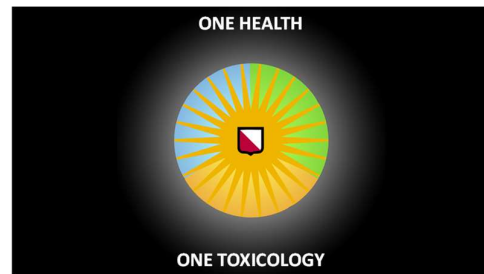


Inaugural Speech

Professor Juliette Legler

“One Health, One Toxicology”

13-12-2018, Utrecht University



Dear Rector magnificus, Dean Dhert, esteemed colleagues, family, friends. A warm welcome to all of you on this beautiful December day. Welcome to my inaugural lecture entitled “One health, One toxicology.” Before I start my lecture, I would like to do two things. First of all, I would like to thank Mr Jaap Jan Steensma, who just played the organ so beautifully. In case you didn’t recognize the music, that was the theme song from the computer game the Legend of Zelda. Mr Steensma played it especially for my son Vincent, probably the first time this music has ever been played on a 300 year old organ.

The second thing I would like to do before I start my lecture is to just to take a moment to let this all sink in. I would like to be still for a moment and absorb these special surroundings, really feel this moment of being here, with you all, and do my best to make time stand still.

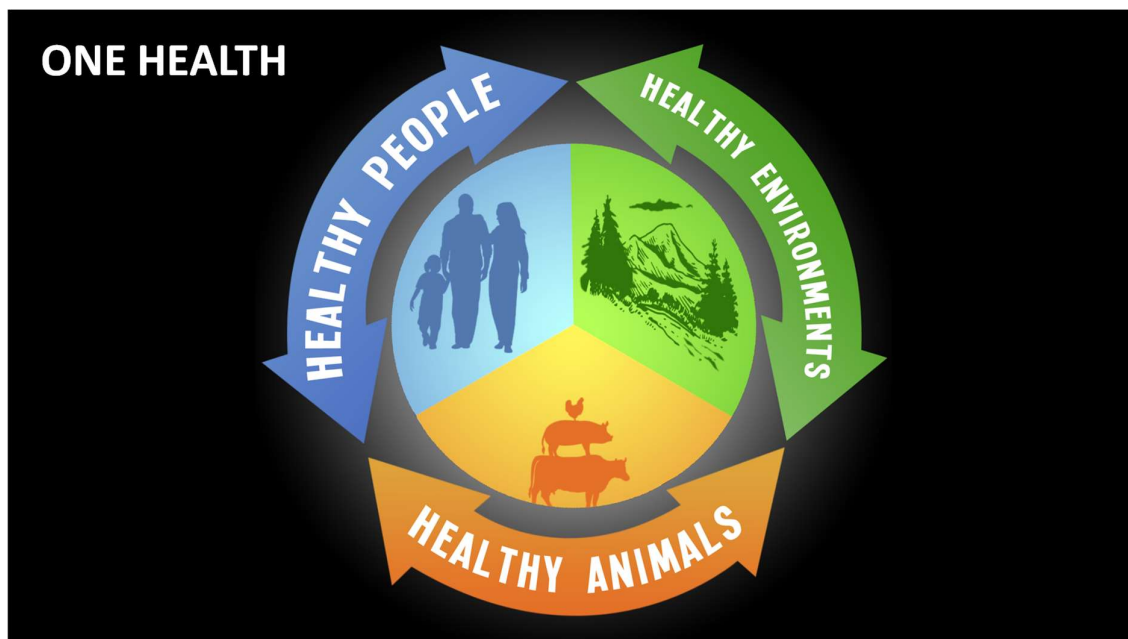
Let me take you back 11 months, to the 29th of January 2018, and if you would, imagine you are me, on a tour of these university buildings for the first time, a tour for new staff of the university. Imagine coming into this Auditorium for the first time. The auditorium was empty, light was flooding in, what I could see were the high ceilings, the stained glass windows, the tapestries on the wall, the organ, the pulpit I am standing at now. I was taken aback by the beauty and grandeur of this room. I was told that this is where the inaugural lectures of new professors are held, and immediately all my hesitations about given an inaugural lecture, my second in 5 years, vanished into thin air.

What an honor to be up here, speaking to you all in these surroundings. This auditorium is the oldest part of this Academy building and dates back to 1462. Originally, this was the ‘kapittelzaal’, or the chapter room, where clergymen and religious figures from the Dom Cathedral and beyond would come to read the Bible, receive training, and discuss religion. In 1579 the Union of Utrecht was signed in this room. The Union of Utrecht signified a definitive separation from Spain and the start of the independent state of the Netherlands.

The signing of the Union of Utrecht was the result of long negotiations between three forces that were powerful at the time: in Dutch: ‘Geestelijkheid’, Ridderschap, Stadsbestuur; In English: the Church, the Chivalry, and the City Council. The Union of Utrecht, the coming together of these three forces, resulted in something that was truly paradigm shifting for that time: this Union ensured complete personal freedom of religion and freedom from

persecution based on religion, something that was truly unique in Europe at that time and set the foundation for all constitutional laws to follow¹.

One Health



Fast forward 421 years, and here I am, standing in these beautiful and historical surroundings to talk about another ‘triforce’ that is shifting paradigms in the fields of human and veterinary medicine and environmental sciences: the concept of One Health. One Health is a concept that integrates three domains of health: human health, animal health and environmental health. The concept is built on the understanding that there is really only ‘one’ health shared by humans, animals and the ecosystem, and what affects one, affects all three. Healthy humans need healthy animals and healthy environments. Similar to this concept, I believe that we should strive for only “one” toxicology. But first a bit more about One Health.

One Health is defined as “the collaborative effort of multiple disciplines to attain optimal health for people, animals and our environment²”. It integrates human, veterinary, wildlife, and environmental health disciplines at multiple levels. One Health seeks to increase communication and collaboration across disciplines to protect the health of all species on the planet. This is something that fundamentally appeals to me, given my roots in ecology and environmental sciences. The principles of One Health provide a framework for individuals and institutions to integrate knowledge on health. After all, the grand challenges we are faced by our planet – climate change, pollution, loss of biodiversity – these grand challenges require grand and integrated actions and solutions.

Although the term “One Health” is fairly new - the similarities and differences between human health and animal health has formed the basis of comparative medicine for centuries.

¹ <https://historiek.net/unie-van-utrecht-1579-betekenis/74900/>

² https://www.onehealthcommission.org/en/why_one_health/what_is_one_health/

At my department, the Institute for Risk Assessment Sciences, IRAS, we recently celebrated 100 years of One Health, marking the 100th anniversary of Utrecht University's status as the place for higher veterinary education with the inception of the motto 'Tot heil van mens en dier' ("To the benefit of man and animal alike"³).

On October 11, 1918, Professor Hendrik Schornagel stated in his inaugural lecture 'Not only does the veterinarian serve the community by curing sick animals and promoting the hygiene of animals, but he also has the task to guard against adverse influences that threaten public health⁴.' The seeds of the concept of One Health were sown a long time ago, and today, One Health is a main strategic focus of the Faculty of Veterinary Medicine.

Clearly the interplay between human and animal health is extremely important in the One Health concept. One Health research has had its biggest impact up to now within these interconnected domains of human and animal health, in particular in terms of infectious diseases. With 75 percent of all emerging human infectious diseases originating in animals, it is not surprising that research in One Health has largely focused on the battle against emerging zoonoses originating in domestic animals or wildlife. A zoonosis is an infectious disease that can be transmitted between animals and humans, for example rabies, Ebola, and influenza.

In the Netherlands, outbreaks of antibiotic resistant bacterial infections and Q fever in livestock have led to concerns about the health effects associated with living close to farms with intensive animal husbandry. The research programme 'veehouderij en gezondheid omwonenden' (safety and health of residents living close to intensive agriculture) is an example of a successful collaborative effort between human and veterinary health experts to increase understanding of the sources and risks of these infectious agents⁵.

This research has shown that Q fever transmission to humans is very rare, and the presence of pathogenic bacteria do not really differ between people living close to intensive agriculture and those who live farther away. Ground breaking research in this context led by Prof Dick Heederik and his group at IRAS suggests that it is not only the transmission of these zoonoses between animals and humans that is of concern when living close to agricultural areas. The inhalation of elevated levels of fine particles in these areas that are associated with increased sensitivity to specific lung infections is important⁶. In other words, factors specific to the environment of the area, like the presence of fine particles in the air, are key to understanding health effects in these regions.

³ Personal communication, Prof. Peter Koolmees

⁴ <https://www.uu.nl/nieuws/honderd-jaar-one-health-bij-de-faculteit-diergeneeskunde>

⁵ <https://www.rivm.nl/veehouderij-en-gezondheid/onderzoek-veehouderij-en-gezondheid-omwonenden-vgo>

⁶ Smit LAM, et al. Increased risk of pneumonia in residents living near poultry farms: does the upper respiratory tract microbiota play a role? *Pneumonia*. 2017. doi: 10.1186/s41479-017-0027-0.

Environment in One Health

This example illustrates that the impact of the environment on health cannot be underestimated in a One Health paradigm. Yes, there are interrelated factors between humans and animals that are very important, such as transmission of pathogens, but without considering the role of the environment in this equation, we are underestimating health impacts. I will illustrate this further with another example that clearly indicates the importance of environment in health. This refers to the '2 Cs' - climate change and chemicals – a term I first heard from my dear friend and colleague Professor Ake Bergman.

We have all heard of climate change and how it refers to changes in weather patterns over time, changes which are linked to human activities in the past 100 years, in particular the increased production of greenhouse gases like CO₂ and methane.

We can feel the effects of climate change in our personal lives, certainly after the hot summer and drought we just experienced in Europe, and we hear the reports of rising temperatures, extreme weather conditions, and rising sea levels. But we may not really comprehend are the full effects this massive global environmental change on our health. Climate change is associated with many health effects, to name a few: heat related diseases and cardiovascular failure, the spread of disease vectors and pathogens to new parts of the world, increase in allergies and asthma, mental health issues and many more.

Looking at the second 'C' - chemicals - we can lump exposure to chemicals in one term : 'pollution.' Pollution is defined as 'is the introduction of substances or energy into the environment, resulting in deleterious effects of such a nature as to endanger human health, harm living resources and ecosystems'⁷. This includes air pollution which is made up fine particular matter and associated chemicals, water pollution, soil pollution, heavy metals, but also-called chemicals of emerging concern such as microplastics and endocrine disrupting chemicals that I will come back to later.

The World Health Organisation reports that ¼ of all deaths in the world are due to environmental causes⁸. Pollution is the largest environmental cause of disease and death in the world today, responsible for an estimated 9 million premature deaths worldwide. If we look more closely at the causes of premature death by pollution, we see that by far most of these deaths are not due to infections, but due to non-infectious diseases, the so-called non-communicable diseases like cardiovascular and metabolic disease, cancer and respiratory disease.

In other words, environmental factors like pollution have a major influence on the major noncommunicable diseases (NCDs) of our time.

⁷ <https://www.eea.europa.eu/archived/archived-content-water-topic/wise-help-centre/glossary-definitions/pollution>

⁸ https://www.who.int/quantifying_ehimpacts/about/en/

Environment and NCDs in One Health

So the role of environment in One Health is very important and we need to broaden our understanding of One Health from infectious diseases to non-infectious diseases. Let's look at another example of a non-communicable disease, obesity. Obesity is a metabolic disorder that I have been researching in a toxicological context for some time now. If we look at this map published recently in the Lancet, we see that the number of overweight and obese people in the world outnumbers the number of underweight people⁹. The World Health Organization reports that 1 in 3 children in Europe are overweight or obese¹⁰. Childhood obesity is a major risk factor for a number of serious health effects later in life, including Type 2 Diabetes, nonalcoholic fatty liver syndrome and other metabolic disorders.

If we look at obesity from a One Health perspective, we see that much work has been done in the domains of human and animal health. We know from studies in humans that obesity is a very complex multifactorial disease, with genetic, cultural, social, psychological, biological and environmental factors playing a role. The rise in obesity in companion animals and livestock has paralleled the rise in obesity in humans. At the faculty of Veterinary Medicine, innovative research is conducted on obesity in animals within a One Health approach, for example on the psychological bond between owner and pet, and how this can influence obesity and help in weight loss, as well as research on the metabolic syndrome in horses and cats, or on the effects of overweight on reproductive success in cows. I am very keen to collaborate with my new colleagues in the Veterinary faculty, to extend these important studies to considering the role of the environment in obesity, in particular the role of environmental exposures to pollution.

In recent years our research has shown that exposure to synthetic chemicals in our food and environment can play a role in obesity. In particular, chemicals with endocrine disrupting activity such as some industrial chemicals, pesticides and plastics additives, can affect the development of fat cells early in life. We have observed the increase in the number of fat cells and the amount of fatty tissue in laboratory animals such as mice and zebrafish following early life exposure to some endocrine disrupting chemicals^{11,12}. Epidemiological studies in humans have reported associations with levels of these chemicals at birth and weight gain throughout childhood¹³.

⁹ NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016. doi: 10.1016/S0140-6736(16)30054-X.

¹⁰ <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>

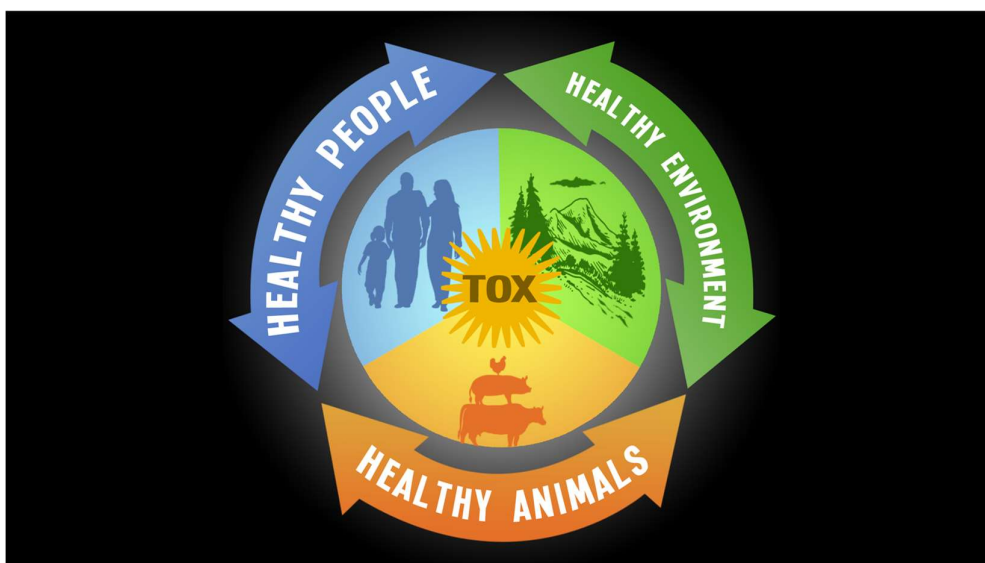
¹¹ Wassenaar PNH, Trasande L, Legler J. Systematic Review and Meta-Analysis of Early-Life Exposure to Bisphenol A and Obesity-Related Outcomes in Rodents. Environ Health Perspect. 2017 doi: 10.1289/EHP1233.

¹² den Broeder MJ, et al. Altered Adipogenesis in Zebrafish Larvae Following High Fat Diet and Chemical Exposure Is Visualised by Stimulated Raman Scattering Microscopy. Int J Mol Sci. 2017 doi:10.3390/ijms18040894.

¹³ Legler J, et al. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. J Clin Endocrinol Metab. 2015. doi: 10.1210/jc.2014-4326.

Environmental chemicals, certainly if the exposure is during the early sensitive periods of development, have the potential to increase susceptibility of individuals to gain weight, by mechanisms we do not yet entirely understand, something I'll come back to a little later in my lecture. The impact of better understanding the role of the environment and environmental exposures in disease is potentially enormous, because environmental exposures can be reduced or prevented, for example by stricter regulations or by consumer choice. And as we all know, preventing a disease from occurring makes much more sense than treating it once it has occurred.

Up to now the impacts of pollution on health and wellbeing have been largely left out of projects and programs organized under the banner of One Health. My IRAS colleague Roel Vermeulen and his group at IRAS are making great headway in this respect by unravelling the exposome, the totality of environmental chemical exposures during a lifetime, and how these exposures relate to health. But there is also a very important and complementary role reserved here for the most exciting discipline in the world, Toxicology.



Toxicology and One Health

Toxicology, the discipline that studies the adverse effects of chemical substances on living organisms, can contribute enormously to One Health. Looking at the tri-force of human, animal and environmental health, toxicology contributes to all three. Toxicological studies on the impacts of chemicals in laboratory animals and wildlife have benefitted human health enormously. In turn, veterinarians and biologists have learned a lot from accidental or intentional poisonings in humans in order to protect the health of both domestic and wild animals. In the realm of environmental and ecotoxicology, so much is known about how chemicals affect the functioning of the ecosystem and the provision of ecosystem services that are so essential to the wellbeing of the planet.

One Health Toxicology at IRAS

I believe it makes total sense to position toxicology strongly within One Health Research. To this end, we at the Division of Toxicology at IRAS have decided to focus on two main streams of toxicology in the coming years, 1) mechanistic toxicology and 2) predictive toxicology.



Mechanistic Toxicology

First, mechanistic toxicology. This is the stream of toxicology that seeks to unravel the molecular mechanisms, or to use a more modern term, the molecular initiating events, those first changes at cellular level, that when activated, lead to a cascade of cellular and organs changes that can ultimately result in a negative effect on health. Increased knowledge on the specific genes and proteins that are changed by chemical exposures will help us understand the potential effects of chemicals across species. This is because molecular mechanisms are generally highly conserved across species. Understanding molecular mechanisms also helps us develop better, more sensitive test systems to ensure that chemicals are properly tested before they hit the market. Better *a priori* toxicity testing will benefit all aspects of One Health.

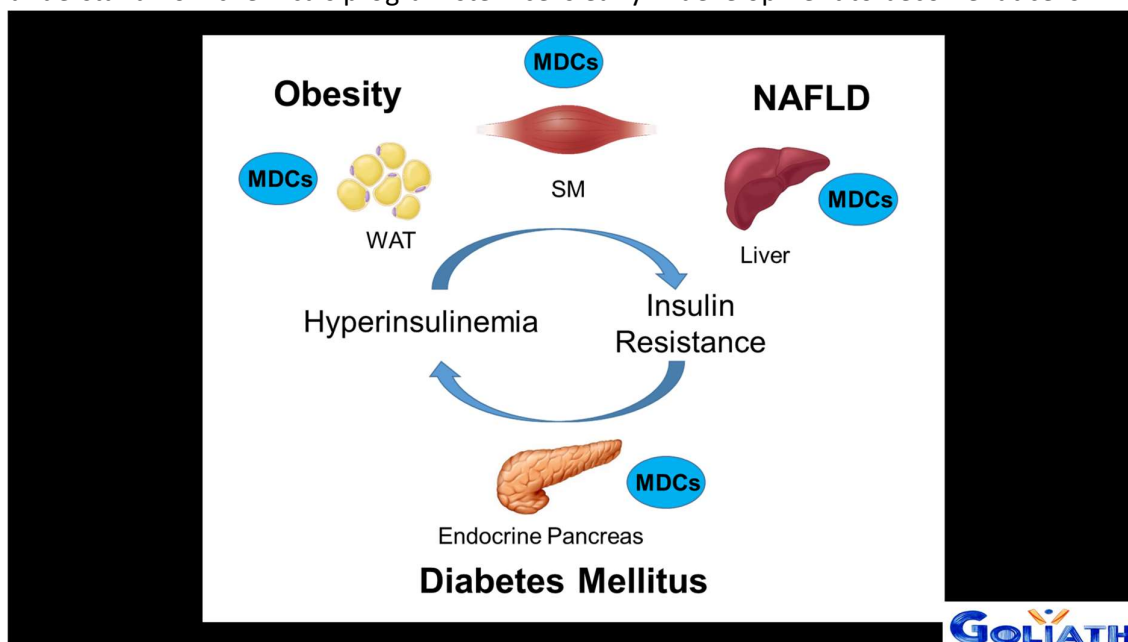
A focus on improved mechanistic understanding of chemicals is a common thread running through the research at the Division of Toxicology. In the words of the leader of our Neurotoxicology group, Dr. Remco Westerink, who is also a passionate scuba diver, we need to “dive more and dive deeper”. To name just one example, Remco is developing in vitro neurotoxicity assays using human induced pluripotent stem cells to try to understand the mechanistic differences in male and female response to chemicals that affect the brain. Though I should probably warn him that it won’t be easy to figure out the female brain.

Dr. Raymond Pieters, leader of our Immunotoxicology group, is particularly interested in how chemicals – both natural and synthetic - affect the innate immune system during early life and how these effects can persist into adulthood. In the words of Raymond: “the immune system is a continuum of development’. Raymond works in a true One Health way, working on gut organoids and cellular systems in species ranging from chicken and pig to rat to human, as well as zebrafish and nematodes.

GOLIATH

In my own research field of endocrine toxicology, we will spend the next five years trying to better understand the mechanisms by which endocrine disrupting chemicals play a role in obesity. Within the European H2020 project GOLIATH (official title: Beating Goliath: Generation Of Novel, Integrated and Internationally Harmonised Approaches for Testing Metabolism Disrupting Compounds), we will study the process of how human stem cells during early development differentiate to fat cells and how chemicals affect this process. We will do this in a truly system biology approach by studying the genes, metabolites and lipids in these processes, in a collaboration with international experts in transcriptomics, metabolomics and lipidomics.

And I’m so excited that Dr. Jorke Kamstra has recently joined our team, not only to help me manage this huge project but to also to further develop our molecular mechanistic work in human fat cells. In collaboration with Dr. Erik Kalkhoven from the Utrecht Medical Centre, we have big dreams of applying state of the art single cell sequencing for the first time to better understand how chemicals program stem cells early in development to become fat cells.



Not only will we study obesity in GOLIATH, we will also study the effects of endocrine disrupting chemicals on the onset of three interrelated metabolic diseases: obesity, diabetes

and nonalcoholic fatty liver disease. We will work with the renowned endocrinologist Prof Angel Nadal, who will study how chemicals disrupt insulin secretion in the pancreatic beta cell, the first hallmark of diabetes. We will also study the role of chemical exposures on lipid metabolism in the human liver cell, which is disrupted in the onset of fatty liver disease.

The overall goal of this work is to better understand how these chemicals – which we now call metabolism disrupting chemicals or MDCs – work at the molecular level, how these molecular mechanisms are interrelated, and how we can use this knowledge to develop the best, most robust and sensitive bioassays or test methods in human cells possible. Importantly, our mechanistic work at cell level will link closely to human population studies, thanks to our collaboration with Roel Vermeulen and Prof. Greet Schoeters and her group from VITO Belgium. This collaboration between toxicologists and epidemiologists ensures that the mechanistic work we do in the lab is translated to real health impacts measured in humans, and that the chemicals we select to study are the most relevant in terms of human exposure.

We plan to go from assay development to pre-validation and uptake in the OECD test guideline programme in 5 years, a very ambitious plan. The methods developed in GOLIATH will represent the world's first methods for testing chemicals for their potential to cause metabolic disorders. International acceptance of the test methods developed in GOLIATH is really important, and we look forward collaborating with Professor Andreas Kortenkamp in this respect, given his expertise in EU and international endocrine disruptor policy and regulations.

Our mechanistic work involves not only using human cells, but also the zebrafish. As many of you know, I love my fish, and zebrafish has been one of the main models in my research for the past 20 years. There are so many advantages to this model, such as the similarity in biological pathways and processes between the fish and higher vertebrates. Actually, zebrafish are a perfect One Health model, because the effects we measure in this model fish can be predictive of effects both in humans and in fish in the environment.

It is transparent so you can see everything that happens during development and you can make these kinds of spectacular images such as this one. The wealth of information on the genome, and the wealth of approaches for studying how genes work during development, for example through transgenesis or crispr/cas genome editing techniques, make it a great model. This particular image on the cover of Science of this year is unfortunately not from one of my fish, but it is a spectacular example of how modern single cell RNA sequencing was used to profile thousands of individual cells during early development¹⁴. This technology allows us to understand the fate of each cell during development. The possibilities of this technology for understanding mechanisms of toxicity at cell level are endless.

¹⁴ Two weeks after my lecture, this technology was named the scientific breakthrough of 2018, according to 12000 scientists <https://www.volkskrant.nl/wetenschap/losse-cellen-volgen-is-de-wetenschappelijke-doorbraak-van-2018-volgens-12-duizend-wetenschappers~b2f295de/>

So you can imagine how excited I am that we finally have our fish swimming around in Utrecht, thanks to our collaboration with Dr Rudiger Schulz from the Faculty of Science. I have grand plans for our Utrecht Life Sciences Campus becoming a Centre of Excellence for toxicological research in zebrafish, certainly given the proximity to the Hubrecht Lab, and the imminent move of the RIVM to our campus, with zebrafish toxicologists like my dear colleague Dr Leo van de Ven.

For the coming years our focus is on further developing our zebrafish larval model of obesity, and extending it to an integrated model for the role of chemicals in metabolic disorders. Using multiple transgenic models, PhD candidate Marjo den Broeder will investigate not only the development of the fat cells, but what happens to the regulation of insulin by developmental exposure to chemicals, as well as the metabolism of lipids in the liver. And she will continue to examine underlying epigenetic mechanisms of toxicity within our valued collaboration with dr Leonie Kamminga from Nijmegen.

And I realize this is perfect model to study the role of inflammation and microbiome in metabolic disease, so Professors Johan Garsson and Aletta Kranenveld, I will appear at your door one of these days!

Predictive Toxicology

The second stream of toxicology that our group will focus on in the coming years is predictive toxicology. Predictive toxicology really goes hand in hand with mechanistic toxicology. It refers to the ability to predict and identify effects in a living organism without performing an actual test in the living organism. In other words, it uses computational toxicology, computer modelling and in vitro cell-based testing to predict the toxic effects in an animal.

This approach fits excellently in the 3R paradigm - reduce, refine and replace experimental animal use in toxicity testing. Toxicity and safety testing of chemicals uses a significant portion of the 500,000 experimental animals used in the Netherlands on a yearly basis. Improving our predictions based on in vitro tests and computational models has great potential to bring these numbers down.

Research in the in vitro toxicology group or our division, led by Dr Nynke Kramer, focuses on the key components needed for extrapolating in vitro results in a cell based assay to the complex situation of a living organism. This includes kinetic modelling – where does the chemical go in the in vitro test, how is it metabolized, and how comparable is this to the in vivo situation, as well as development of quantitative adverse outcome pathways for use in risk assessment. This work is nicely complemented by the research of our exposure scientist Dr Chiel Jonker, and his expertise in measuring and quantifying the bioavailable concentrations of chemicals. Nynke is also developing a niche in PBPK modelling in a variety of species, research that benefits greatly from our collaboration with veterinary pharmacologist Prof. Ronette Gehring.

Animal free chemical risk assessment?

Our focus on animal free predictive toxicology fits very well in the ambitions of the Dutch government to become world leader in animal free research and teaching. Our research in this field also aligns with the strategy of Utrecht University, which has been at the forefront of alternatives to animal experimentation for many years, and is recognized for its expertise in 3Rs.

The University has the ambition to reduce animal use in research and education by 80% by the year 2030, and I feel honored to be in a position to help shape this transition. My first year here in Utrecht has been filled with awe by the developments in the fields of organoid culture, regenerative medicine, microfluidics and biofabrication. One examples of these exciting developments is the 3D bioartificial kidney model developed by Prof Roos Masereeuw at the Department of Pharmaceutical Sciences within the Faculty of Science. This model has great potential as a nephrotoxicity model and I will use my part-time appointment at Pharmaceutical Sciences to better get to know this model and other models within the U-AIM HUB and promotor their use and acceptance as alternatives to animal testing in regulatory toxicology.

The ambition to reduce animal use in research and education by 80% is huge. Can we really do this? And how? This brings me to the term I first heard in an inspirational discussion with Prof. Aldert Piersma, reproductive toxicologist at RIVM and IRAS. This term he used was 'evolution or revolution'. Evolution refers to what is now underway in terms of replacing animals in toxicity testing. Though the European chemicals regulation REACH encourages the use of in vitro alternatives, the gold standard is still the rodent study for human health, and the fish study for environmental health. These animal studies are entrenched in law, and a long time is needed to fully develop, validate the in vitro tests we need to replace them, and then to determine their applicability in risk assessment and regulation. In other words, the status quo is evolution.

The alternative to evolution is REVOLUTION! And with Revolution, Aldert meant: Let's do something completely different! Let's skip the animal testing all together! Let's go right to the human or the organism we want to protect! Let's make use of all the advancements in DNA and associated omics technologies from the past decade, let's mine all the knowledge we have on biological pathways involved in health and disease, let's mine all of the clinical and epidemiological data we have and let's design sophisticated computer models to predict if an exposure to a chemical will lead to an adverse effect. This would mean that we would need to integrate all the data we have on biology, the chemical properties of the chemical, and the toxicity data in a big data, toxicology ontology approach.

With the advent of artificial intelligence and machine learning we will be able to develop the algorithms that will integrate these ontologies and accurately predict toxicity. The possibilities of this revolutionary, big data approach to chemical risk assessment have inspired me and will

be one of the focal points of our research in the coming years. We have teamed up with Dr Cyrille Krul of the Utrecht University of Applied Sciences, Dr Anne Kienhuis of RIVM and other members of the U-AIM hub, to bring together a multidisciplinary consortium and develop the contours of the first virtual, truly animal-free chemical risk assessment of the future. A really exciting and ambitious goal, that is forcing us to think about all the aspects of risk assessment, from scientific to legislative to ethical, that would need to be changed if we no longer used the animal test as the gold standard.

Do we need all these chemicals?

So while the possibilities of mechanistic and predictive toxicology within a One Health framework fill me with optimism for the future, I can't help but still feel this nagging shadow looming over me. Even with the promise of artificial intelligence, high throughput screening, the advent of green chemistry, I still worry about how we as toxicologists and risk assessors can ever get a handle on the sheer numbers of synthetic chemicals out there.

As of this morning the chemical abstract service has registered over 144 million unique chemicals in its registry. More than 20000 industrial chemicals have been registered with the European Chemicals Agency. The US claims to have more than 80000 chemicals in commerce. The combinations are endless and their potential health effects are largely unknown. When I'm in a bad mood and troubled, I think to myself: we'll never get to the bottom of all these chemicals in my lifetime, maybe not even in my children's lifetime.

I know my toxicologist friends in the audience would say, "come on Juliette, the fact that all the chemicals are in the environment and in our bodies does not mean they all cause harm. It's the dose that makes the poison". And I agree with them, but all the while still feeling that nagging sensation from the knowledge that we often do not know the dose in our bodies or the concentration in the environment. Or we don't know what the chemicals are. Recently my PhD student Hania Dusza has discovered unknown chemicals with endocrine disrupting properties in the amniotic fluid that surrounds babies during development. This troubles me, makes me feel like David in this picture.

I think many of you were at the Veterinary Science Day about a month ago, where we were treated to an entertaining presentation by Bas Haring, a well-known professor in the public understanding of science. Bas encouraged us to be 'disobedient scientists' and to ask the questions you really want to ask. One of the questions I have always really wanted to ask is 'do we really need all these chemicals?' I don't think that most of us are even really aware of all of these chemicals.

When I asked Prof Derek Muir of Environment Canada, world renowned environmental chemist who has spent years of his life measuring chemicals, making inventories of chemicals and prioritizing which chemicals we should focus on first, he told me of an example of the

short chained chlorinated paraffins, chemical lubricants used in the metalworking industry. When these chemicals were banned due to their persistence and toxicity, industry complained that they were absolutely essential for their industrial processes. However, when forced to look for alternatives, it turned out that they could use water instead!

Are we using all these chemicals just because we can? So I asked the question why do we need so many chemicals to Dr Chunxia Wang, director of research funding at the National Science Foundation of China, thinking about how China produces over 60% of the world chemicals. She answered: producing new chemicals is what chemists do. Chemistry is an important field of science and of course it is of huge economic importance.

But surely we don't need all of these chemicals? Have we lost track of why we created them in the first place and which ones are essential and which ones are not? I will be giving this question a lot of thought in this next stage of my career. I will start to research what we can do now to transition to a world with less chemicals.

I realize that I also need to find more opportunities to talk to the public. Not to scare them, but to increase awareness and to provide the best scientific information possible to educate and motivate people to make their own decisions about the use of chemicals. My recent collaboration with Prof Nico van Straalen got me thinking about the role of the public in the use of chemicals. And this work did make the cover of *Science*¹⁵. Nico and I scrutinized the regulation of glyphosate, the constituent of the herbicide Roundup, probably the most controversial pesticide in the world. Last year, the European Citizens Initiative resulted in over 1 million signatures collected from people across Europe, calling for a stop to the use of this pesticide. We argued in our commentary that we cannot ignore the voice of the public in deciding the use of a chemical. There is a need for societal assessment in pesticide registration, and a need for a broader societal discussion about the use of chemicals.

Involving the public can actually lead to surprising results. I recently had the pleasure to be part of an evaluation committee of KWR water cycle research institute. Not only was I inspired by the research done in the group of Professors Annemarie van Wezel and Pim de Voogt to track chemicals of emerging concern in our water, I was able to hear firsthand about the use of citizen science approaches to get members of the public directly involved in evaluating the quality of drinking and surface water¹⁶. In this example, the water boards opened up and were fully transparent with their clients - the citizens - about the challenges of creating water of good chemical quality. Their clients did not react with concern or outrage as expected. By involving them, citizens actually felt more confident about the quality of their water, and much more aware of what is actually in our water.

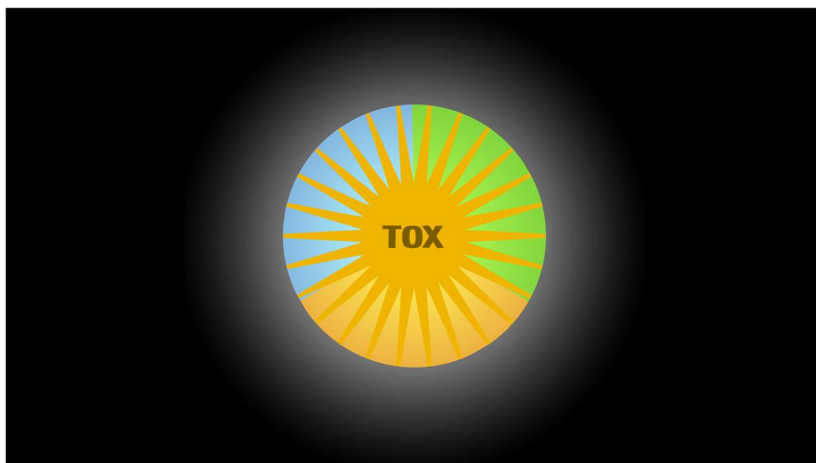
¹⁵ van Straalen NM, Legler J. Decision-making in a storm of discontent. *Science*. 2018 doi: 10.1126/science.aat0567.

¹⁶ Brouwer et al. Public Participation in Science: The Future and Value of Citizen Science in the Drinking Water Research. *Water* 2018 doi:[10.3390/w10030284](https://doi.org/10.3390/w10030284)

So what I've learned about these examples is that in the next few years, in order to answer that nagging question about why do we need so many chemicals, I will need to step out of my comfort zone, communicate more with the public and build a bridge to the social sciences. A bridge that will start at our own Copernicus Institute of Sustainable Development and will hopefully take me to Mexico to the most famous social scientist I know, Professor Thomas Legler (who also happens to be my brother).

So to conclude, I've talked to you in this lecture about the power and promise of the integrated One Health approach. To truly attain One Health, the importance of the environment and environmental exposures to chemicals must be considered in all aspects of health. The Toxicology division at IRAS is on a mission to be world leading in mechanistic and predictive toxicology, a mission that is based on the real interconnections between humans, animals and the environment. My own personal mission to get more to the bottom of the drivers of our chemical use might just turn out to have as much impact as my scientific research. We shall see.

One Health, One Toxicology



Coming back to the title of my lecture, One Health, One Toxicology. I think the future is not only about how toxicology can serve One Health, but also how we toxicologists ourselves can become ONE and in doing so transcend our own

boundaries in our mission to protect health. One Toxicology would mean blurring the lines between human and environmental toxicology, sharing information and expertise across disciplines, and across professions including academia and industry, and no longer working in the silos of human risk assessment and environmental risk assessment of chemicals.

With all this in mind, I proposed the theme of next year's 40th Anniversary conference of the Netherlands Society of Toxicology – innovation through integration. A very exciting programme for this conference is coming together and new ideas are forming¹⁷. This is what happens when you bring people together from different expertise, viewpoints and backgrounds. In working on this conference I've also had the opportunity to work with a group

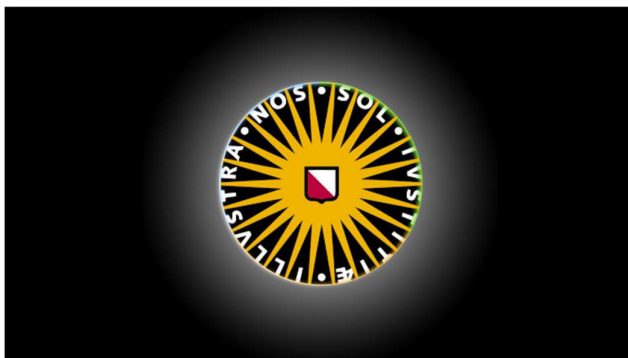
¹⁷ www.toxicologie.nl/meeting2019

of talented PhD students in toxicology from different Dutch universities. Unfortunately I do not have enough time to talk about my plans for teaching and training in toxicology, to keep this field thriving, but when I work with these PhDs I am so impressed by their intelligence, professionalism, creativity, I think the future of our field is in very good hands.

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Acknowledgements

I would like to take to take this opportunity to thank a number of people who mean so much to me in my professional and private life. You have already heard many names during my lecture. These are the names of my colleagues and collaborators and they are all my heroes, to them I owe much gratitude. A few people I haven't



named yet. I would like to thank Utrecht University, in particular Dean Wouter Dhert, for the opportunity I have been given to work here at this inspirational university, I feel truly privileged to be in the position I am. I extend these thanks to Prof Martin van den Berg, who saw something in me already a few years ago and without whose support, I might not be standing here. Also to Prof Dick Heederik and the management team of IRAS, and Prof. Wim Hennink, head of the Department of Pharmaceutical Sciences, many thanks for your warm welcome.

I have to take a moment to thank the people who laid the foundations of my career. My promoter in Wageningen Prof Jan Koeman, and co-promoters Tinka Murk and Bart van der Burg. Unfortunately Jan and Tinka could not be here today. Tinka inspired the environmental toxicologist in me, and Bart was pivotal in introducing me to the world of molecular biology at the Hubrecht Lab. This love for the combination of toxicology and molecular biology has never left me.

I spent almost 15 years at the vrije universiteit Amsterdam, at the Institute for Environmental Studies, now the department Environment and Health. This was an important time in my career, where I had much freedom to develop my research, and where I discovered my passion for teaching and mentoring. I am most grateful to the students, PhDs, postdocs and my former colleagues who enriched my life. I look forward to our continued collaboration.

I spent two years at Brunel University London, and while I didn't stay as long as I expected, I would not want to have missed this experience. I am most grateful to my colleagues at Brunel, in particular my dear friend Andreas Kortenkamp, thank you for joining us today.



This leads me to the present, and the Division of Toxicology at IRAS. As the new leader of this group, I feel I am standing on the shoulders of the giants of the 'Utrechts toxicologie': Herman van Genderen, Joep van den Bercken, Willem Seinen, Bob Kroes, Bas Blaauboer, Joop Hermens, Martin van den Berg. It is a daunting task. But a task made easier because of this fantastic team of dedicated and talented researchers shown here, with such great support from Petra, Evelyn and Ingrid. Also the collaboration with our RIVM colleagues Aldert Piersma and Flemming Cassee is much appreciated. Thanks to you all, and may my 'greenness' help bring out your own true colors.

A special thanks to two special ladies, Hania Dusza and Marjo den Broeder, for continuing to believe in me. For travelling the world with me, despite great personal sacrifice. You can call me anytime, even at 5 in the morning during my holidays!

So a few quick words to my family. First my Saturday morning family. How can something that is so exhausting be so energizing at the same time? In the words of my son who has started kickboxing with me: how can you call the people you punch your friends? Well I do! A warm thanks to Mark Bresser and to all of you die-hards for my weekly dose of laughter, pain and stress relief.

To my real family, my family on my side and my family on Guus' side. Thank you all for being here today, for coming from near and far to support me. Your constant support means so much to me. Just a few weeks ago we lost my dear brother in law Kenny, and it is at those difficult moments like that we realize how important family is and how important being there for each other is.

It all started with these two, my mom and dad, who married 56 years ago on a cold December night in Toronto. Two immigrants from Europe who raised four children in Canada, who would all grow up to be strong, successful and caring people, travel the world and raise talented children of their own. My father is no longer with us, but I feel he is always close, and I just have to look in the mirror to see him. I'm so happy my dearest mom is here today, and I thank you mom, for the way you raised me is what has made me the person I am today.

And last but certainly not least, my dear husband Guus and my children Vincent and Diana. Thank you. Thank you for being so patient with me. I realize I am the luckiest woman in the world to have such a wonderful family and such a wonderful job. I could not do it without you.



So let me end with this beautiful sunny picture taken by my beautiful sunny daughter Diana. You may have noticed that the sun was a common theme in my slides, the sun borrowed from the symbol of this university, and also meant to reflect my own optimistic nature. Despite my critical notes and concerns, I am optimistic about the future of One Health and One Toxicology in responding to the grand challenges of our time. And so as we move in a moment from this historical auditorium to the beautiful Senaatzaal upstairs, enjoy a drink while a multitude of past professors of this university look down on you. Celebrate, feel humbled by the history, but be assured that the future is bright.

Ik heb gezegd!