te ontwikkelen voor een betere risicobeoordeling van chemische stoffen. Tot nu was het zo dat een risicobeoordeling van chemische stoffen vaak gebaseerd wordt op de uitkomsten van dierstudies en die zijn niet één op één te vertalen naar mensen. Nynke Kramer (Universiteit Utrecht) en haar team hebben een koppeling gerealiseerd van data uit *in vitro* tests voor het vaststellen van mechanismen van toxiciteit, met computermodellen die *in vitro* data vertalen naar een toxisch (giftig) effect in een organisme (QIVIVE – Quantative *In Vitro-In Vivo* Extrapolation). Door deze combinatie kunnen onderzoekers betere informatie verkrijgen voor de risicobeoordeling van chemische stoffen en medicijnen. Binnen dit project is vooral gefocust op toxische effecten in de nieren; in klinische studies zijn deze effecten vaak de reden waarom een medicijn niet op de markt gebracht kan worden.

De samenstelling van het relatief kleine consortium van Risk-IT is organisch gegroeid zoals Nynke toelichtte op vragen uit de zaal. Dat ging verrassend makkelijk en Bas Blaauboer, onderdeel van het team, vulde aan dat interesse in het project en onderling vertrouwen daarbij een belangrijke rol speelden. Het was duidelijk dat de doelen en belangen van de consortiumpartners, waaronder de Universiteit van Würzberg, het Fraunhofer Intsituut en BASF, parallel liepen. De samenwerking met de industrie was voor dit project zeer waardevol. Industriële partners beschikken vaak over heel veel ongepubliceerde data. Er waren voor dit project geen restricties voor het gebruik ervan. Het helpt ook om daar van het begin af aan duidelijke afspraken over te maken, benadrukte Bas. Nynke en Bas hebben ook ervaren dat een consortium met een klein aantal partners makkelijker te managen is. Grote consortia met veel matching zijn niet perse de beste oplossing voor alle vraagstukken.

Formule voor succes: verschillende perspectieven, dezelfde wetenschappelijke taal

Een soortgelijke koppeling van computermodellen met resultaten uit een *in vitro* methode is opgezet binnen het project van Teun de Boer (UMC Utrecht) en András Horvath (Nanion Technologies). In dit geval zijn er humane hartspiercellen gekweekt uit menselijke stamcellen, waarvan de elektrische activiteit kan worden gemeten met de zogeheten Patch Clamp-methode (electrofysiologie). De in samenwerking met Nanion ontwikkelde techniek is in staat om elektrische signalen in individuele cellen te meten door Dynamic Clamping. Met de klassieke methode is dit niet mogelijk. Nanion combineert dit met geautomatiseerde Patch Clamping zodat er veel metingen in een korte termijn gedaan kunnen worden. De uitkomsten worden met een geavanceerd computermodel vertaald naar effecten op het hart in patiënten. Door cellen van mensen te gebruiken is niet alleen de voorspellende waarde van de test veel groter geworden, het opent ook de deur naar ‘personalised medicine’. Een patiënt krijgt dan een behandeling die op zijn eigen cellen is getest, waardoor de voor de patiënt beste behandeling kan worden gekozen met zo min mogelijk bijwerkingen.

De samenwerking tussen de onderzoeksgroep van Teun de Boer en Nanion, een bedrijf in München dat instrumentarium en diensten levert voor analyses, verliep soepel. Volgens András Horvath komt dat omdat Nanion een onderzoek-georiënteerd bedrijf is. Daar komt bij, zoals Teun toelicht, dat András en hijzelf dezelfde wetenschappelijke achtergrond hebben en tegelijkertijd vanuit verschillende perspectieven, namelijk wetenschap en bedrijfsleven, aan dit project werkten. Dezelfde wetenschappelijk taal spreken vergemakkelijkt de samenwerking.

Publiek-private samenwerking voor proefdiervrije innovatie is maatwerk

Tijdens de podium-discussie gingen de sprekers met elkaar in gesprek en kreeg het publiek de kans om vragen te stellen. Uiteraard was daar ok ruimte voor het onderwerp samenwerking. Uit de presentaties eerder die middag kwam het beeld naar boven dat er geen vast recept is te geven voor publiek-private samenwerking. De genoemde projecten zijn voorbeelden van geslaagde samenwerking tussen private en publieke partijen. Er blijkt vaak een grote bereidheid tot samenwerking en ook ➜

dat private en publieke partijen gezamenlijke belangen hebben. Samenwerkingen komen doorgaans tot stand doordat men bijvoorbeeld dezelfde achtergrond heeft of op een andere ‘organische’ manier. De sprekers waren het eens dat het cruciaal is om veel tijd en energie te steken in het vormen van netwerken. Wanneer een netwerk voldoende kritische massa heeft, leiden de interacties tot kansen en het identificeren van gezamenlijke belangen. Bijeenkomsten zoals MKMD On Tour bieden kansen om te netwerken, ideeën op te doen en mensen te ontmoeten die werken aan iets dat complementair is aan het eigen werk. Eigen initiatief blijft hierbij belangrijk.

Samenwerking ontstaat dus niet vanzelf. Soms is een bundeling van kennis en expertise nodig om die samenwerking verder te faciliteren. In Utrecht richten ze daar hubs voor in, zoals U-AIM voor de ontwikkeling van proefdiervrije innovaties. Door het samenbrengen van mensen met kennis en ervaring op dit terrein, heeft U-AIM een breed overzicht van de lokaal aanwezige expertise en technieken. Daardoor kunnen zij de juiste experts koppelen aan private partijen om een specifieke vraag te beantwoorden. En kan er bij de ontwikkeling van een nieuwe methode al in een vroeg stadium rekening gehouden worden met de wensen van de stakeholders en regulatoire vereisten, aldus Damiën van Berlo, Scientific Programme Officer bij U-AIM.

De projecten van Evita van de Steeg, Nynke Kramer, Teun de Boer en de U-AIM hub laten zien dat publiek-private samenwerking essentieel is als we de kwaliteit van proefdiervrij biomedisch onderzoek willen verbeteren. Afhankelijk van de betrokken personen, hun netwerken en de specifieke vraag van een publieke of private partij om een techniek of methode te verbeteren of te ontwikkelen, wordt het consortium gevormd en de samenwerking ingevuld. Er kan wel geleerd worden van elkaars ervaringen en dat is wat er ook gebeurde tijdens deze tweede editie van MKMD on Tour. ■

Inschrijving register

Voorletters	Achternaam	Datum inschrijving	Datum afloop
L.	Wagenaar	03-06-2019	03-06-2024
J.W.H.	Sanderink	03-06-2019	03-06-2024
A.C.	Punt	03-06-2019	03-06-2024
J.E.F.	Arnauts	03-06-2019	03-06-2024
D.	van Berlo	26-08-2019	26-08-2024
R.	van Herwijnen	26-08-2019	26-08-2024

Inschrijving TiO

Voorletters	Achternaam	Opleider	Datum inschrijving
E.J.P.	Hermans	Prof.dr. A.J. Murk	03-06-2019
C.	Liu	Prof.dr.ir. I.M.C.M. Rietjens	03-06-2019
W.	Zheng	Prof.dr.ir. I.M.C.M. Rietjens	03-06-2019

TERUG NAAR INHOUD