

# TCDD



TOXICOLOGIE

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SPECIAL THEME

## PETROLEUM TOXICOLOGY

- PETROLEUM-CAUSED AIR POLLUTION AND ITS EFFECTS ON HUMAN HEALTH
- ENVIRONMENTAL IMPACT OF NON-PETROLEUM BASED "BIO" ALTERNATIVES
- CONCERN OVER BENZENE IN PERSONAL CARE PRODUCTS
- ENKELE FEITEN EN MISVERSTANDEN OVER (MICRO)PLASTICS IN ONZE LEEFOMGEVING

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# Editorial

Dear reader,

As a newly appointed member of the editorial team of the TCDD, I would like to introduce myself. I am Ali Dehghani, 35 years old, and I am doing my PhD at the Utrecht University, Faculty of Science, division of Pharmacology, since February 2020. I am doing my research in the field of immunopharmacology by testing the potential toxicity of air pollutants in in-vivo and in-vitro models. Also, I completed my master's degree in occupational health and toxicology at the Shahid Beheshti University of Medical Sciences, Tehran, Iran. My thesis focused on assessing the effect of simultaneous exposure to formaldehyde and noise on oxidative stress in a murine model.

I had the opportunity to work in the toxicology field from in-vitro to human experiments. As a researcher, I worked on projects related to toxicology in the pharmaceutical industry, hospitals, and other industries.

Toxicology is enjoyable as it explores the cause-and-effect relationship through experiment and investigation. It also explores the mechanism of action of chemicals through different pathways in humans and other living organisms.

Being a member of the editorial team of the TCDD, aside from my PhD, is a wonderful opportunity to learn more and discuss toxicology broadly.

In this TCDD, a special focus will be on petroleum-related topics, including air pollution and its effects on human health.

On behalf of the editorial team,

*Ali Dehghani*



## News from the board

Welcome to the May edition of the TCDD! It's hard to believe that this will be my last contribution to the News from the Board, after almost 3 years as president, and having the dubious distinction of being the first president in the history of NVT to lead our society during a pandemic and a war! It has been an honour to work with the NVT board and members in the past years. I will continue to work for our society in the future, to support the best profession in the world, to keep it alive and kicking for generations to come. I was reminded of this again last week, during our new PET course 'Current Topics in Toxicology:' what a diverse, dedicated and talented group of people toxicologists are!

Our annual meeting is only a few weeks away (May 24-25 at Reehorst, Ede) and I am so excited to see you all again in person! The organising committee has put together an excellent programme. The NVT board is looking forward to hosting the closing session on May 24 entitled 'Future proofing NVT: moving our sections forward.' As you know, NVT is made up of seven specialty sections, including Occupational Toxicology, Environmental Toxicology, Genetic Toxicology, Risk Assessment, Teratology and Reproductive Toxicology, Toxicological Pathology, and Pharmaceutical Toxicology. Our sections differ in size and scope. Some sections have many active participants, while others struggle to attract sufficient participants for their activities. Some sections are focussed on specific topics in toxicology while others cover a very broad topic. Addressing the needs of both fundamental and applied toxicologists in the current sections can be a challenge.

In the past year, the NVT board has held discussions with section chairs to query the current status of the sections, and to discuss challenges and opportunities. From these discussions it became clear that it is time to take a good look at our sections, and design a strategy for moving our sections forward in the future. As a starting point, we would like to know more about the opinions of NVT members on the current sections, and hear your ideas on the future of our sections. We will be sending out a survey through the email soon, and hope you will take a few minutes to fill it in. Results of the survey will be discussed at the annual meeting.

I wish all the best to our upcoming president, Prof. Paul Jennings, and have every confidence that the future is bright with Paul at the helm.

Kind regards,

*Juliette Legler*



# Petroleum-caused air pollution and its effects on human health

Exposure to air pollution is one of the top five human health risk factors globally. According to the World Health Organization (WHO) 4.2 million deaths every year occur as a result of exposure to outdoor air pollution. Around 99% of the world's population live in places where air quality levels exceed WHO limits. Although there are some natural sources of urban air pollution, most of the sources are anthropogenic and largely depend on the activities of people (1).

The major anthropogenic activities are transportation, domestic use of fossil fuels, industrialization, power generation, and combustion. Petroleum products provide the majority of energy for all these activities. Petroleum is the main fossil fuel of the two largest energy consuming sectors in the US, the industrial sector (32%) and transportation sector (29%), while the numbers are

different in Europe, with 61.23% in transportation sector and 20.5% in industrial sector (4). The most consumed petroleum product is gasoline, which constituted for about 44% of all U.S. petroleum consumption in 2020.

The quality of urban air is indicated by the quantity of certain gaseous and particulate pollutants in the air, like Ozone (O<sub>3</sub>) (through its atmospheric precursors volatile organic compounds and nitrogen oxides [NO<sub>x</sub>]), Particulate Matters, PM<sub>10</sub>, PM<sub>2.5</sub> (particles < 10 μm and < 2.5 μm in aerodynamic diameter, respectively), Sulfur Oxides (SO<sub>x</sub>), Nitrogen Oxides (NO<sub>x</sub>), Carbon monoxide (CO) and Volatile Organic Compounds (VOCs). Below, we discuss the adverse health effects that are can be caused by the pollutants in urban air.

Transport is responsible for more than two thirds of all NO<sub>x</sub> emissions and accounts for a significant amount of the total emissions of other pollutants in Europe. When petroleum-based products are burned, they release

nitrogen oxides into the atmosphere, which contribute to the formation of smog and acid rain causing the loss of animal and plant life. The most common nitrogen-related compounds emitted into the air by human activities are collectively referred to as nitrogen oxides. Breathing air with a high concentration of NO<sub>2</sub> can irritate airways in the human respiratory system. ►

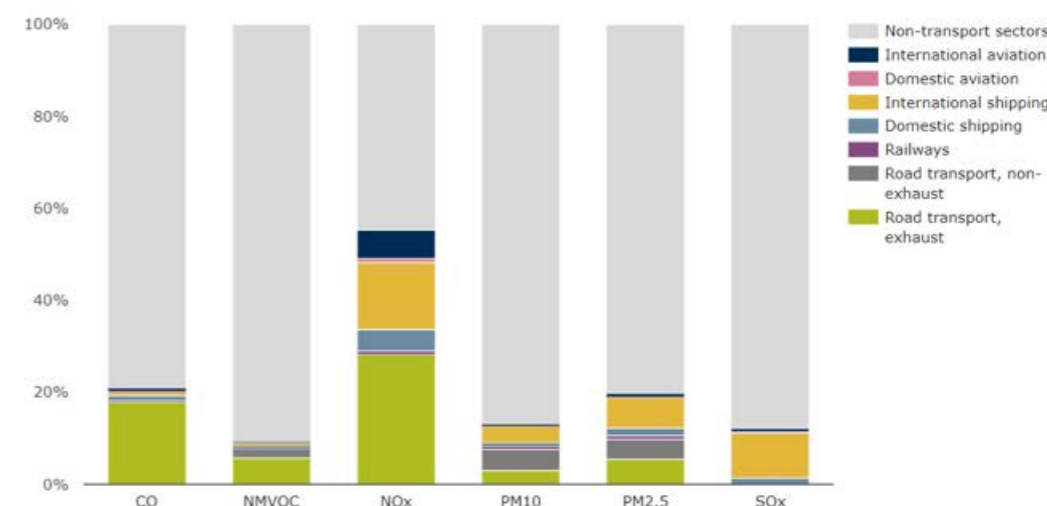


By Ali Dehghani

Figure 1: transportation is the main source of air pollution



Figure 2: Contribution of the transport sector to total emissions of the main air pollutants in Europe (4)



PM pollution is a mixture of solid particles and liquid droplets found in the air and is the largest environmental health risk factor. PM in vehicle exhaust has been declared as a probable carcinogen to humans and also has been linked to various other adverse health impacts. Fine particulates (PM<sub>2.5</sub>) have been reported to be more toxic to humans than larger particles as they can deposit in lower parts of pulmonary system that easily reach the blood circulation. WHO states that both short and long-term exposures to PM has been associated with a wide range of health problems, including cardiovascular disease, respiratory issues, lung cancer, and adverse birth outcomes.

Ozone, the main ingredient in forming smog, is another exceptionally dangerous air pollutant that results from burning fossil fuels. Ozone can cause adverse respiratory effects such as difficulty of breathing (e.g., shortness of breath and pain when taking a deep breath) and inflammation of the airways in the general population.

**Figure 3:** maternal air pollution exposure can worsen asthma symptoms in children



Short-term exposures to sulfur dioxide (SO<sub>2</sub>) can harm the human respiratory system and make breathing difficult. People with asthma, particularly children, are sensitive to these effects of SO<sub>2</sub>. Carbon monoxide is another harmful pollutant that binds to hemoglobin in the blood, reducing the ability of blood to carry oxygen. This interferes with oxygen delivery to the body's organs. The most common effects of CO exposure are fatigue, headaches, confusion, and dizziness due to inadequate oxygen delivery to the brain.

The developing fetus and children are more susceptible to the many adverse effects of air pollutants from fossil-fuel combustion than adults; the developing brain is especially susceptible to the toxic effects of air pollution. This differential susceptibility to air pollution is due to their rapid growth, developing brain, and immature respiratory, detoxification, immune, and thermoregulatory systems. In addition, exposure to air pollution during pregnancy increases risk of premature birth and low birth weight. It will also make children more susceptible to respiratory diseases.

Moreover, the air pollutants emitted from motor vehicles include aldehydes (acetaldehyde, formaldehyde, and others), benzene, 1,3-butadiene, a large number of substances identified as polycyclic organic matter (including polycyclic aromatic hydrocarbons [PAHs]), and metals. Some of these chemicals are classified as human carcinogens (IARC, 2010, 2012) (6).

Last but not least, climate change resulting from petroleum-related pollution affects the geographical distribution of many infectious diseases, as do natural disasters. The only way to tackle this problem is through public awareness coupled with a multidisciplinary approach by scientific experts; national and international organizations

must address the emergence of this threat and propose sustainable solutions.

#### References:

1. U.S. energy information administration. Independent statistics and analysis. <https://www.eia.gov/energyexplained/oil-and-petroleum-products/use-of-oil.php>
2. American geoscience institute. <https://www.americangeosciences.org/>
3. U.S. environmental protection agency. <https://www.epa.gov/nutrientpollution/sources-and-solutions-fossil-fuels>.
4. European environment Agency. 2021. <https://www.eea.europa.eu/data-and-maps/indicators/transport-emissions-of-air-pollutants-8/transport-emissions-of-air-pollutants-8>
5. Handbook of Biofuels, Chapter 29 - Enzymatic and microbial biofuel cells: current developments and future directions. 2022, Pages 551-576.
6. International agency for research on cancer. <https://monographs.iarc.who.int/list-of-classifications/>

# Environmental impact of non-petroleum based “bio” alternatives

Petroleum based goods and products are highly integrated in our daily lives. Even if humanity could settle into a more basic living standard, in which reduced mobility and material needs would be accepted, the need for synthetic materials and resources would stay. Industrial chemicals form the basis of many modern industries, and though natural alternatives may reduce our needs, it is improbable that we could go without. Nevertheless, the alternatives ought to be safe, not only for ourselves but also for our environment.



By Carolien Schophuizen

## Bio-fuel

Petroleum, crude oil and even natural gas can be replaced by alternatives derived from natural materials. Different generations of biofuels are classified based on the sources used for the production (table 1)<sup>5</sup>. Bioethanol and biodiesel are examples of first-generation biofuels made mainly from food crops. Bioethanol is made from starchy foods such as cereals, sugar crops, and biodiesel is made from oil seeds. The second-generation biofuels, can be produced from wood, wood wastes, crop residues, and energy crops such as switch grass. These lignocellulose materials are processed using advanced technologies. The third-generation biofuels encompass those produced from waste materials and fourth-generation biofuels are still under conceptual stage, and based on inexhaustible raw materials.

Table 1: Biofuel generations <sup>5</sup>

Biomass feedstock	1st generation biofuels	2nd generation biofuels	3rd generation biofuels	4th generation biofuels
Vegetable oil	Pure Plant Oil (PPO) Virgin Plant Oil (VPO) Straight Vegetable Oil (VGO) Fatty Acid Methyl Ester: FAME			
Fermentable biomass	Biogas/Substitute Natural Gas			
Starch/sugar	Ethanol/Ethyl Tertiary Butyl Ether (ETBE)			
Lignocellulose		Ethanol Fischer-Tropsch (FT) diesel Dimethyl Ether (DME) Methanol Mixed Alcohols (MA) Substitute Natural Gas: (SNG)		
Waste material			Ethanol Bio gas	
Solar energy				biofuel production (in research level)

In 2009 the RIVM published a report on the toxicity and (modelled) degradability of model substances of the first-generation biofuels<sup>6</sup>. The environmental (bio)degradability and toxicity of biofuels was evaluated. From this research it was concluded that biofuels are relatively easily degradable in the environment, and that their toxicity is limited. However, the additive ethyl-t-butyl ether (ETBE), could pose a problem. ETBE is obtained from bio-ethanol, and it is nearly non-degradable in anaerobic environmental compartments. Moreover, ETBE may migrate freely in the environment, due to its high water-solubility.

Some of the changes caused by the presence of biodiesel and diesel fuel in soil pertain to the microorganisms present<sup>3</sup>. The impact of diesel oil and biofuels on the number and activity of soil microorganisms is not entirely conclusive. Both the growth and reduction of their number have been noted. In an experimental study in which biodiesel was introduced in soil a diverse reaction of the soil organisms was observed<sup>3,4</sup>. In particular, lipolytic and amylolytic microorganisms as well as *Pseudomonas fluorescens* bacteria were sensitive to the presence of fuels, especially biodiesel. Fungi growth was stimulated by the tested fuels, even at a high dose. Though the sensitivity of plants differed between species (e.g. Monocotyledonous sugar sorghum were more sensitive to the presence of fuels than dicotyledonous white mustard), there was a significant negative impact of contamination level on plant growth and development. Biodiesel, to a greater extent than conventional fuel, adversely affected the survival and volume of earthworms. It is yet unclear how the soil toxicity develops over time.

The results from the ecotoxicology test do hint at a possibility that some soil organisms could be applied as toxicity indicators, or used for biological remediation of soils

contaminated with (bio-based) fuels.

### Bio-Plastics

In the struggle against plastic-soup, and plastic litter, bio-degradable or bio-based plastics are already being developed. Of course, there are more alternatives to plastic, such as recycled metal and glass, but these plastic alternatives may fill the needs of some of the world-demand for plastic material. Most bioplastics are corn-based, and for this the farming of crops would also be required. However, are these alternatives also safe, considering the chemicals required for production and exposure of humans to these substances? Recent investigations indicate that bio-based plastics can contain chemicals (i.e. polyethylene (Bio-PE), polyethylene terephthalate (Bio-PET), polybutylene adipate terephthalate (PBAT), polybutylene succinate (PBS), polylactic acid (PLA), polyhydroxyalkanoates (PHA)) that show baseline toxicity, oxidative stress and endocrine disrupting properties when extracted from the parent material<sup>9</sup>. These *in-vitro* toxicities are difficult to translate to in-life situations. Bioplastics are currently mainly applied in agricultural environments and as packaging materials. For example, *in-vivo* toxicity studies in terrestrial ecosystems have shown that: PLA can induce genotoxicity in plants, leaching chemicals could promote phytotoxic effects that affect germination, root development, and plant areal growth and soil bacteria<sup>1, 2, 7, 8</sup>.

The use of bio-based alternatives does come with its own challenges. Of course, there are many more aspects to consider, such as the release of combustion gasses and particulate matter from fuel, the CO<sub>2</sub> impact of petroleum alternatives, human exposure to leachables, and potentially toxic components or impurities that may also be present in naturally sourced materials. Indicating that though these alternatives may be promising, their “bio” status does

not necessarily imply that they are better or safer from a toxicological point of view.

### References:

1. Adhikari, D., Mukai, M., Kubota, K., Kai, T., et al., Degradation of bioplastics in soil and their degradation effects on environmental microorganisms. *Journal of Agricultural Chemistry and Environment*, 2016. 5(01): p. 23.
2. Balestri, E., Menicagli, V., Ligorini, V., Fulignati, S., et al., Phytotoxicity assessment of conventional and biodegradable plastic bags using seed germination test. *Ecological indicators*, 2019. 102: p. 569-580.
3. Hawrot-Paw, M. and Izwiokow, M., Ecotoxicological effects of biodiesel in the soil. *Journal of Ecological Engineering*, 2015. 16(5).
4. Hawrot-Paw, M., Koniuszy, A., Zając, G., and Szyszlak-Bargłowicz, J., Ecotoxicity of soil contaminated with diesel fuel and biodiesel. *Scientific Reports*, 2020. 10(1): p. 1-9.
5. Kularathne, I., Gunathilake, C., Rathneweera, A., Kalpage, C., et al., The effect of use of biofuels on environmental pollution—A review. *Int. J. Renewable Energy Res.*, 2019. 9(3): p. 1355-1367.
6. Peijnenburg, W. and den Hollander, H., Short overview of the toxicity and (modelled) degradability of model substances of the 1st generation biofuels. RIVM letter report 630177002, 2009.
7. Serrano-Ruiz, H., Martín-Closas, L., and Pelacho, A., Application of an *in vitro* plant ecotoxicity test to unused biodegradable mulches. *Polymer Degradation and Stability*, 2018. 158: p. 102-110.
8. Souza, P.M.S., Corroqué, N.A., Morales, A.R., Marin-Morales, M.A., et al., PLA and organoclays nanocomposites: degradation process and evaluation of ecotoxicity using *Allium cepa* as test organism. *Journal of Polymers and the Environment*, 2013. 21(4): p. 1052-1063.
9. Zimmermann, L., Dombrowski, A., Völker, C., and Wagner, M., Are bioplastics and plant-based materials safer than conventional plastics? *In vitro* toxicity and chemical composition. *Environment International*, 2020. 145: p. 106066.

# Concern over Benzene in Personal Care Products

In what seems to be just the tip of the iceberg, multiple recalls of personal care products have occurred in the past two years due to benzene contamination.

Benzene, a well-established human carcinogen, has been found in a wide range of consumer products leading to product recalls and public concern. Naturally occurring in petroleum, benzene can be found in petroleum-derived raw materials used in consumer products. The source of the benzene as an impurity is not always known but it is typically either a residual, a byproduct or a cross-contaminant. As we are exposed to benzene from a wide variety of sources, ranging from outdoor air to food, it is worth examining our exposure to this carcinogen and try to establish limits, where deemed relevant.

Benzene, mainly through its active metabolites including benzene oxide and benzoquinones (figure 1), is a risk factor for acute myeloid leukemia and myelodysplastic syndrome. In the EU, benzene is classified as a category 1A carcinogen and is on the Cosmetics Regulation list of prohibited substances (Annex II)<sup>1</sup>. Though its use is banned, its presence as an unintentional impurity is allowed as long as it is in conformity with the requirement for products to be safe (Article 3). There are no specific limits and it is up to the safety assessor to establish the safety of the product, including the presence of any unavoidable and prohibited impurities. The responsibility of the formulator is to use raw materials with the lowest possible level of impurities that are prohibited substances or avoid them altogether, if that is possible. Moreover, if the information provided by the

raw material supplier is incomplete, as it relates to the level of expected impurities, the end-product must be tested.

The FDA puts a limit of 2 ppm benzene in pharmaceutical products where their use is unavoidable<sup>3</sup>. It was therefore concerning when Valisure, an independent quality assurance laboratory, found multiple sunscreen products containing benzene levels that “significantly surpass” the 2 ppm FDA restriction. The FDA regulates sunscreen products, which are considered nonprescription drugs, in order to ensure safety and effectiveness. Valisure tested 300 sunscreens and found nearly a third to contain detectable levels of benzene. The company also tested 260 hand sanitizers and found nearly a fifth to contain detectable levels of benzene. Valisure later tested antiperspirant body sprays and found that 54% of the samples tested had detectable levels of benzene while “some batches contained up to nine times the conditionally restricted FDA concentration limit of 2 parts per million (ppm).<sup>4</sup>” This led to recalls from Proctor & Gamble Company<sup>5</sup> (figure 2), Blistex Inc.<sup>6</sup>, TCP HOT Acquisition LLC dba HRB Brands<sup>7</sup>, as well as Johnson & Johnson<sup>8</sup>.

Many of the sunscreen ingredients are petroleum-derived and can therefore be a potential source of the contamination. Another possibility is carbomer, an acrylic acid polymer used as a thickening agent, which is sold

in grades using benzene as solvent (source of residual benzene) as well benzene-free grades meant for personal care products. Though not confirmed, it is possible that the wrong grades were purchased to produce the contaminated sunscreens.

Some of the benzene contamination can be linked to COVID-19. As the demand for hand sanitizers increased so did the demand for ethanol, which went to the vast majority of the hand sanitizers. In order to accommodate the demand, a substantial portion of the ethanol came

By Barae Jomaa

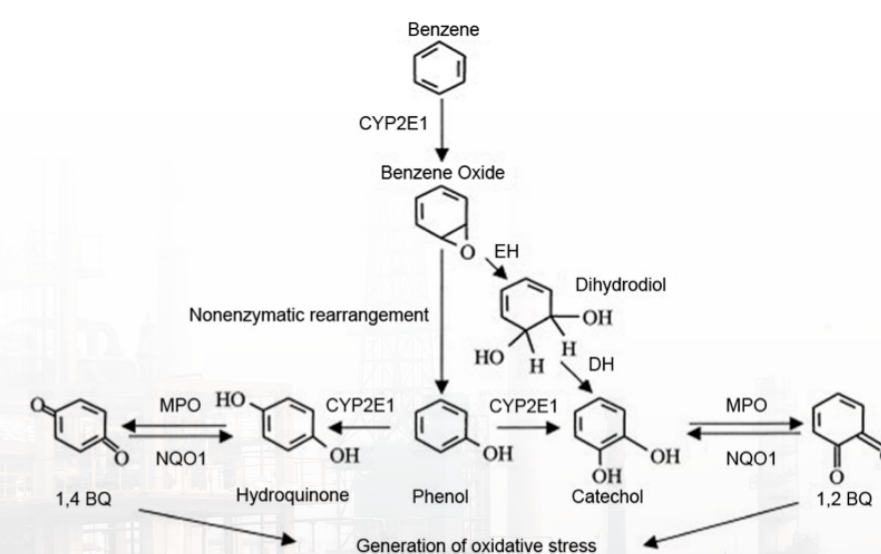
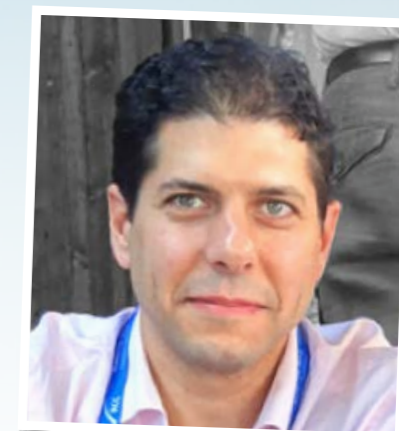


Figure 1: Benzene bioactivation, based on Bauer et al., 2003<sup>2</sup>

from ethanol produced for fuel and therefore provided circumstances where cross-contamination could occur<sup>9</sup>. In terms of body sprays, Procter & Gamble's recall notice<sup>10</sup> mentioned that their "review showed that unexpected levels of benzene came from the propellant that sprays the product out of the can." Many of the contaminated spray products are formulated with butane, isobutene or propane as propellants, which may be derived from petroleum.

Benzene is also found in fragrances and the International Fragrance Association (IFRA) recommends "the level of Benzene has to be kept as low as practicable and should never exceed 1 ppm in the fragrance compound/mixture or fragrance oil."

Unfortunately, benzene exposure through personal care products is not the only source of exposure to benzene. A smoker typically inhales 2 mg of benzene per day as compared to 0.2 mg a day for a non-smoker, making

**Figure 2:** Procter & Gamble recalled several aerosol dry conditioner and aerosol dry shampoo spray products due to the detection of benzene. Image source: Procter & Gamble Company.



smoking the leading source of exposure for individuals in this group<sup>11</sup>. Valisure mentioned that Procter & Gamble's Old Spice Pure Sport (contaminated) antiperspirant spray would contain 28 ppb of benzene in a 1 m<sup>3</sup> cloud. 1 ppb of benzene = 3.2430 µg/m<sup>3</sup> at 20°C<sup>12</sup>, in other words, 90.8 µg of benzene are present in a 1 m<sup>3</sup> cloud. A default value for inhalation is 1.25 m<sup>3</sup> / hour and deodorant spray default exposure duration is 5 minutes based on the RIVM exposure fact sheet. 3 applications totals 15 minutes of exposure. During that period 0.3125 m<sup>3</sup> are inhaled. A worst-case estimate if we consider no ventilation, would be around 30 µg of benzene inhaled per day as a result of antiperspirant spray use. That's more than a tenth of the 0.2 mg a day of benzene inhaled by non-smokers – a potentially significant exposure.

Air concentrations of benzene in the US have been reported as: remote areas, 0.51 µg/m<sup>3</sup> (0.16 ppb); rural areas, 1.50 µg/m<sup>3</sup> (0.47 ppb); and urban/suburban areas, 5.76 µg/m<sup>3</sup> (1.8 ppb). Much higher concentrations are present during the refueling of cars with levels of 3.2 mg/m<sup>3</sup> (1 ppm) having been measured<sup>13</sup>. The Health Council of the Netherlands established that the adverse health effects of benzene "can be prevented by maintaining the concentration of benzene in the air lower than 0.7 mg/m<sup>3</sup> (0.2 ppm), as an eight-hour weighted average concentration."<sup>14</sup>

Over the past two years, it has become increasingly clear that benzene is present all around us, not only in the air we breathe but also in the personal care products that we use on a daily basis. Mounting evidence indicates that chronic exposure is associated with both hematotoxicity and leukemia with no evidence of a threshold. It is therefore likely that there isn't an absolutely "safe" level of exposure with certain subpopulations being at greater risk of chronic benzene poisoning<sup>15</sup>.

### References:

1. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (Text with EEA relevance). OJ L vol. 342 (2009).
2. Bauer, A. K. et al. Genetic susceptibility to benzene-induced toxicity: role of NADPH: quinone oxidoreductase-1. *Cancer Res.* **63**, 929–935 (2003).
3. US FDA. Q3C — Tables and List Guidance for Industry. 10 (2017).
4. Lee, B. Y. FDA: P&G Recalls Antiperspirant Sprays Due To Cancer Risk Of Benzene. *Forbes* <https://www.forbes.com/sites/brucelee/2021/11/24/fda-pg-recalls-antiperspirants-body-sprays-due-to-cancer-risk-of-benzene/>.
5. Research, C. for D. E. and. P&G Issues Voluntary Recall of Specific Old Spice and Secret Aerosol Spray Antiperspirants and Old Spice Below Deck Aerosol Spray Products Due to Detection of Benzene. U.S. Food and Drug Administration <https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/pg-issues-voluntary-recall-specific-old-spice-and-secret-aerosol-spray-antiperspirants-and-old-spice> (2021).
6. Nutrition, C. for F. S. and A. Odor-Eaters® Issues Voluntary Nationwide Recall of Specific Lots of Odor-Eaters® Spray Powder and Odor-Eaters® Stink Stoppers® Spray Due to Benzene Contamination. U.S. Food and Drug Administration <https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/odor-eaters-issues-voluntary-nationwide-recall-specific-lots-odor-eaters-spray-powder-and-odor> (2021).
7. Research, C. for D. E. and. TCP HOT Acquisition LLC dba HRB Brands Issues Voluntary Nationwide Recall of Sure and Brut Aerosol Sprays Due to the Presence of Benzene. U.S. Food and Drug Administration <https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/tcp-hot-acquisition-llc-dba-hrb-brands-issues-voluntary-nationwide-recall-sure-and-brut-aerosol> (2022).
8. Research, C. for D. E. and. Johnson & Johnson Consumer Inc. Issues Voluntary Recall of Specific NEUTROGENA® and AVEENO® Aerosol Sunscreen Products Due to the Presence of Benzene. U.S. Food and Drug Administration <https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/johnson-johnson-consumer-inc-issues-voluntary-recall-specific-neutrogena-and-aveeno-aerosol> (2021).
9. Benzene in Sunscreens & Sun Care Products. HAPPI [https://www.happi.com/issues/2021-11-01/view\\_features/benzene-in-sunscreens-sun-care-products/](https://www.happi.com/issues/2021-11-01/view_features/benzene-in-sunscreens-sun-care-products/).
10. Nutrition, C. for F. S. and A. P&G Issues Voluntary Recall of Aerosol Dry Conditioner Spray Products and Aerosol Dry Shampoo Spray Products. U.S. Food and Drug Administration <https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/pg-issues-voluntary-recall-aerosol-dry-conditioner-spray-products-and-aerosol-dry-shampoo-spray> (2021).
11. Wallace, L., Pellizzari, E., Hartwell, T. D., Perritt, R. & Ziegenfus, R. Exposures to benzene and other volatile compounds from active and passive smoking. *Arch. Environ. Health* **42**, 272–279 (1987).
12. UK Department for Environment Food & Rural Affairs (DEFRA). Conversion Factors Between ppb and µg m<sup>-3</sup> and ppm and mgm<sup>-3</sup>. [https://uk-air.defra.gov.uk/assets/documents/reports/cat06/0502160851\\_Conversion\\_Factors\\_Between\\_ppb\\_and\\_ppm.pdf](https://uk-air.defra.gov.uk/assets/documents/reports/cat06/0502160851_Conversion_Factors_Between_ppb_and_ppm.pdf).
13. Benzene. (World Health Organization, 1993).
14. Ministerie van Volksgezondheid, W. en S. Benzene - Health-based recommended occupational exposure limit - Advisory report - The Health Council of the Netherlands. <https://www.healthcouncil.nl/documents/advisory-reports/2014/02/21/benzene-health-based-recommended-occupational-exposure-limit> (2014).
15. Smith, M. T. Advances in understanding benzene health effects and susceptibility. *Annu. Rev. Public Health* **31**, 133-148 2 p following 148 (2010).

**Figure 1:** Bauer, Alison & Faiola, Brenda & Abernethy, Diane & Marchan, Rosemarie & Pluta, Linda & Wong, Vicki & Roberts, Kay & Jaiswal, Anil & Gonzalez, Frank & Butterworth, Byron & Borghoff, Susan & Parkinson, Horace & Everitt, Jeffrey & Recio, Leslie. (2003). Genetic susceptibility to benzene-induced toxicity: Role of NADPH: Quinone oxidoreductase-11. *Cancer research.* **63**. 929-35.

# Enkele feiten en misverstanden over (micro)plastics in onze leefomgeving

Plastics zijn een belangrijk deel van onze leefomgeving geworden en we omgeven onszelf met steeds meer plastics in allerlei soorten en vormen. De zorg groeit over de mogelijke gevolgen van de toenemende berg plastic voor mens en milieu. Deze zorg wordt deels gevoed door allerlei terechte maar ook onterechte berichten over de aanwezigheid van plastics in onze leefomgeving, waarbij de impliciet uitgesproken zorg vaak niet wordt onderbouwd door gedegen toxiciteitsstudies. Op dit moment bestaan er dan ook nog vele misverstanden over de plastics-problematiek, in ieder geval is duidelijk dat plastics hun nut hebben bewezen, maar helaas is het voor mens en milieu jammer dat plastics veelal weinig waarde hebben nadat ze eenmaal zijn gebruikt.

## Wat zijn plastics eigenlijk?

**Plastics** zijn kunststoffen die bestaan uit lange molecuulketens (polymeren) die voor het grootste deel afkomstig zijn uit de petrochemische industrie. De meest geproduceerde plastics zijn polypropyleen (drinkrietjes), polyvinylchloride (bouwmaterialen), polyethyleen (plastic tasjes) en polystyreen (wegwerpbekers/frietbakjes).

**Microplastics** zijn kleiner dan 5 millimeter en groter dan 1 micrometer. Soms wordt als ondergrens voor de grootte van microplastics 0.1 micrometer aangehouden. Plastics kleiner dan 0.1 micrometer (100 nanometer) worden **nanoplastics** genoemd. Microplastics komen in het milieu terecht door verweren van grotere stukken plastic of door directe uitstoot van deze kleine plastic deeltjes. Het duurt in het algemeen vele tientallen jaren voordat grotere stukken plastic tot microplastics zijn verweerd. Als vuistregel geldt:

hoe kleiner een deeltje, des te gemakkelijker wordt het door mens en dier opgenomen.

## Enkele feiten over plastics

Plastics zijn werkelijk overal om ons heen. Of het nou om harde kunststoffen gaat zoals in het dashboard van je auto of in je iPhone, of om zachte plastics zoals de alom bekende plastic boodschappentas, de drinkrietjes, of zelfs het plastic om één wortel in de supermarkt: overal kom je plastics tegen in een enorme variëteit aan producten. In sommige gevallen gaat het hierbij om toepassingen waar geen gelijkwaardige vervangingen voor zijn, zoals in woningisolatie en in allerlei medische toepassingen. Kijk bijvoorbeeld maar eens rond in het ziekenhuis: overal kom je kunststoffen tegen, van onderzoekshandschoenen tot steriele spuiten en van bloedzakken tot hartkleppen. Dankzij

By *Willie Peijnenburg*

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hun uitzonderlijke barrière-eigenschappen beschermen plastics uitstekend tegen besmettingen.

Bij toepassingen waarvoor in principe wél vervangingen zijn, of waarbij sommige mensen vraagtekens zetten over nut en noodzaak (zoals het plastic om één enkele wortel of komkommer), wordt onder meer geprofiteerd van het gegeven dat plastics goedkoop en in enorme hoeveelheden te produceren zijn. De productie en het gebruik van plastics nemen nog steeds toe en hebben inmiddels astronomische hoogtes bereikt. Zo wordt geschat dat er wereldwijd per jaar meer dan 400 miljoen ton plastic wordt geproduceerd, waarvan de helft binnen 4 jaar weer afval wordt. De grootschalige productie van plastics kwam in de vijftiger jaren van de vorige eeuw op gang. Sindsdien is meer dan 8 miljard ton geproduceerd. Meer dan 6 miljard ton van deze productie is inmiddels weggegooid. En van die enorme berg is 79 % op vuilnishopen of in de natuur beland, terwijl 12 % verbrand is<sup>1</sup>. Slechts 9 % is gerecycled. Zoals gezegd: Plastic heeft nu eenmaal weinig waarde als je het eenmaal hebt gebruikt!

Aan de andere kant wordt steeds vaker de vraag gesteld of we in ons dagelijks leven niet met minder plastics kunnen: is het noodzakelijk om wortels en komkommers met plastic te omhullen, of om microplastics te verwerken in tandpasta en in badschuimproducten. Ook kunnen we ons afvragen ►

of de populaire fleecetruien niet van een ander materiaal gemaakt kunnen worden. De vraag hoe zinvol het is om plastic wegwerptassen door herbruikbare papieren tassen of door andere alternatieven te vervangen, is deels beantwoord door Deense onderzoekers: zij voerden een levenscyclusanalyse (LCA) uit voor verschillende alternatieven van plastic wegwerptassen in supermarkten<sup>2</sup>. Als maat voor de vergelijkbaarheid van de alternatieven voor plastic hebben ze berekend hoe vaak de alternatieven gebruikt moeten worden om eenzelfde milieu-impact te hebben als het gebruiken van een nieuwe plastic draagtas bij elk bezoek aan de supermarkt. Hierbij is uitgegaan van het scenario dat de tassen een volume van 22 liter hebben en gebruikt worden om 12 kilogram aan boodschappen van een supermarkt naar huis te vervoeren. In onderstaande tabel staan de resultaten voor enkele van de meest gangbare alternatieven weergegeven.

**Tabel. Aantal malen dat een alternatief voor plastic wegwerptassen hergebruikt dient te worden voordat het minder invloed op het milieu heeft als een plastic wegwerptas.**

Plastic wegwerptas (referentie)	1
Gerecyclede plastic wegwerptas	2
Gerecycled polyester	35
Bioplastic	42
Gerecyclede PET flessen	84
Ongebleekte papieren tas	434
Katoenen tas	7,100
Milieuvriendelijke katoenen tas	20,000

Deze analyse laat in feite zien dat op basis van milieuoverwegingen zeker het aanschaffen van een (milieuvriendelijke) katoenen tas taboe moet zijn voor iemand die twee keer per week een supermarkt bezoekt. Ook is het onwaarschijnlijk dat het mogelijk is om meer dan 400 keer een papieren tas te hergebruiken.

**Zorgen over plastics**

Alleen al vanwege de enorme hoeveelheden plastics die jaarlijks worden geproduceerd en gebruikt, is het vanzelfsprekend dat we plastics in allerlei soorten, vormen en groottes in het milieu aantreffen. Er zijn nog vele vragen over de effecten die deze plastics hebben op water- en bodemorganismen. Ook is nog grotendeels onbekend of plastics effecten op de gezondheid van de mens hebben. Wél weten we dat plastics persistent zijn in het milieu en dat het tientallen jaren (en wellicht zelfs langer) duurt voordat een wegwerp plastic tas of een plastic drinkflesje verweerd is. Bovendien worden bij deze verwerking kleinere plasticdeeltjes gevormd waarvan aangetoond is dat ze schadelijker zijn dan de oorspronkelijke plastics. Ook blijkt dat de inspanningen om bioafbreekbare plastics te ontwikkelen nog te weinig resultaten hebben opgeleverd om deze op dit moment als een veilig alternatief voor de gangbare plastics te beschouwen. Hierbij zij opgetekend dat het nagenoeg onmogelijk is om een dekkend overzicht te maken van de informatie die steeds sneller beschikbaar komt over het gedrag en de effecten van plastics in het milieu. Dagelijks/wekelijks worden overzichten van de wetenschappelijke vooruitgang over dit onderwerp gepubliceerd, en zelfs is nu het stadium bereikt waarbij er overzichten van overzichten in de wetenschappelijke literatuur verschijnen.

De enorme hoeveelheden plastics die in omloop zijn, tezamen met de onzekerheden over hun veiligheid voor mens en milieu, leiden tot steeds meer zorg. Enerzijds zorg van de burger voor een schone leefomgeving en anderzijds zorg bij de overheid over de duurzaamheid van plastics. Feitelijk doet het er hierbij niet toe in hoeverre plastics schadelijk zijn - de belangrijkste overweging is dat we simpelweg geen persistente stoffen in het milieu willen hebben. Ook willen we geen plastics in ons eten of drinken. Voor zowel overheden als zeker ook voor

allerlei belangenorganisaties is dit reden om te pleiten voor het verminderen van het gebruik van plastics en voor het vervangen van plastics door milieuvriendelijker alternatieven. Op Europees niveau wordt er bijvoorbeeld gewerkt aan de zogenaamde restrictie voor het gebruik van microplastics in producten die in Europa op de markt worden gebracht. Deze restrictie leidt naar verwachting tot een verminderde emissie van microplastics van 500,000 ton in de komende 20 jaar<sup>3</sup>, hetgeen overeenkomt met minder dan 4 % van het totale gebruik in Europa. Nederland heeft zich daarnaast als doel gesteld om te komen tot een veilig en duurzaam gebruik van plastics. Hierbij wordt in het kader van de circulaire economie gestreefd naar hergebruik, terwijl in het kader van de Europese 'green deal in chemical risk assessment' gestreefd wordt naar een niet-giftig milieu waarbij plastics alleen gebruikt worden als het niet anders kan.

Alhoewel plastics al sinds lange tijd gebruikt worden, zijn er nog veel onduidelijkheden over plastics in het milieu, over plastics in ons voedsel, en over mogelijke effecten van plastics op mens en milieu. Het jammere van misverstanden over plastics in het milieu is dat ze de aandacht afleiden van de zaken die écht aangepakt moeten worden om het probleem bij de bron aan te pakken. Daarnaast leiden enkele van de volgende mythes tot acties die als een druppel op een gloeiende plaat beschouwd kunnen worden:

**1 – Plastics zijn niet voornamelijk een water-probleem:** de overgrote berg aan plastic vervuiling is te vinden op de landbodem. Zo wordt er alleen in Europa en Noord-Amerika per jaar al meer dan 800,000 ton op de landbodem gestort terwijl de vracht microplastics naar de oceanen wereldwijd ruwweg 300,000 ton bedraagt.

**2 – In de oceanen drijven géén eilanden van 'plastic soep' rond.** Dergelijke eilanden bestaan niet en niet meer ►

dan ruwweg 1 % van alle plastics drijft in de oceanen, de rest bevindt zich dieper of ligt zelfs op de bodem van de oceanen. Acties zoals het “Ocean clean up” project hebben dan ook voornamelijk een symbolische waarde. Feitelijk doen we nog steeds niets om de bestaande plastic vervuiling op te ruimen.

**3** – Niet alleen de natuur heeft last van plastic vervuiling. Het is als toerist immers niet prettig recreëren tussen plastic afval op het strand, vissers hebben last van plastic in hun vangst, en watergangen kunnen dichtslibben door plastic afval.

**4** – Bioafbreekbare plastics zijn niet per sé de oplossing. Het grote probleem is dat de omstandigheden in het milieu slecht zijn voor de afbraak van bioafbreekbare plastics. Bovendien zijn die plastics niet volledig afbreekbaar. De technologie voor het maken van bioafbreekbare plastics is in ontwikkeling en hopelijk komen er snel volledig bioafbreekbare alternatieven op de markt. Bovendien moet bedacht worden dat bioafbreekbare plastics bijdragen aan de opwarming van de aarde doordat ze omgezet worden in CO<sub>2</sub>.

Tot op heden werd aangenomen dat microplastics te groot zijn om door planten te worden opgenomen om vervolgens in ons voedsel terecht te komen. Dit omdat microplastics simpelweg te groot zijn om door de poriën van plantenwortels te dringen. Recent hebben we voor de eerste keer laten zien dat planten (in dit geval sla en tarwe) wel degelijk microplastics kunnen opnemen<sup>5,6</sup> (zie afbeelding).

Momenteel wordt veel onderzoek verricht naar plastics in het milieu en de gevolgen van deze plastics. Uit dit onderzoek komt geen eenduidig beeld naar voren:

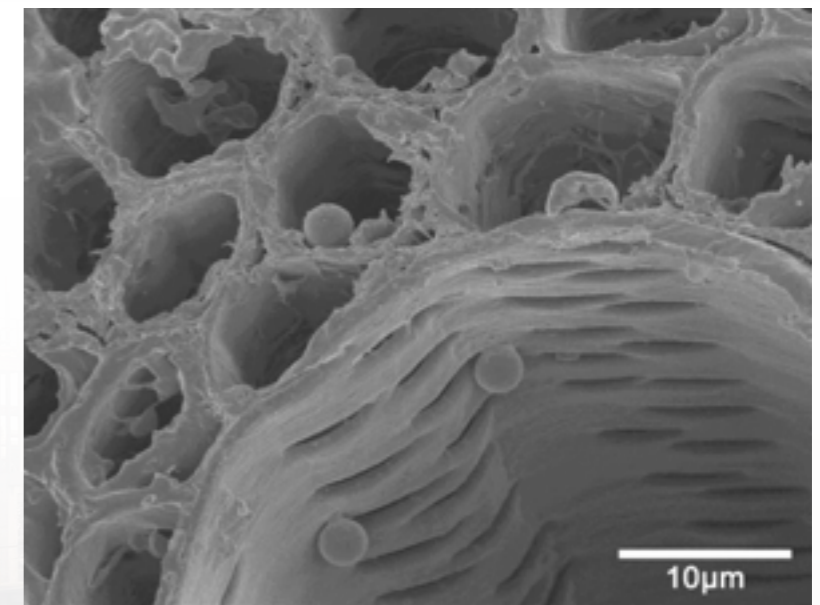
verschillende studies laten zien dat milieueffecten mogelijk zijn maar vaak zijn deze effecten pas waarneembaar bij (irrealistisch) hoge gehalten aan plastics. De volgens de auteurs ‘allereerste’ risicoanalyse van microplastics in oceanen liet bijvoorbeeld zien dat bij de huidige toename van gebruik van microplastics, pas in 2100 sprake zal zijn van duidelijk waarneembare effecten op het ecosysteem in de oceanen<sup>4</sup>.

#### Samenvattend

De grote vraag is of de voordelen van plastics (toepassingsmogelijkheden) opwegen tegen de nadelen (persistente vervuiling met verwachte impact op mens en milieu). Vooralsnog is deze vraag niet te beantwoorden en het is zelfs de vraag of dit antwoord wel nodig is voor het aanpakken van plastics in onze leefomgeving. In de overgang naar een duurzame, meer circulaire gerichte economie, komt steeds meer de overtuiging naar voren dat het niet verstandig is om komende generaties op te zadelen met persistente stoffen die we in een dermate grote hoeveelheid geproduceerd hebben dat ze effecten op mens en milieu kunnen hebben. In ieder geval is duidelijk dat een ieder van ons iets aan het probleem kan doen. Dit kan met name door zorgvuldig om te gaan met plastics en ze alleen te gebruiken als het echt noodzakelijk is. Zoals de levenscyclusanalyse laat zien, moet zelfs dan goed worden overwogen of de alternatieven milieuvriendelijker zijn. Helemaal vermijden van plastics in onze tuin en microplastics in ons eten is helaas een moeilijke opgave, maar we kunnen er zelf wel iets aan doen om de hoeveelheden zo klein mogelijk te maken.

#### REFERENTIES

- 1 - <https://www.scientias.nl/we-al-zon-83-miljard-ton-plastic-gemaakt/>
- 2 - <https://orbit.dtu.dk/en/publications/life-cycle-assessment-of-grocery-carrier-bags>
- 3 - <https://echa.europa.eu/hot-topics/microplastics>
- 4 - G. Everaert, L. Van Cauwenberghe, M. De Rijcke, A. Koelmans, J. Mees, M. Vandegheuchte, C. Janssen. Risk assessment of microplastics in the ocean: Modelling approach and first conclusions. *Environmental Pollution*, 242, 1930-1938, 2018.
- 5 - L. Li, Y. Luo, R. Li, Q. Zhou, W. Peijnenburg, N. Yin, J. Yang, C. Tu, Y. Zhang. Effective uptake of submicrometre plastics by crop plants via a crack-entry mode. *Nature Sustainability*, 1-11, 2020.
- 6 - 352. Y. Luo, L. Li, Y. Feng, R. Li, J. Yang, W. Peijnenburg, C. Tu. Quantitative tracing of uptake and transport of submicrometre plastics in crop plants using lanthanide chelates as a dual-functional tracer. *Nature Nanotechnol.*, 1-10. DOI: <https://doi.org/10.1038/s41565-021-01063-3>, 2022.



**Afbeelding:** Polystyreen microplastics (grootte 2 μ) in de wortels (xyleem) van een tarweplant<sup>5</sup>.

# “Not So Pretty”:

HBO Max's new docuseries focuses on the beauty industry and safety of beauty products.

Not So Pretty is a new HBO docuseries from filmmakers Kirby Dick and Amy Ziering. The four-part series, which will be released on HBO Max on April 14 (in the US, we do not know whether the series is already available in the Netherlands). Actress and influencer Keke Palmer narrates the story. In each episode, light is shed on the perceived hidden dangers of the ingredients in our cosmetics, and the impact they may have on our bodies.



In a scene from the trailer, an expert “reveals” that one of the largest buyers of petroleum is the beauty industry. In another scene, a scientist analyzes several beauty samples to discover that they contain asbestos, a harmful ingredient that can increase the risk of several serious diseases, including asbestosis, mesothelioma and lung cancer. Although this documentary aims to inform the general public about the actual content of the products they use on a daily basis, it is questionable whether the documentary provides a nuanced picture of the hazards versus the risks for the consumer. Nevertheless, it seems like an interesting docuseries to (critically) follow as a toxicologist, and to see how it is received in society.

<https://www.imdb.com/title/tt13142526/>



# Development of an *in vitro* model system to investigate systemic immunotoxicity



By Jasper Koning

Our skin and oral mucosa form a first line of defense against environmental factors. Whereas our skin in general does not tolerate any incoming foreign substances, our oral cavity is trained to tolerate the daily high load of foreign materials. Dental biomaterials are often metal-based and can leach degradation products into the oral cavity. Although in general this is well tolerated and does not lead to oral symptoms, these orthodontic biomaterials can elicit a systemic reaction in predisposed individuals resulting in adverse skin reactions such as skin rash or allergic contact dermatitis. Removing the dental metal from the oral cavity will eventually resolve the problem. This intriguing clinical observation led to this study with the aim to develop a new method for investigating systemic immunotoxicity *in vitro* in human model systems.

Currently, there are many *in vitro* models that allow for testing localized toxicological events on skin and gingiva and these models are used to distinguish between sensitizers and non-sensitizers. The majority of these models are relatively simple, lack immune cells and do not contain the complexity to test interaction between multiple organs.

Within Skinlab in the department of Molecular Cell Biology and Immunology in Amsterdam UMC, we have a longstanding expertise and interest in 3D tissue engineering of human skin and gingiva with the aim to develop *in vitro* models emulating human biology as close as possible that can be used for drug discovery, pre-clinical studies and safety testing. In the past, we developed 3D models for human gingiva as well as human skin with integrated Langerhans cells. Langerhans cells are immune

cells located in the epidermis. When they come across a potentially harmful substance, they transition into an antigen presenting cell and migrate out of the skin (innate immune response) via the lymphatic vasculature towards the draining lymph nodes where they can then present the antigen and induce an immune response. Our reconstructed organ models consist of a differentiated and stratified epithelial barrier which are air exposed and cultured on a fibroblast populated hydrogel. The Langerhans cells are incorporated in the epidermal layer of the reconstructed skin constructs.

Once we had the models, we faced the challenge of culturing 2 physically separated model organs together in a physiological environment that allows for cross-organ communication.

**Paper:** Jasper J. Koning, Charlotte T. Rodrigues Neves, Katharina Schimek, Maria Thon, Sander W. Spiekstra, Taco Waaijman, Tanja D. de Gruijl, Susan Gibbs. *A Multi-Organ-on-Chip Approach to Investigate How Oral Exposure to Metals Can Cause Systemic Toxicity Leading to Langerhans Cell Activation in Skin*. **Frontiers Toxicology** **15 February 2022**. <https://doi.org/10.3389/ftox.2021.824825>

We found the solution in the rapidly evolving multi organ-on-chip technology and used the HUMIMIC chips from TissUse, Berlin, Germany. These platforms allow for the simultaneous culture of multiple organ models in a microfluidic circuit under physiologically relevant flow and tissue to fluid ratios.

We incorporated our reconstructed human gingiva (RHG) and reconstructed human skin models with integrated ►

Langerhans cells (RHS-LC) into the microfluidic device and let them stabilize for 24 hrs. Next, we topically exposed our gingiva model with nickel-ions for 24 hrs and the cultures were left another 24 hrs in the chip before final analysis. We found that the cultures remained stable over time based on glucose uptake and lactate release, retained their histology when compared to skin constructs that were not incorporated in the chip.

Since the aim of this study was to establish a model for systemic toxicity we determined nickel-ions in the circulation beneath both constructs and found that nickel-ions penetrated through the gingiva constructs into the circulation as one would expect to occur in humans. Then the question remained whether these nickel-ions were able to activate Langerhans cells in the skin constructs. Indeed, we observed that Langerhans cells disappeared from the epidermis in the skin construct upon exposure of the gingiva to nickel-ions. How this is mediated remains unknown and requires further study.

Of course, there were limitations to this study. The sample size was relatively low with only 3 independent experiments being performed. The organ models are also relatively small, which limits the number of possible read-outs but the future holds great promise. Incorporation of sensors into chips would ease the workload for monitoring culture stability and the use of multiplex and omics-technologies allow for assessing cytokines and metabolites at larger scale and in small volumes.

Also, the performed study is technically challenging and considerable experience is required to build the constructs. However, this is the first study to describe systemic toxicity

and immune cell activation in a multi-organ setting and can provide a framework for studying other organoids in the future.



**Figure 1:** experimental overview of HUMIMIC multi-organ Chip with reconstructed human gingiva (RHG) and reconstructed human skin with Langerhans cells (RHS-LC). M = medium reservoir

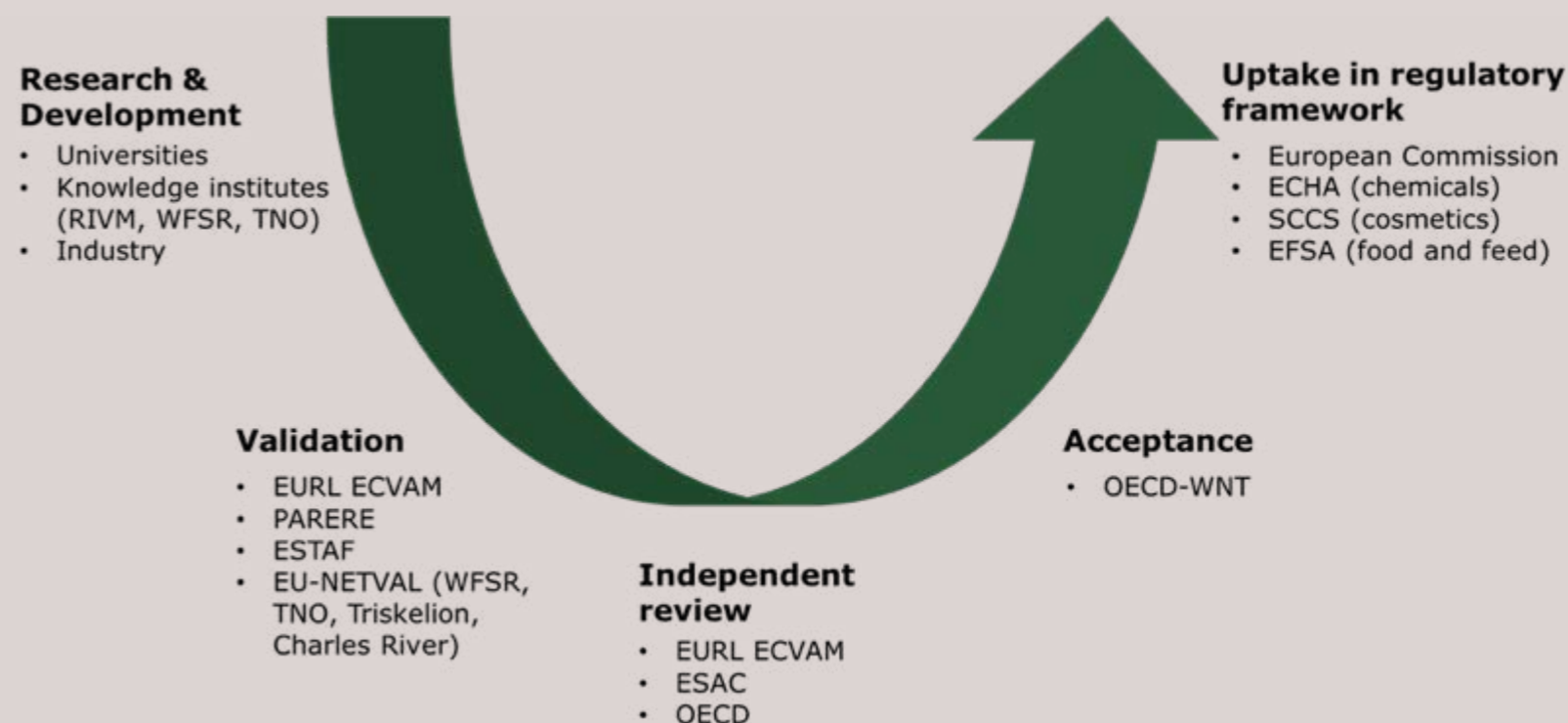
# 5 things you may not know yet about the implementation of New Approach Methodologies in chemical safety assessment

Victoria de Leeuw,  
Jelle Vriend, Lianne de Wit-Bos, Jacqueline van Engelen, Anne Kienhuis

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The field of toxicology and implementation of New Approach Methodologies (NAMs) in chemical safety assessment is slowly evolving. NAMs typically include *in vitro*, *in chemico* and *in silico* methods that could contribute in safety assessment. The idea is that one day these NAMs will replace current animal testing. But how do these NAMs find their way into the regulatory frameworks? Who is involved at each phase and how is the Netherlands represented? We have asked these questions to 27 (inter)national experts to find out.

There are many stakeholders involved in the implementation of NAMs for the safety assessment, including hazard and risk assessment, of chemical substances (see figure). Universities, knowledge institutes and industry are the main drivers for development of NAMs. The next step is to validate a NAM. This, in general, is coordinated by a validation centre. The European validation centre is the EU Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM). Committees consisting of regulators in the Preliminary Assessment of Regulatory Relevance (PARERE) and stakeholders from industry and non-governmental organisations (NGOs) in the ECVAM Stakeholder Forum (ESTAF) are part of the evaluation done at EURL ECVAM. These committees are consulted at this stage to assess the regulatory and user relevance. EURL ECVAM also coordinates the independent review by a scientific committee, EURL ECVAM Scientific Advisory Committee (ESAC), after the validation. After a positive review, the Organisation for Economic Co-operation and Development (OECD) Working group of the National Coordinators for the Test Guideline programme (WNT),



*Implementation curve of NAMs. This curve describes the phases that a new NAM has to pass through from research to uptake in regulatory frameworks. RIVM: National institute for Public Health and the Environment, WFSR: Wageningen Food Safety Research, TNO: the Netherlands Organisation for applied scientific research, EURL ECVAM: EU Reference Laboratory for alternatives to animal testing, PARERE: EURL ECVAM Preliminary Assessment of Regulatory Relevance, ESTAF: ECVAM Stakeholder Forum, EU-NETVAL: European Union Network of Reference Laboratories for the Validation of Alternative Methods, ESAC: EURL ECVAM Scientific Advisory Committee, OECD: Organization for Economic Co-operation and Development, OECD-WNT: OECD Working group of the National Coordinators for the Test Guideline programme, ECHA: European Chemicals Agency, EFSA: European Food Safety Authority, SCCS: Scientific Committee for Consumer Safety.*

which consists of national coordinators of all the member states, can decide to adopt the NAM as a test guideline as the next step in regulatory acceptance. As a final step, this test guideline needs to be taken up in the relevant regulatory frameworks (e.g. for chemicals, cosmetics, food). In Europe, this is up to the member states in the European Commission.

Currently, there are only NAMs implemented for relatively straightforward toxicological endpoints such as eye and skin irritation, skin sensitisation and dermal uptake. NAMs are also implemented in first tiers of carcinogenicity and endocrine disruption testing. However, for most endpoints there are no validated and/or accepted NAMs available yet. In 2017, RIVM published an overview of the steps and (Dutch) organisations involved in the implementation of NAMs, a so-called landscape. Last year, we updated the landscape of New Approach Methodologies chemical safety assessment based on interviews with (inter)national experts. Here are some of the most interesting insights we gained from talking to these experts.

#### **Validation is a flexible process**

While many think validation is a rigid process, it turns out that validation is actually a flexible process. There are no specific rules or protocols that one needs to follow. Strictly speaking, NAMs do not need to be taken through all the steps of the implementation curve. However, for a NAM to become regulatory accepted, the validation principles need to be met, which include robustness, relevance, accuracy, reproducibility and transferability of the NAM(s). The way evidence is gathered for these principles, is up to the one who submits the NAM(s).

#### **We all speak toxicology, right?**

It appears that people working along the implementation

curve do not speak the same language. That is for example illustrated from the definition of validation, which is not well-defined according to some stakeholders, while for other stakeholders it is very clear. While we use the same words, we should be vigilant that the field of NAM implementation is vast and that there is more than one definition for seemingly common concepts. To be on the same page all stakeholders should speak a language that all can understand, e.g. use of the same terminology. In this way, collaboration between all parties can push the implementation of NAMs in the regulatory framework forwards.

#### **Commitment all the way**

Commitment is required from all stakeholders for the uptake of NAMs in the regulatory framework. It is not always clear for all stakeholders how and when NAMs are ready for this. Similarly, changing old habits in regulatory toxicology takes time to build trust and confidence and thus requires long term plans.

Investments for NAMs are highest in the research and development phase, as reflected by the multitude of current research projects and initiatives (e.g. Virtual Human Platform for Safety Assessment (VHP4Safety) and Animal-free Safety assessment of chemicals Project cluster for Implementation of novel Strategies (ASPIS)). However, cooperation and coordination in all phases of the implementation curve seem insufficient to push NAMs to the next level, i.e. from research to validation. Currently, the organisation that wants to validate a NAM needs to fund this, and funding is often not included in research project. Optionally a validation study can be coordinated by EURL ECVAM and laboratories in the EU Network of Laboratories for the Validation of Alternative Methods (EU-NETVAL). A promising trend, though, is the use of case studies in

various research projects that involve various stakeholders, including regulatory authorities already in the research and development phase and that put NAMs to the test according to some but not all the principles of validation.

#### **Willingness towards NAM implementation**

All interviewees are positive regarding the potential of NAMs, and most even see benefits in testing with NAMs over animal testing. Advantages of NAMs include their use for toxicological endpoints or substances for which no proper animal tests are available or possible, e.g. for testing the effects of advanced materials or endpoints like respiratory sensitisation. NAMs could also provide more data using smaller amounts of test substance and gain mechanistic insights. On the other hand, most stakeholders agree that for chronic toxicity the use of NAMs instead of *in vivo* testing is still a long way to go. NAMs do often not yet mimic human biology in such a way that complex toxicological endpoints can be assessed. And even if they do, it is not possible to simply sum up the individual NAMs to assess the safety of a chemical substance. A way to integrate the data from NAMs in a human-relevant biological context is yet to be developed. It is interesting to note that stakeholders have different points of view on timelines in relation to full application of NAMs. The opinions on this are literally multiple decades apart.

#### **And what about society?**

We were asked multiple times “where is society in this implementation curve?”. NGOs represent the general public’s voice through e.g. funding programmes, ESTAF and the OECD. Officially, individual citizens can give input at the end of the validation/independent review step, where there is a moment for public consultation before the ESAC opinion is published. But in practice we can say that using NAMs for safety assessment is not a thing average Joe and Jane ►

talk about. The situation is very different in e.g. the energy transition, where public debate is thriving. Do we want to ignite a similar discussion for safety assessment in the closed field of toxicology to move NAMs forward?

**Conclusion: Technology is not the only driver**

In the past years, sophisticated and promising NAMs have been developed and slowly, but surely, have found their way into regulatory toxicology. We have seen the successful uptake of *in vitro* tests for eye irritation and damage, and skin irritation and skin sensitisation by the OECD. The positive attitude of NAMs in regulatory toxicology is promising but we are still miles away from a full safety assessment based on NAMs. Technology development in the first phase of the implementation curve is important, but multi-stakeholder cooperation in the subsequent phases towards acceptance and uptake is just as important, potentially with a role for society that needs to be further investigated. In the coming decade it would be interesting to see how technology development and acceptance together can work towards better fit-for-purpose NAMs for chemical risk assessment.

Got curious about the landscape? You can download it here ([Landschap New Approach Methodologies | RIVM](#)) from the RIVM website. This is a living document, so any comments on the text or things that are missing in your view can be emailed to [victoria.de.leeuw@rivm.nl](mailto:victoria.de.leeuw@rivm.nl) and [jelle.vriend@rivm.nl](mailto:jelle.vriend@rivm.nl).

# Impressions

## from the SOT Annual Meeting

The SOT conference is something I always look forward to as there is so much information on a wide variety of topics related to the field of toxicology. I attended several sessions on topics that closely fit my own expertise as a researcher at Wageningen Food Safety Research, but I also like how the SOT conference provides me the opportunity to attend sessions outside my own field of expertise to broaden my horizon. The conference was a hybrid event and I attended the virtual side of it. The on-line sessions are convenient and you actually have access to more content as you can watch recorded sessions of parallel sessions, but as with all virtual conferences, I missed the interactions and discussions with other attendants.

This was especially apparent when presenting a poster, so I look forward to attending the next meeting in person again. I was involved in the following two posters that were presented at the SOT conference.

See the following articles ►



By Meike van der Zande



# Transport of Perfluoroalkyl Substances (PFAS) In a Human Induced Pluripotent Stem Cell (hiPSC) Derived Intestinal Epithelial Cell Layer In Comparison With Human Primary Intestinal Epithelial Cells and Caco-2 Cells.

AWF Janssen,  
L Duivenvoorde,  
N Pinckaers,  
B van der Hee,  
A Noorlander,  
LL Leenders,  
J. Louisse,  
M van der Zande

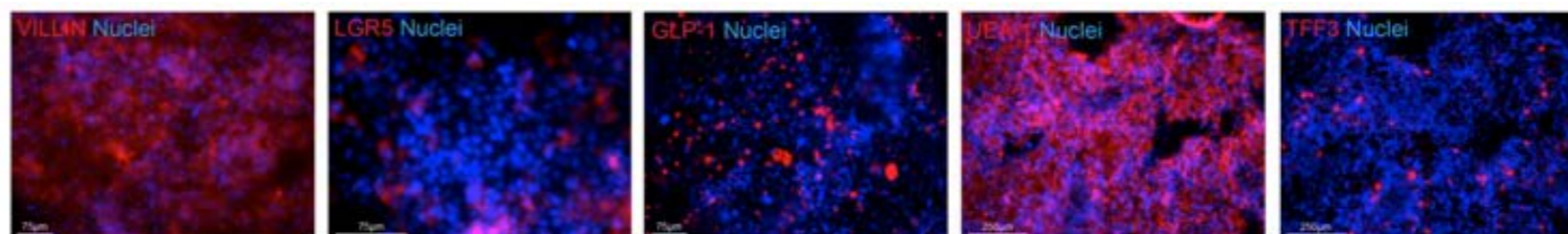
Perfluoroalkyl Substances (PFAS) are chemicals that are used in a wide variety of industries and products. PFAS are persistent and people can be orally exposed to PFAS via diet, which leads to concerns for human health as indicated by EFSA. Toxicokinetics have been studied in human blood, but little is known about the transport of PFAS over the intestinal barrier. Currently, the most widely applied *in vitro* model for transport studies is the human intestinal epithelial cell line Caco-2. However, this model has high transepithelial electrical resistance values, consists of only consists of only a single cell type and lacks a mucus layer. Human induced pluripotent stem cells (hiPSCs) can be differentiated into an intestinal epithelial cell (IEC) layer. This novel 2D *in vitro* model consists of different intestinal cell types that are present in native tissue and facilitates apical exposure for transport studies.

In this study we aimed to first characterize the IEC model, followed by a transport study evaluating 4 PFAS (PFOS, PFOA, PFNA, PFHxS) and GenX. The IEC model was characterized by studying the cellular make-up and gene expression profiles (RNA seq) and by studying the transport properties using six model compounds which were compared with Caco-2 cells, a human primary IEC-based model and human *in vivo* data.

The hiPSC-derived IEC model consisted of enterocytes, goblet cells, enteroendocrine cells and Paneth cells, and contained a mucus layer. The IEC model was able to discriminate between 3 low and 3 high permeable compounds with good comparability between the tested models, but exhibited moderately higher Papp values. PFAS transport in the IEC model (Papp values) was in the following order PFHxS>PFOA>PFNA>GenX>PFOS. Like

for the model compounds, the order of the transport of PFAS was highly similar between the models, where Papp values were highest for the IECs and lowest for Caco-2. Interestingly, the transport of GenX varied between the three models with the highest transport in the IEC model and little to no transport in the other models. In conclusion, intestinal transport of PFHxS was highest in all models and the IEC model has been shown to be a promising *in vitro* model to study transport over the intestinal barrier.

Fluorescence microscopy images of the IEC layer stained for intestinal differentiation marker (VILLIN), stem cells (LGR5), enteroendocrine cells (GLP-1), paneth cells, goblet cells and mucus (UEA1), and mature goblet cells (TFF3).



# Human liver-on-a-chip as a model for biotransformation and chronic toxicity studies

A.A.C.M. Peijnenburg,  
L. Duivenvoorde,  
N. Pinckaers,  
T. Nguyen,  
J. Louisse,  
M. van der Zande

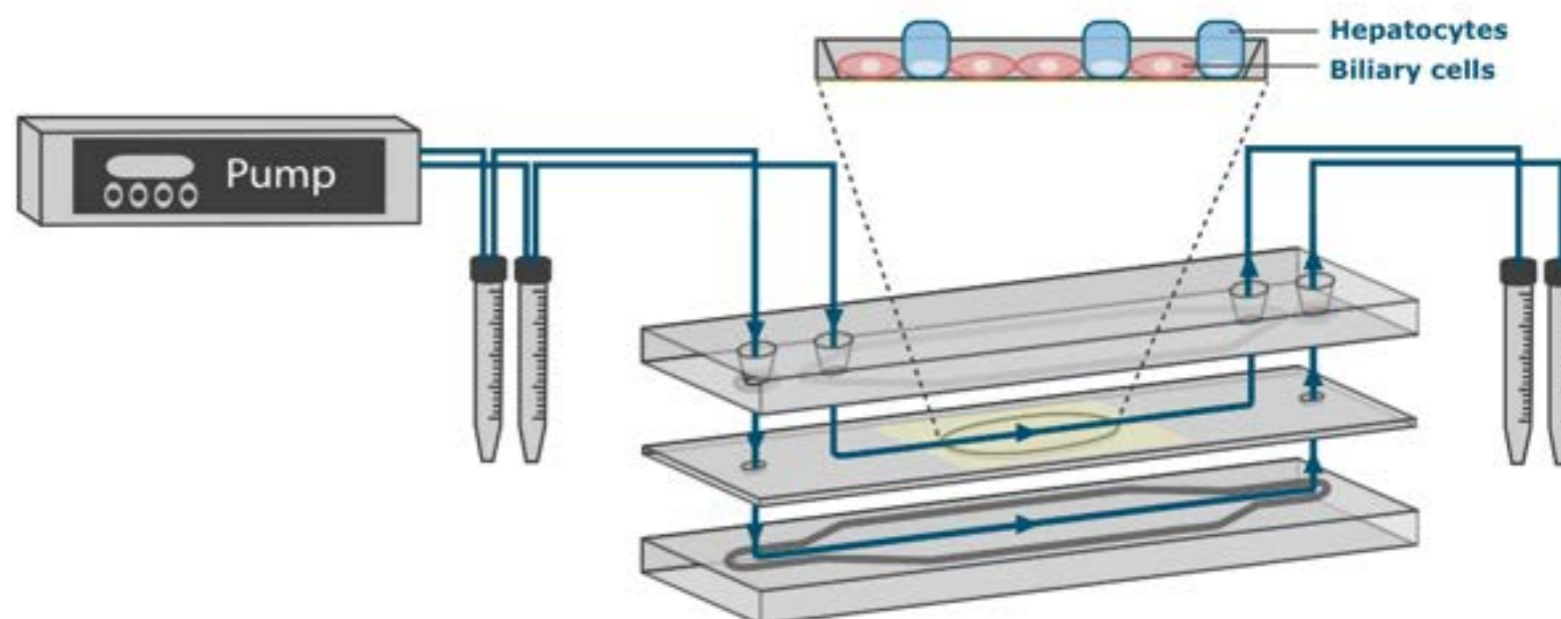
Organ-on-chip (OoC) concepts are promising to improve current *in vitro* models that often fail to mimic organ complexity, and as such may facilitate the replacement of animal models. In the current study, we aimed to develop a liver-on-a-chip model based on HepaRG cells, with a high relevance for biotransformation studies. Flow conditions have been shown to be important in improving longevity and functionality of primary hepatocytes, but the impact of flow on HepaRG cells is largely unknown.

We studied the influence of fluid flow on cell morphology, CYP enzyme activity, CYP inducibility and gene expression of genes encoding CYP enzymes and transporter proteins in HepaRG cells cultured in a microfluidic OoC device during 8 weeks of culture and we compared these parameters with those measured in HepaRG cells cultured under standard static conditions and with those of human primary hepatocytes. Since the OoC-device is a closed system, bicarbonate/CO<sub>2</sub> buffering was not possible, requiring application of another buffering agent, such as HEPES. In order to disentangle the effects of HEPES from the effects of flow, we also applied HEPES-supplemented medium in static cultures and studied gene expression and CYP activity.

We found that cells cultured under fluid flow conditions in the OoC-device, as well as cells cultured under static conditions with HEPES-supplemented medium, showed more stable gene expression levels. Furthermore, cells cultured in the OoC-device showed relatively high baseline CYP1 activity, and their gene expression levels of selected CYPs and transporters were most similar to gene expression levels in human primary hepatocytes. However, there was a decrease in baseline CYP3A4 activity under fluid flow

conditions compared to HepaRG cells cultured under static conditions. In summary, this study shows that HepaRG cells cultured in the OoC-device were more stable than in static cultures, being a promising *in vitro* model to study hepatotoxicity of chemicals upon chronic exposure.

*Design of the OoC-device. The chip consists of three glass layers that are pressed together in a chip holder. The silicone gaskets on the upper and lower slide (that are shown in dark grey) form a leak-free boundary for the apical and basolateral compartment. The blue arrows indicate the flow in and out of the chip. The yellow oval in the middle layer represents the porous membrane on which the HepaRG cells are grown. (Duivenvoorde et al. Scientific Reports, 2021; <https://doi.org/10.1038/s41598-021-89710-6>).*



# 2022 SOT Annual meeting

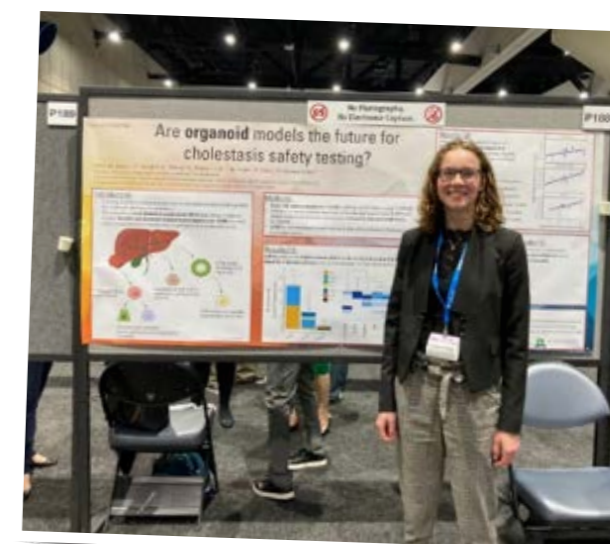
## (San Diego, US), 27th – 31st of March, 2022

Currently available preclinical *in vitro* and *in vivo* models are only about 50% predictive of cholestatic drug induced liver injury. Cholestasis is a subset of drug induced liver injury and refers to an impeded bile flow from the liver to the sinusoids. The subsequent accumulation of bile acids is toxic for the hepatocytes. In order to study cholestasis, one would need a hepatic *in vitro* model with the ability to emulate human liver functionality to synthesize and secrete bile acids. In our study, we uniquely compared two well established *in vitro* models, namely HepaRG cells and Sandwich Cultured Human Hepatocytes (SCHHs), and thirdly, an organoid model. We performed bile acid profiling of 18 different bile acids using LC-MS/MS and we evaluated gene expression of selected target genes in the *in vitro* models. The organoids produced (very) low amounts of bile acids compared to HepaRG cells and SCHHs, and also the gene expression of the target genes was more different from a liver biopsy than the gene expression profiles of HepaRG cells or SCHHs. From the results we have to say that the organoids used here cannot serve as a better *in vitro* alternative for cholestasis testing than HepaRG cells or SCHHs.

During the conference I got many valuable insights. Firstly, it was really inspiring and fun to finally meet fellow toxicologists from outside WUR-TOX. At WUR-TOX, we are highly focused on developing New Approach Methodologies, and it was eye opening to see how many *in vivo* studies are still being performed today. We had some discussions with toxicologists who performed *in vivo* studies, and talked about possible *in vitro* alternatives. One scientist who studied developmental toxicity in rats pointed out that he had tried 12 different *in vitro* tests and none of these tests gave good results. This indicates how crucial animal testing still is in the safety assessment of chemicals. We have a long road to go before we can fully replace

animal tests, and for some fields of toxicology this road is more challenging than for others.

I was also introduced to the application of artificial intelligence (AI) in risk assessment of chemicals. The importance of a good training dataset was pointed out several times, because AI predictions are as good as the training dataset. Throughout the years a lot of data has been gathered which could be used for a training dataset, but a lot of the data is not accessible. After proper data curation, I definitely see how AI could be a part of the (early steps of) safety assessment of chemicals.



By *Véronique de Bruijn*,  
Wageningen University & Research

Lastly, we attended a talk about the importance of protein binding. The amount of protein in exposure medium, whether it is BSA or serum or another source, determines how much of a chemical actually enters the cell. In physiologically based kinetic modeling, protein binding is already taken into account, but also for *in vitro* exposures it is important to consider how much of the compound actually enters the cell, or just be sure to add a physiological amount of a protein source.

My take home message from the conference is the urge to standardize New Approach Methodologies, so they can become a robust and reliable replacement for animal testing.

Although I “planted” some trees to compensate the CO<sub>2</sub> emission from the flight, I cannot claim that the event was climate neutral. However, I am currently combining the conference with a road trip in the US, which has been on my bucket list for multiple years, so I am saving out that one flight!

# Society for Research on Nicotine and Tobacco (SRNT) 2022 annual meeting

Baltimore, MD, United States of America, 15-18 March 2022

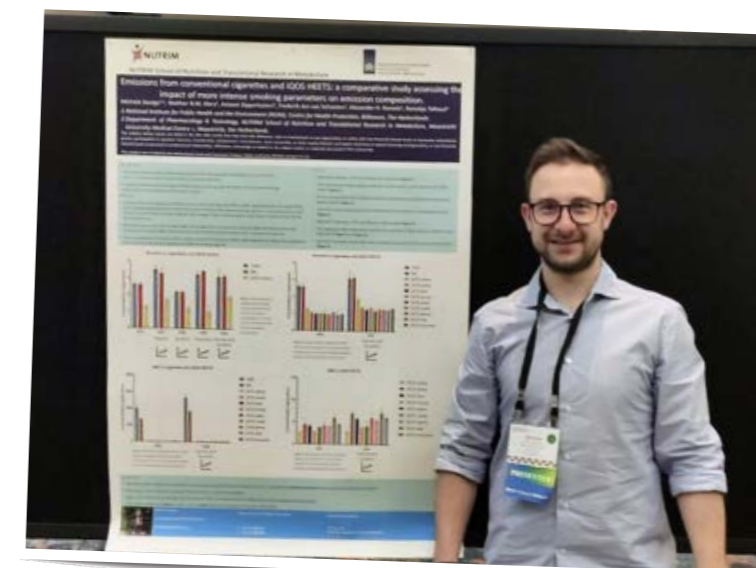
## What the presentation was about

The heated tobacco product iQOS is gaining more and more popularity worldwide, due to the industry claims of reduced toxicity. However, a detailed chemical characterization of iQOS emissions is lacking. In this study, emissions from two conventional cigarettes (CCs) and from nine iQOS HEETS were compared applying Health Canada Intense (HCI) and a total of four more intense smoking topographies. In such more intense regimes, puff volume, puff duration and puff frequency were systematically increased. The concentration of nicotine and four tobacco-specific nitrosamines (TSNAs) were quantified in the emissions of all products.

All the assessed iQOS HEETS delivered around 55% less nicotine and 95-98% less TSNAs than cigarettes. Of note, aerosols from the assessed iQOS HEETS showed significant differences in TSNAs levels, likely due to their different tobacco composition and the presence of flavorings. Higher puff volume and puff duration majorly impacted iQOS HEETS emissions, whereas CCs emissions were mainly affected by higher puff frequency.

## The three most interesting learning/insights taken from the conference

SRNT 2022 gave me the opportunity to properly meet a relatively new research field: during this 4-days conference, I could learn the latest insight in nicotine and tobacco research, and also meet colleagues from all over the world working in these research areas. A very interesting oral presentation introduced the concept of third hand smoke (THS) and discussed its health impact on human and mice lung. When a cigarette is consumed, residual chemicals (including nicotine) are left on indoor surfaces, and they form THS. Such chemicals are potentially harmful to humans once they are touched, and can induce severe health effects. Mice exposed to THS for one month only showed increased levels of circulating inflammatory cytokines, and tumor-promoting factors compared to unexposed mice.



By Michele Davigo, Maastricht University,  
Department of Pharmacology and Toxicology

Another very interesting talk addressed the epidemiological diffusion of tobacco and cannabis use, and mainly investigated the reasons for co-use of these products. This study unraveled that young Hispanic/Latino Americans have the highest change to develop co-use of tobacco and cannabis addiction, mainly due to their economic and social status.

A very significant and charismatic person I had the pleasure to meet at SRNT 2022 is Jamie Brown, from the department of Epidemiology and Public Health of University College



London. In his very interesting poster, he showed the results of a meta-analysis to associate smoking status with SARS-CoV-2 infection, hospitalization and mortality from COVID-19. Interestingly, this study unraveled that current smokers appear to be at reduced risk of SARS-CoV-2 infection, while former smokers appear to be at increased risk of hospitalization, increased disease severity and mortality from COVID-19.

A new highly relevant technique that was presented at SRNT 2022 involved a two-items approach to classify use of tobacco, alcohol or marijuana. For instance, people that consumed five or more drinks in a row on one or more days were rated 1, as well as participants that used tobacco and/or marijuana at least once in the past 30 days. By contrast,

individuals that did not show any tobacco or marijuana-related dependency or did not drink alcohol in the last 30 days were rated 0. Albeit very simple, this approach allows to numerically cluster the individuals, in order to obtain detailed information of their dependency status of tobacco, marijuana and/or alcohol.

#### Scientific “take home message” from this conference

SRNT 2022 showed the need for a worldwide cooperation to reduce tobacco and cannabis consumption, and that dependencies are highly affected by the social and economic status of the individuals.

#### Ways the conference organization and presenter strived to make the conference a climate neutral event

All the cutlery and glasses offered at SRNT were produced from recycled material, and the used items were collected to undergo a subsequent recycling step.

#### REGISTRATIE CIE

## Inschrijving Register

Voorletters	Achternaam	Datum inschrijving	Datum afloop registratie
I.M.	Omwenga	12-04-2022	12-02-2027
E.E.J.	Kasteel	12-04-2022	12-02-2027
E.J.P.	Hermans	12-04-2022	12-04-2027
S.	Yang	12-04-2022	12-04-2027
J.	Odink	12-04-2022	12-04-2027
J.E.F.	Nicolas	12-04-2022	12-04-2027

## Inschrijving TiO

Voorletters	Achternaam	Opleider	Datum inschrijving
N.E.T.	Pinckaers	Prof.dr. F.G.M. Russel	12-04-2022
L.	Zheng	Prof.dr.ir. I.M.C.M. Rietjens	12-04-2022
R.M.L.	van Deun	Prof.dr. F.G.M. Russel	12-04-2022

# AIO toxafette -Lei Wang

In the toxafette, PhD-students working in the toxicology field get the chance to open up about their experiences in performing research. Every issue a new candidate answers a series of questions, and then pass the baton to a fellow PhD-student. This time Lei Wang from Utrecht University takes the stand.

## Can you introduce yourself?

My name is Lei Wang and I came from China. I am at the end of my PhD research at the Utrecht University, Pharmaceutical science department and Pharmacology division. My PhD-project is about COPD and comorbidities.

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

COPD is a complex chronic inflammatory lung disease in which patients also experience other comorbid diseases besides the symptoms in the lung. These can include metabolic disorders, muscle weakness, cognitive disorders and intestinal symptoms. Cigarette smoking and exposure to pollutants are major causes for COPD. However, currently there is no treatment to cure COPD. Therefore, it is very important to find a way to relieve the symptoms and decrease the incidence for developing comorbidities. Our project employs a cigarette smoke exposure induced murine model to investigate the potential link of lung and other organs, especially in the gut-lung axis. It will guide us to find more therapeutic solutions in future research.

## What was your motivation to start a PhD program?

First of all, since I was doing my masters in the lab, I found that I really enjoy the academic environment. This motivated me want to continue with doing research. Secondly, the more knowledge I gain, the more I want to discover and learn new things. Last but not least, the enthusiasm to improve career prospects in my field motivated me a lot to start a PhD program.

## Why did you choose a subject in toxicology?

Actually, my main major is pharmacology, however, toxicology is the study of the adverse effects of chemicals on living systems. It is very important for us to know the potential mechanisms and effects before investigating the potential therapeutics. In addition, toxicology provides critical information and knowledge that can be used by regulatory agencies in preventing diseases and other health outcomes.

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

There will be more novel research focusing on the disease's underlying mechanisms, epidemiology and therapeutic management. Hopefully future researchers and clinicians will use their knowledge to help more patients.

## Would you consider qualifying yourself as European Registered Toxicologist (ERT), why or why not?

Yes, I would like to consider to qualify myself as European Registered Toxicologist. I would like to join because I would like to improve my career development and support development and education within the field of toxicology.



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

I would like to continue with academia by doing a postdoc. If there is a nice opportunity, I can also consider going to another country.

## If everything is possible, what would you like to do during your PhD?

I would like to do many things during my PhD. In short, I would be very interested in some collaboration with clinical trials. In addition, I would like to experience some exchange with other research institutes and join conferences to communicate more about research.

## What question do you propose for the next candidate?

If everything is possible, what do you want to do with the knowledge you have gained from performing your PhD-research?

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

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

