NUMMER 44
MEI 2025

TCDD
TOXICOLOGIE

SPECIAL THEME

Occupational safety matters

- THE LONG ROAD TO SAFE WORK: A HISTORY OF OCCUPATIONAL HEALTH
- WORKPLACE TOXINS: A HIDDEN OBSTACLE TO STARTING A FAMILY
- A FUTURE IN WHICH PEOPLE NO LONGER BECOME ILL FROM SUBSTANCES THEY ARE EXPOSED TO AT WORK

NEDERLANDSE VERENIGING VOOR TOXICOLOGIE

Colofon

Toxicologische Communicatie, Data en Documentatie (TCDD)

Bestuur
Voorzitter
Frederik-Jan van Schooten, *Maastricht University*

Vice-Voorzitter
Paul Jennings, *Vrije Universiteit Amsterdam*

Secretaris
Hester Hendriks, *Rijksinstituut voor Volksgezondheid en Milieu*
Yvonne Staal, *Rijksinstituut voor Volksgezondheid en Milieu*

Penningmeester
Laura Hondebrink*, NVIC, UMC Utrecht*

Lid
Hans Bouwmeester, *WUR*
Anne Kienhuis, *Rijksinstituut voor Volksgezondheid en Milieu*
Joanne Salverda, *Nouryon*

Secretariaat
Secretariaat Hester Hendriks,
Rijksinstituut voor Volksgezondheid en Milieu
Postvak 1, Postbus 1, 3720 BA Bilthoven
E-mail: secretaris@toxicologie.nl

Redactie
Héloïse Proquin, *National Institute for Public Health and the Environment (RIVM)*
Damiën van Berlo, *National Institute for Public Health and the Environment (RIVM)*
Marcha Verheijen, *Maastricht University*
Jelmer Faber, *Maastricht University*
Barae Jomaa, *Colonial Chemical*

Webredactie
webmaster@toxicologie.nl

Lidmaatschap en Adreswijzigingen
Ledenadministratie NVT, p/a KNCV
Postadres: Loire 150, 2471 AK, Den Haag
tel. 070 - 337 87 97
Via NVT website na inloggen
http://www.toxicologie.nl
E-mail: administratie@toxicologie.nl

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

Contributie NVT
Incl. abonnement TCDD 50,= euro
(extra kosten EEMS: 10,= euro)

Indien u ervoor kiest zelf uw contributie over te maken, dan worden € 5,- administratiekosten in rekening gebracht.

Sluitingsdata kopij 2025
September 12, 2025,
November 14, 2025

Kopijbus
redactie@toxicologie.nl

Website NVT
http://www.toxicologie.nl

Vormgeving
Marleen Mulder
Green Bean Design
www.greenbeandesign.nl

TCDD
TOXICOLOGIE

Inhoud

4 Editorial/redactioneel

5 News From the Board

7 Nieuws van de secties

10 Obituary - John Parsons

Special Theme: Occupational Safety Matters

11 The Long Road to Safe Work: A History of Occupational Health

13 Workplace Toxins: A Hidden Obstacle to Starting a Family

15 A future in which people no longer become ill from substances they are exposed to at work

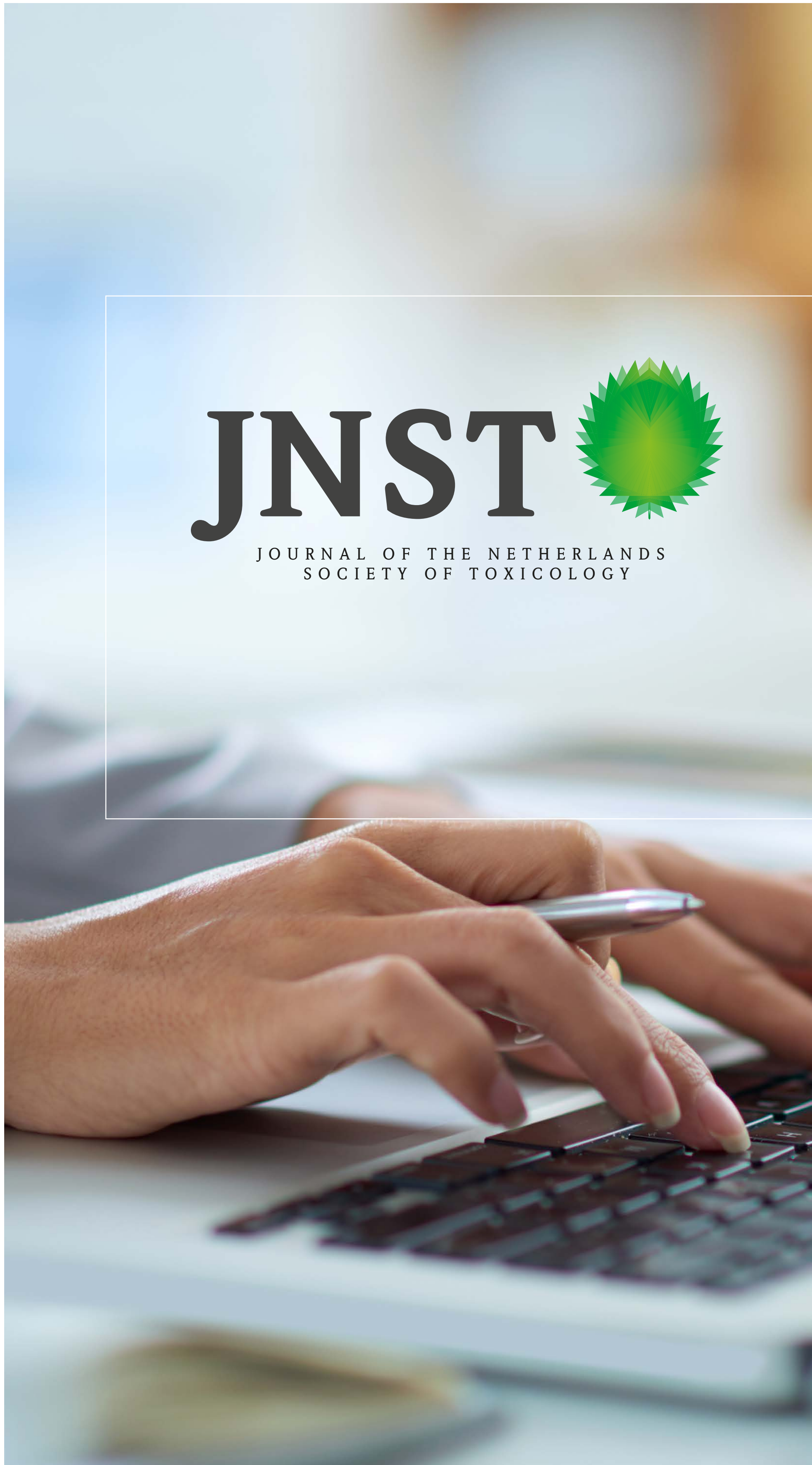
17 Perspectives in Toxicology - Animal Testing for PROTACs & Molecular Glue Degraders: Necessity or Not?

19 Toxafette Vaios Fytsilis

21 Events and announcements

Journal of the Netherlands Society of Toxicology

22 Fluoridation Under Fire: Health Risks or Benefits to Public Health?



Submit your paper!

Call for submissions

to the Journal of the Netherlands Society of Toxicology

- Submissions can be made through ScienceOpen.
- A free account must be made with ScienceOpen prior to submission.
- Author guidelines can be found by following this link: Journal of the Netherlands Society of Toxicology – ScienceOpen.
- There is no deadline for submission.
- Once the submitted papers are accepted and have completed the peer review process, they will be available online and the journal entries will be appended to the TCDD.

Editorial

In this edition, we will discuss occupational health and the application of toxicology to chemical hazards in the workplace. We will start with the history of occupational health: did ancient Egypt or Greece know about workplace health risks? Did they put in place some preventative measures? We continue by discussing pregnant women in factories. They are usually forgotten and yet they are key to the healthy renewal of the population. The program Lexces will also be described. We did not forget about the usual toxafette, this time by Vaios Fytsilis.

We wish you a good read and we will meet again after the summer.

Sincerely,

Héloïse Proquin

Photo by Jess Bailey on Unsplash

A message of solidarity

Summer is coming! And with it comes new energy and inspiration. Let's take a moment to reflect on what binds us: a shared passion for toxicology and a drive to make a positive impact through science.

The Netherlands Society of Toxicology (NVT) is deeply alarmed by recent developments under the current U.S. Administration that threaten the future of environmental research and public health.

Significant staff reductions at key agencies - including the U.S. Environmental Protection Agency (EPA), the Department of Health and Human Services (HHS), the Food and Drug Administration (FDA), the National Institute for Occupational Safety and Health (NIOSH), and the National Institutes of Health (NIH) - risk dismantling critical scientific infrastructure. These institutions are essential for ensuring clean air and water, drug safety, and the protection of both environmental and occupational health. Furthermore, reports of funding cuts to leading research institutions are a cause for deep concern.

Equally troubling are the recent actions aimed at halting or restricting programs related to diversity, equity, and inclusion (DEI). The NVT strongly believes that diversity enriches the scientific community, and that equity and inclusion are vital for fostering innovation, collaboration, and progress in research.

These measures not only endanger American scientific excellence, but their impact will echo globally. Science transcends politics and borders - it is fundamental to protecting both human and environmental health worldwide.

The NVT expresses its strong solidarity with our U.S. colleagues. Your work matters profoundly, and we support your continued ability to conduct the excellent science upon which we all depend.

Prof. Dr. F.J. van Schooten

On behalf of the Board of the Netherlands Society of Toxicology

NvT Annual Meeting

June 4-5, 2025

Our annual meeting is only a few weeks away – June 4–5 at Congresscentrum De Reehorst in Ede – and I am so excited to see you all again in person! The organising committee has put together an excellent programme centered on the timely theme "From Lab 2 Law: Bridging the Gap from Science to Policy."

As the role of science in policymaking comes under increasing pressure, this meeting will explore how toxicological research can continue to inform effective regulation. Toxicology has real-world impact in protecting human, animal, and environmental health, and this is our moment to highlight that.

Please join us to show not only the strength but also the fun and energy of our society – I look forward to seeing you there!

Future Proofing and Interest Groups
We're pleased to share that NVT members will be invited to join a German-Dutch Interest Group on Endocrine Disruption, following recent discussions between the NVT Board/Future Proofing and our sister organization, the German Society of Toxicology (DGT). Keep an eye on your email for more information and an invitation to express your interest. This initiative also offers a valuable opportunity to explore the concept of interest groups for other topics in the future.

Wishing you a great summer! Let's keep working together to make toxicology open, relevant, and fun.

SECTIE MILIEUCHEMTOX

Analytical Solutions

3 juni 2025

Op 3 juni a.s. vindt het Analytical Solutions congres plaats met het thema "Artificial Intelligence Solutions for Laboratory Technology" en de MCT-sectie verzorgt wederom deel van het programma, waaronder keynote spreker Anneli Kruve (https://www.analyticalsolutions.nl/). Hier zal ook de tweejaarlijkse proefschriftprijs voor het beste proefschrift binnen de milieuchemie en toxicologie worden uitgereikt. Het congres is in De Reehorst, op de dag voorafgaand aan de jaarlijkse NVT-meeting op dezelfde locatie. Een mooie gelegenheid om beide bijeenkomsten mee te maken!

Na de succesvolle edities in 2022, 2023 en 2024 organiseert de MCT-sectie, in samenwerking met de UvA, VU, WUR en de Universiteit Antwerpen, een vierde PFAS-symposium. Dit keer in Amsterdam op donderdag 25 september 2025. Iedereen die geïnteresseerd is in het voorkomen, lot en blootstelling aan PFAS in het milieu, bioaccumulatie en de mogelijke eco(toxico)logische risico's van PFAS is van harte welkom. Registratie opent binnenkort (https://mct.kncv.nl/en/mct-detailpage/1449/4th-environchemtox-symposium-on-pfas/about).

Door *Milo de Baat, Assistant Professor in Water Quality & Ecotoxicology, University of Amsterdam*

SECTIE ARBEIDSTOXICOLOGIE

Presentaties van het middagsymposium "Een batterij aan nieuwe risico's? Gevaren van lithium-ion batterijen op de werkvloer" online beschikbaar

Op 20 maart 2025 organiseerde de sectie Arbeidstoxicologie in samenwerking met de Contactgroep Gezondheid en Chemie (CGC) een middagsymposium over risico's van lithium-ion batterijen. Tijdens deze bijeenkomst kwamen achtereenvolgens een introductie op de werking en samenstelling van lithium-ion batterijen, resultaten van brandexperimenten, informatie over acute gezondheidseffecten en de praktische omgang met batterijen in de afvalverwerkingssector aan bod. De presentaties van dit symposium zijn te vinden op de website van de CGC: 20 maart 2025 - Een batterij aan nieuwe risico's? - Contactgroep Chemie en Gezondheid. Op deze webpagina zal ook een uitgebreid verslag van de bijeenkomst beschikbaar komen.

Het volgende symposium van de CGC is op 19 juni 2025. Dit wordt georganiseerd in samenwerking met de Nederlandse Vereniging voor Arbeids- en Bedrijfsgeneeskunde en heeft als titel "Je gaat het pas zien als je het doorhebt".

SECTIONS PHARMACEUTICAL
TOXICOLOGY & RISK ASSESSMENT

Summary of the symposium:
extractables and leachables: a concern for your health?

The symposium started with a short introduction by **Daan Touw**, who presented a few pictures of thoracic X-rays which showed that even implants after a certain amount of time could show lesions, in other words: parts of the implants had disappeared.

In hospital pharmacies, ready-to-administer drugs are prepared by filling plastic syringes with solutions of these drugs. This is done to reduce the work of the nursing staff, especially for operating rooms and for Intensive Care units.

Since plastic syringes are designed for one-time-only use within a limited timeframe (usually 24 hours), syringes must be qualified for their new intended use and storage.

The Dutch Association of Hospital pharmacists (NVZA) has published guidelines for this qualification (Appendix 2; GMP-z3). This monograph includes different tests to study leakables and leachables.

These tests comprise different testing solutions such as NaCl 0.9% and glucose 5%. Also, the time is specified.

The following aspects are studied: Appearance (Clarity, colour and visible particles), pH, Weight of the syringe (Any permeation?), Subvisible particles. The content must meet the requirements for parenterals. Further, the presence of silicone oil is tested (Syringes contain silicone oil as a lubricant) and closure integrity is tested.

An example of such a product is: Fentanyl 0.05 mg/ml in syringes. Primary packaging material is tested and was qualified. However, after one year of storage the product was out of specification (many leachables visible using HPLC-DAD analysis)! Is this related to fentanyl or is this related to our syringes?

This needs thorough investigation, for example using HR-MS or GC-MS. For many hospitals, however, this is not possible.

This illustrates that the filled product needs to be included in the qualification of the syringes.

In the second presentation (**Yolanda Ponstein**), it was shown how the risk assessment of compounds which were detected in a medication was done in real practice. The presenter made clear what kind of considerations had to be taken into account in order to reach a conclusion on the safety of the complete product.

After a coffee and tea break, in the third presentation (**Bianca van de Ven**), leachables from food contact materials and products in contact with drinking water were shown. All types of materials and all types of substances will make contact with food, ranging from plastic, metals (cans), coatings (pans), colorants (inks on packaging) and rubber/silicone (sealing rings), to name just a few, and these can migrate into the food.

There is European legislation for certain materials or substances (e.g. bisphenols, nitrosamines, etc) with the aim to protect the consumer, and cut-off levels for substances that migrate into food; but a fact is that there are still gaps in this legislation.

There are several systems in place to ensure the good quality of drinking water, but the reality is that compounds can also migrate into drinking water (from pipes, tubes, fittings, taps, etc). There is collaboration between several European countries in order to harmonise the systems.

In the last presentation (**Albert Feilzer**), it was shown that also in dentistry there are several scenarios in which exposure to foreign materials takes place. Apart from food and drinks, also medications, cosmetics and medical devices come in contact with the oral cavity. This was described as: “the mouth is a battle ground where biological, chemical and physical forces interact constantly”. Due to the multitude of mechanisms, it was shown that also orally applied metals are subject to deterioration. Even gold will eventually dissolve to some extent, and it is possible to measure this in the body. But of more concern is that certain metals which are known to cause allergy (e.g. zinc, chrome) are also included in most dental crowns, and will eventually leak, potentially causing allergic adverse events like rash, oedema, etc.

There is legislation all over the world, but the challenge lies in the fact that each region/country has their own separate registration process, resulting in differences in testing protocols. The EU Medical Device regulation is a unified framework which applies to all EU members states. A device which is approved will get a CE mark, to make visible that the product complies with EU regulations.

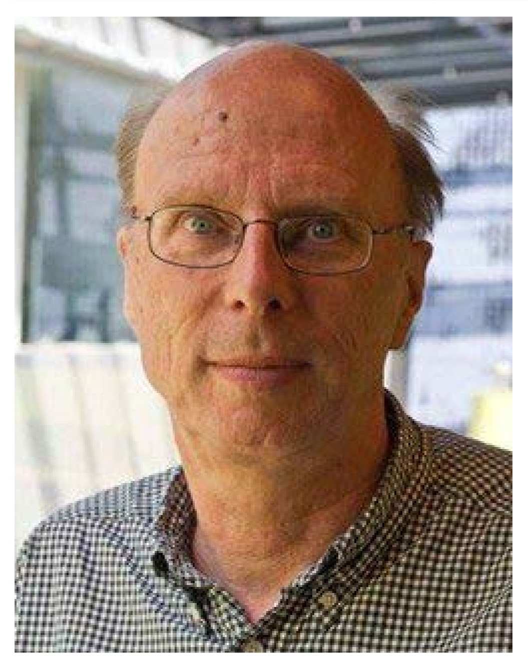
Despite all the regulations, there are still improvements possible: e.g. nickel has been almost completely abandoned from cosmetics, but is still present in e.g. medical devices, and even stainless steel might contain 10-14% of nickel. The overall message was that leachables can lead to adverse effects, but often it might be difficult to recognize this effect. You only see it, when you are looking for it.

The symposium was concluded with a Panel discussion, moderated by **Marjolijn Woutersen**.

All together a very interesting session, which was an eye-opener for many of us.w

Dr. John Parsons

In memory of Dr. John Parsons, a former board member of MilieuChemTox and a friend. John was nationally and internationally known for his great expertise in environmental chemistry. He will always be remembered for his drive and dedication to his work and his colleagues, as well as for being a very kind colleague with a good sense of humour, a love of music, and great scientific curiosity.



He has been an active and dedicated board member of MilieuChemTox for thirteen years. MilieuChemTox is the professional association for environmental scientists, a fusion of the KNCV Environmental Chemistry section, the NVT Environmental Toxicology section work, and the field of Geochemistry in the Netherlands. He helped to share knowledge and strengthen the profession. It has been a real pleasure to work with him and to have him on our team for so many years

John Parsons' research interest was on the sorption, biodegradation and bioavailability of persistent organic pollutants (POPs) and his expertise in these fields was recognized internationally. At the University of Amsterdam, John led and participated in several large EU projects. He also contributed to building a bridge between environmental chemistry and ecotoxicology, testing both the environmental fate and effects of compounds. He was the prime supervisor of many successful PhD studies and students loved John´s erudite knowledge of the microbial biodegradation of chemical pollutants.

John also greatly contributed to many scientific publications and the Open Online Textbook on Environmental Toxicology, generously sharing his knowledge with all of us.

After his formal retirement in 2018, John remained active as a scientist, regularly visiting the University of Amsterdam to discuss research results with students and colleagues. He joined the Dutch ARES group (Association of Retired Environmental Scientists) in 2019, where he became very active in projects dedicated to defining persistence, including the development of the Persistence Assessment Tool (PAT) software to support the regulatory evaluation of chemicals.

With his open and enthusiastic curiosity and energy, he successfully motivated students to contribute, collaborate, and become active in the field of environmental science. John was a great scientist and a very humble and kind man. He will be greatly missed and remembered. Our thoughts are with his family, colleagues, and friends.

Obituary as originally published in November 2024 here: https://mct.kncv.nl/k/en/n3288/news/view/217900/156167/obituary-john-parsons.html

The Long Road to Safe Work: A History of Occupational Health

By *Héloïse Proquin*

In order to know where we are going, it is important to know where we come from. We all wonder if occupational health started with the industrial revolution or if we were aware of some dangers before that.

WHEN DID PEOPLE MAKE THE LINK BETWEEN OCCUPATION AND DISEASE? AND WHEN DID WE START TO DO SOMETHING ABOUT IT?

As early as the 4th century BC, Hippocrates described symptoms of lead poisoning in a metal worker[1]. Furthermore, Egypt, Greece and Rome recognized some forms of occupational diseases affecting miners who were engaged in one of the oldest industries[2,3]. In ancient Greece and Rome miners used bags, sacks, animal bladders as masks to decrease dust exposure[3].

The Egyptians had doctors called "sounou" paid by the society. The Egyptians could receive a free treatment from them during expeditions and journeys[2].

During the Middle Ages, medieval craftsmen, such as masons, faced risks from handling caustic substances like lime, which caused skin burns and diseases. Some masters provided gloves for protection, but many workers laboured bare-handed[4]. Additionally, as mining became more industrialized, workers were further exposed to toxic metals such as lead and mercury. The dangers of mining, including exposure to dust and fumes, were recognized, though not systematically studied until later[5].

The enlightenment on occupational diseases started with the industrial revolution. In 1700, an Italian physician, Bernardino Ramazzini, published the results of his comprehensive studies in *De Morbus Artificum Diatriba* (Diseases of Workers) which described an association between irritating chemicals, dust, metals and other abrasive agents covering 54 different occupations like bakers and millers[6]. Later, in 1761, John Hill reported an association between snuff, a tobacco product, and nasopharyngeal cancer. In 1775, Percival Pott, an English surgeon, identified a high incidence of scrotal cancer among chimney sweeps, linking it to soot exposure[7]. This was one of the first epidemiological studies to associate a specific occupational exposure with cancer, leading to early legislation aimed at reducing occupational disease[3].

The 20th century brought significant institutional advances. In 1912, Thomas Legge published principles of control and proposed the first British occupational exposure limit for lead[8]. Subsequently, pioneering research was done on mercury and lead intoxication, silicosis, and the health effects of organophosphorus insecticides. These efforts led to the development of industrial hygiene laboratories and the design of instruments for monitoring workplace exposures.

By the mid-20th century, occupational toxicology had become a recognized scientific discipline, closely linked with industrial hygiene, occupational medicine, and regulatory policy.

WHICH ARE THE MOST KNOWN OCCUPATIONAL DISEASES?

A few worth mentioning occupational diseases are described below. Some of them helped to introduce more safety to the workers and bans of certain products.

The case of the "Canary girls"[9]
During the First World War, over one million women were employed in the munitions industry. Three hundred deaths occurred due to explosions (silk clothing being banned to prevent the occurrence of static electricity). The manufacture of tri-nitro toluene (TNT) involved the use of nitric and sulphuric acids, the fumes from which turned both skin and hair yellow (hence 'Canary Girls'). Toxic jaundice was reported in 400 women with 100 deaths occurring. Pregnancy in these women gave rise to yellow 'Canary Babies'.

The case of the "Radium girls"
Also during the First World War, in 1917, the US Radium Company produced a radium-infused paint which was used to paint numbers on clock and watch dials that glowed in the dark. Women undertaking this work would lick their brushes to produce a fine point and some developed jaw abnormalities, severe anaemia, leukaemia, and sarcomas. Some of these clocks and watches are still on the market and can be sometimes found in flea market.

The case of Asbestos
Asbestos exposure in the construction industry was very common in the past. Already in 1930, Mereweather and Price[10] found that the greater the exposure to asbestos fibres the greater the risk of developing mesothelioma. By 2015 a total of 157,000 persons were recorded as having asbestosis, with 3600 deaths.

The case of pneumoconiosis and silicosis[9]
Respiratory disease from breathing dust dates back to ancient Greece. Agricola in 1556, reported lung problems from dust inhalation in miners, and these have been known in history as miner's phthisis, grinders asthma and potter's rot. The pneumatic hammer drill (1897) and sandblasting (1904) led to an increase in silicosis, and by 1990 the number deaths in miners due to pneumoconiosis in the UK reached 29,000. Moreover, pneumoconiosis and silicosis have been associated with an increased risk of tuberculosis, lung cancer, scleroderma, systemic lupus erythematosus and rheumatoid arthritis in these occupations.

WHAT ARE THE EMERGING OCCUPATIONAL RISKS?

Some emerging occupational risks are yet to be clearly defined. For example, workers now have to dismantle batteries of cars, and these batteries are not fully empty while they are doing this. Therefore, they are at high risk of an electric shock and/or an explosion.

Another example would be related to the exposure to nanomaterials and/or advanced materials. These products are more and more used in many different settings, but the exposure risks are not clear yet.

The last example would be related to climate change and heat stress from rising temperatures. This could render 2% of global work hours unsafe by 2030, particularly in agriculture and construction. In many countries, no regulation exists for the workers regarding the maximal temperature they are allowed to work outside. Extreme weather and air pollution increase risks of respiratory diseases and accidents.

We have come a long way from the first descriptions of symptoms of mining-related lead poisoning in a metal worker by Hippocrates to now workers working with good safety protections. We can see that occupational health grew up with the desire to improve employee well-being. And it still needs to keep on growing, with the protection of all types of workers.

References:

[1] Wattenberg, E. V. (2014). Occupational toxicology. Encyclopedia of Toxicology (Third Edition). https://doi.org/10.1016/B978-0-12-386454-3.00045-2

[2] Ziskind B., Halioua B., (2007) Occupational medicine in ancient Egypt, Medical Hypotheses, Volume 69, Issue 4, https://doi.org/10.1016/j.mehy.2007.02.014.

[3] GA, A. E. A. (2012). Development of the international and Egyptian occupational diseases' lists-review. Egyptian Journal of Occupational Medicine, 36(2), 215-237.

[4] https://www.etui.org/sites/default/files/2021-05/HM23_Medieval%20craftsman%20builders%20%E2%80%94%20a%20fragmented%20history_2021.pdf

[5] Coleman, M.D. (2014). A brief history of occupational toxicology. In Expert Report Writing in Toxicology, M.D. Coleman (Ed.). https://doi.org/10.1002/9781118432365.ch1

[6] Franco G, Franco F. (2001) Bernardino Ramazzini: The father of occupational medicine. Am J Public Health. 91(9):1382. doi: 10.2105/AJPH.91.9.1382

[7] Brown JR, Thornton JL. Percivall Pott (1714-1788) and chimney sweepers' cancer of the scrotum. Br J Ind Med. 1957;14(1):68–70. doi: 10.1136/oem.14.1.68.

[8] https://www.bohs.org/information-guidance/what-is-occupational-hygiene/history/

[9] Petts D, Wren M, Nation BR, Guthrie G, Kyle B, Peters L, Mortlock S, Clarke S, Burt C. (2021) A short history of occupational disease: 2. Asbestos, chemicals, radium and beyond. Ulster Med J. ;90(1):32-34.

[10] Merewether, E. R. A., & Price, C. W. (1930). Report on Effects of Asbestos Dust on the Lungs and Dust Suppression in the Asbestos Industry. Part I. Occurrence of Pulmonary Pibrosis and Other Pulmonary Affections in Asbestos Workers.

Workplace Toxins: A Hidden Obstacle to Starting a Family

By *Marcha Verheijen*

In any given workplace, whether it's a hospital, a lab, a farm, or a factory, the conversation about occupational safety often centres on acute injuries, ergonomic risk, or respiratory protection. But what about fertility? What about the long game, the subtle, cumulative, and sometimes invisible impact that our work environments may have on our ability to start a family?

Over the last few decades, science has quietly built a compelling case. Work-related exposures can impact reproductive health in profound and often overlooked ways. Fertility problems affect roughly 10–15% of couples globally, and while lifestyle factors like smoking, alcohol, or age at conception are well-known factors, workplace and environmental exposures deserve a seat at the table too (Snijder et al., 2012).

Time to Pregnancy

"Time to pregnancy" (TTP) is one of the most accurate epidemiological indicators of reproductive health (Winker & Rüdiger, 2006). It's simple: how long does it take a couple to conceive once they start trying? Prolonged TTP isn't just a fertility red flag. It's been linked to increased risk of adverse pregnancy outcomes and may hint at deeper issues in reproductive toxicology (Snijder et al., 2012).

Systematic reviews show that exposure to certain chemicals, like **lead and pesticides**, is strongly associated with increased TTP. Agricultural and horticultural workers, for example, may face significantly higher fertility risks, yet are rarely offered proactive counseling or protection unless pregnancy is confirmed, which is often too late (Snijder et al., 2012).

Other substances with confirmed or suspected reproductive toxicity include **organic mercury compounds, carbon disulfide, manganese, glycol ethers**, and **2-bromopropane**. Dibromochloropropane (DBCP), once used as a pesticide, became infamous after it was linked to irreversible infertility in male workers and swiftly pulled from the market (Winker & Rüdiger, 2006).

The Blind Spots in Regulation

And yet, most chemicals in the workplace have **never**

been tested for reproductive effects (McDiarmid & Gehle, 2006). Even when exposure limits (like MAK and BAT values) exist, they are typically designed around general toxicity, not reproductive endpoints. That leaves a glaring hole in our regulatory safety net. In fact, many of the substances with known reproductive risks, like glycol ethers in cleaning agents, perchloroethylene in dry cleaning, or antineoplastics in healthcare, are still widely used in sectors with large numbers of women of reproductive age.

This highlights a more uncomfortable truth. **Protecting only pregnant workers is insufficient.** Many substances, especially lipophilic ones, can accumulate in the body and pose a risk **before pregnancy even begins**, during the crucial early weeks of embryonic development, often before a person even knows they're pregnant (Ove-Hansson & Schenk, 2016).

And let's not forget the other half of the equation. **Preconception exposures in men** — from heat and vibration in professional drivers to chemical exposures in welders and painters — have also been implicated in poor sperm quality, hormonal disruption, and even increased risk of birth defects in offspring (Winker & Rüdiger, 2006; Ove-Hansson & Schenk, 2016).

Not Just About Pregnancy
Occupational reproductive toxicology isn't just about conception. For pregnant workers, exposure to solvents, anesthetic gases, and anti-cancer drugs can increase the risk of miscarriage, malformations, or poor neonatal outcomes (McDiarmid & Gehle, 2006). Postpartum, the concerns continue. Many organic solvents and pharmaceuticals absorbed by the mother are excreted in **breast milk**, meaning return-to-work timing and protections are critical for lactating parents as well.

Toward Smarter, Fairer Protection
One regulatory tension in this space is how to protect reproductive health **without discriminating**, particularly against women. Historically, some well-meaning policies have backfired. By singling out women for special restrictions, they inadvertently reinforced stereotypes and limited job access. That's why experts increasingly advocate for **"unified protection"**: a baseline level of workplace safety that is robust enough to cover all sensitive subpopulations, without isolating or penalizing any one group (Ove-Hansson & Schenk, 2016).

And it's not just about chemicals. **Heat, noise, stress, vibration, magnetic fields** — all of these have been linked to reproductive risks but remain poorly regulated. Reproductive toxicology demands a multidisciplinary approach, blending epidemiology, endocrinology, occupational health, public policy, and yes, social justice.

Where Do We Go from Here?
So, should a couple trying to conceive or a pregnant woman stay home for their own safety? Well, the home isn't always a safe haven either. **Pesticides, herbicides, and rodenticides** are among the most common chemical toxicants found in domestic environments. Even if not applied directly by the pregnant person, these chemicals can be tracked indoors on shoes, clothing, or equipment, posing a secondhand risk (McDiarmid & Gehle, 2006).

Secondhand smoke is another major concern. It contains polycyclic aromatic hydrocarbons, which are known carcinogens and have demonstrated reproductive toxicity in animal studies. These compounds can cross the placenta and even enter breast milk, posing risks throughout pregnancy and into the postpartum period (McDiarmid & Gehle, 2006).

Then there's **home remodelling** — an activity that may seem benign but often involves serious reproductive hazards. Many paints, especially older or exterior ones, contain **solvents and metals**. Paint strippers once commonly contained methylene chloride, which is metabolized into carbon monoxide, a well-known fetal toxin. Today, methylene chloride is banned in paint strippers for consumer use in the EU (since 2012) and the US (since 2019). However, paint strippers may still contain N-methyl-2-pyrrolidone (NMP), which has been linked to miscarriage and developmental toxicity. In the EU, NMP is restricted under REACH regulation requiring safety measures to limit worker exposure, while in the US, the EPA has determined NMP presents "unreasonable risk" but regulatory action is still in process, though major retailers have voluntarily removed these products. Even heat guns used on old lead

TERUG NAAR INHOUD

paint can create inhalable lead dust, a dangerous route of exposure during pregnancy.

And let's not forget the family cat. **Toxoplasmosis**, a parasitic infection that can cause miscarriage or congenital defects, can be transmitted through handling litter. Even this simple task may require a pause or reallocation during pregnancy planning.

What to do?

There's no need to panic, but there is every reason to **pay attention**. We need better data, broader testing, and clearer regulation. But in the meantime, we can start by expanding awareness, in clinics, on factory floors, in HR departments, and among occupational health professionals. A clinician asking about exposures during a preconception visit, or an employer re-evaluating chemical use in a lab — those are small but powerful acts of prevention.

Because when it comes to fertility, there's no such thing as a "neutral" environment. And protecting the next generation starts well before a baby is even on the way.

Sources

1. Snijder, C. A., te Velde, E., Roeleveld, N., & Burdorf, A. (2012). *Human Reproduction Update*, 18(3), 284–300.
2. Winker, R., & Rüdiger, H. W. (2006). *International Archives of Occupational and Environmental Health*, 79, 1–10.
3. McDiarmid, M. A., & Gehle, K. (2006). *Maternal and Child Health Journal*, 10, 123–128.
4. Ove-Hansson, S., & Schenk, L. (2016). *European Journal of Risk Regulation*, 7(2), 404–412.
5. Writing was assisted by ChatGTP to clarify the structure of the story.

A future in which people no longer become ill from substances they are exposed to at work

By *Robin Gommans, RIVM*

It sounds idyllic but that's what we from Lexces strive for. You may have heard from Lexces, as we're making a name for ourselves in the occupational health and toxicology field since July 2022. Lexces is a newly founded expertise centre for the prevention and assessment of occupational diseases caused by exposure to hazardous substances. We're a partnership between 5 institutes* throughout the Netherlands, we are the main drivers of the research on occupational health.

Yearly, around 3,000 people in the Netherlands die from exposure to hazardous substances in the workplace. An even larger number become ill. There's a need for knowledge that can prevent people from getting sick due to their job. That knowledge needs to be amassed from various fields and shared amongst them. That starts with identifying which hazardous substances are found in the workplace, recognising in which situations exposure occurs and detecting occupational diseases at an early stage. Lexces has a research programme in order to gain that knowledge. This programme has three main themes:

<u>Theme A, primary prevention: preventing or reducing exposure to hazardous substances.</u>

Preventing occupational diseases starts with identifying which substances might be hazardous and by preventing exposure. That might seem very obvious, but it's not always clear-cut if something is safe or not. Mind you, people in 1950's worked with asbestos without knowing the disastrous results. The goal of theme A is to gain and spread knowledge on methods and techniques that help us detect hazardous substances in the workplace. This helps us to prevent and reduce exposure of employees to hazardous substances.

<u>Theme B, secondary prevention: preventing occupational diseases</u>

It's not always possible to prevent exposure at work. In some instances you can't completely prevent exposure like in the case of a baker who is exposed to the possible allergen flour dust. In this situation, it's important to have a structure that detects early symptoms of occupational diseases. This is however not up to par in the current situation. Theme B of the work programme focusses on the prevention of occupational diseases by gaining knowledge on the early detection of health implications and improving the diagnostic processes related to occupational diseases.

Theme C, tertiary prevention: prevention or reduction of the risks of complications of people with an occupational disease.
The goal is to have no one who's sick due to exposure to substances at their work. But we're simply not there yet. Therefore, we're focusing on what we can do for the people that already got sick due to their work. This theme aims to gain knowledge to ultimately improve the health care system, specifically related to the occupational sector.

But what if someone already got sick due to their job?
A serious occupational disease can have grave consequences for the employee. These consequences are not only medical in nature but can also be social and financial. Some people are not able to keep their job and need to start over from scratch. Or they might get sick during their retirement from the exposure they had during their work. Ultimately, some people's lives might change because the jobs they had. That's why, in 2023, the Dutch Ministry of Social Affairs and Employment has initiated the Compensation for Substance-related Occupational Diseases (Tegemoetkoming Stoffengerelateerde Beroepsziekten, TSB) regulation. With this one-off compensation (of around 25,000 €), the government aims to offer social recognition to sufferers of serious occupational diseases. Bureau Lexces (RIVM) is one of the organisations that is responsible for the implementation and the execution of the regulation.

Currently, people can apply for the TSB if they have either lung cancer due to asbestos, occupational allergic asthma or CSE (chronic solvent-induced encephalitis, also known as chronic painter's disease). A panel of specialists evaluates the whole work history and medical file of the applicant to determine whether the applicant is entitled to the compensation.

Lung cancer due to asbestos
Asbestos is the most prominent work-related cause of lung cancer. It is estimated that around 600 people in the Netherlands die yearly due to lung cancer because of exposure to asbestos. Asbestos was an element in multiple products such as cement and heaters. These products were mainly used in construction work and on ships. The danger of asbestos is well-known, leading to a complete ban on the production and use of asbestos in the Netherlands in 1993. Due to the long latency period, it can take a long time till the symptoms become visible and people get diagnosed with lung cancer well into their retirement.

Allergic occupational asthma
Asthma is a chronic inflammation of the airways with symptoms such as shortness of breath and coughing. Breathing in allergens might cause someone to develop allergic asthma. There are hundreds of known occupational allergens that can cause allergic asthma, therefore asthma is one of the most prevalent occupational diseases. The most well-known cases are bakers with a flour dust allergy or barbers with exposure to persulfates.

CSE
Chronic Solvent-induced Encephalopathy is a neurological condition due to exposure to organic solvents. It's seen in painters and workers who lay flooring in houses. The symptoms range from changes in character, to memory loss, and concentration problems. All in all, the symptoms are diverse and can be cognitive and physical. The most important thing is to reduce exposure to solvents, as symptoms worsen with more exposure.

This is a short introduction to the research programme and the TSB-regulation. Obviously, there are specific research projects for each theme and there's more elaborate information available. If you want to know more, visit www.lexces.nl or message me!

*The five institutes are IRAS (Institute for Risk Assessment Sciences), NKAL (the Dutch knowledge centre for work and pulmonary disorders Nederlands Kenniscentrum Arbeid en Longaandoeningen), PMA (outpatient clinic Polikliniek Mens en Arbeid), NCvB (the Netherlands Centre for Occupational Diseases) and the RIVM (the National Institute for Public Health and the Environment

Animal Testing for PROTACs & Molecular Glue Degraders: **Necessity or Not?**

By *José Manuel Horcas Nieto, Director of Developmental Toxicology at Toxys*

What are PROTACs and MGDs, and how do they work?
Proteolysis-targeting chimeras (PROTACs) and molecular glue degraders (MGDs) are two classes of protein degrader drugs. These have been developed for the so-called undruggable targets – proteins linked to diseases, to which small molecule inhibitors cannot bind. This clever way around inhibiting a target protein hijacks the natural process of protein degradation via ubiquitin ligases. The PROTAC structure is such that one part is a ligand of the E3 ligase, and another part is a ligand of the protein of interest (POI), thus "gluing" the two molecules together. MGDs are generally small molecules and stabilize the protein–protein interaction surface(s) between the E3 ligase and the POI. In both cases, this gluing/stabilization makes the POI a target for the linked E3 ligase, which then proceeds to repeatedly (poly-)ubiquitinate the POI, tagging it as a substrate for proteasomal degradation. An advantage of this mechanism is that these drugs are effective at very low (nanomolar) concentrations due to their iterative catalytic action, reducing the potential for off-target effects.

A little bit of history…
The first proof-of-concept studies, back in 2001, showed it was possible to activate the degradation of Mouse double minute 2 (MDM2) ligands (targets in human cancer) using the "PROTAC technology". These were quickly followed by studies showing that more ligands could be degraded using the same mechanism, including Von Hippel-Lindau tumor suppressor (VHL), inhibitors of apoptosis (IAP), and Cereblon (CRBN) ligands. Probably the best-known MGD drug targeting the CRBN ligand is thalidomide, which is teratogenic in humans. We now know that thalidomide causes CRBN-mediated degradation of the transcription factor, *SALL4*, which is essential for embryogenic development. Crucially, this mechanism accounts for the species sensitivity to thalidomide teratogenicity, whereby *SALL4* in humans and rabbits is degraded by thalidomide, whereas mice are resistant to this due to variations in the sequence of their *SALL4*. The tragic history of thalidomide has emphasized the need to evaluate the teratogenic potential of similar molecules targeting ligands like CRBN.

PROTACs, MGDs and ReproTracker
SALL4 plays key role in the maintenance of pluripotency and efficient proliferation in human induced pluripotent stem cells (hiPSCs). Therefore, by their very nature of self-renewal and differentiation into different tissues, hiPSCs lend themselves to being ideal *in vitro* test models with which to test potential teratogenic effects of PROTACs and MGDs. This is good news for the ReproTracker assay as it is based on the ability of hiPSCs to differentiate towards three germ layer-specific cell types: cardiomyocytes (mesoderm), hepatocytes (endoderm), and neural rosettes (ectoderm). The endpoints of the assay are biomarker expression and morphological disruptions in the differentiated cells. This assay has been validated and shown to discriminate between teratogenic and non-teratogenic effects of a wide range of chemicals with different mechanisms of action with an accuracy of 85%[1] (sensitivity 85%, specificity 84%).

So, can *in vitro* assays like ReproTracker be used to distinguish between the teratogenic effects of PROTAC and MGD drugs targeting different ligands? To answer this question, we evaluated seven drugs targeting the E3 ligases, CRBN, VHL, and MDM2, in ReproTracker (**Table 1**). Three of the drugs are known to cause teratogenicity in several species, while the preclinical data for some of the newer drugs are not yet available.

ReproTracker can identify tissue-specificity and potency of PROTACs and MGDs
The results of this study revealed that all tested compounds, regardless of their E3-ligase specificity, were identified as teratogens in the ReproTracker assay, at concentrations clearly lower than those able to exert cytotoxicity.

CRBN-based PROTACs and MGDs (thalidomide, lenalidomide, iberdomide, pomalidomide and bavdegalutamide) significantly disrupted the cardiomyocyte differentiation assay, decreasing the expression of *MYH6* and reducing the cardiac contraction ability of the cells at the end of the differentiation. Moreover, all compounds except for lenalidomide impaired the hepatic differentiation, decreasing *AFP* expression and altering the hepatocyte's morphology. The MDM2-based PROTAC Nutlin-3, disrupted the cardiomyocyte differentiation while it also inhibited the development of neural rosettes in the neural differentiation assay, demonstrating then a different mode of action. ARV771, a VHL-based PROTAC was the only compound showing specificity for the hepatocyte differentiation while not affecting any of the other two lineages. The negative control, (S,S,S)-AHPC hydrochloride affected neither of the biomarkers nor morphology at any of the endpoints of the three cell types. This result supports the evidence for specificity and emphasizes the important role of the ubiquitin-proteasome system in driving teratogenicity.

ReproTracker in a WoE for risk assessments of PROTACs
According to the ICH S5 (R3) Guidelines on detection of reproductive and developmental toxicity for human pharmaceuticals, no additional assessment is warranted if a Malformation of Embryo-Fetal Lethality (MEFL) signal is indicated based on its MoA, captured from an *in vivo* or *in vitro* assay, and a MEFL is observed at clinically relevant exposures. In this scenario, ReproTracker can be used as a replacement for animal studies using a Weight of Evidence (WoE) approach to evaluate its teratogenic potential. If the intended plasma concentration in humans is known, then this could be combined with information on the potency of the teratogenic effects in ReproTracker to help interpret the result and prioritize drug candidates.

A safe future for PROTAC and MGDs
PROTACs and MGDs are showing great promise in the treatment of multiple diseases; however, their potential for teratogenic effects requires follow-up testing. To do this, we need to demonstrate that a test system can predict human effects and, considering the species-specific sensitivity, a human model is needed to detect human effects. For this purpose, ReproTracker has demonstrated its potential to position itself at the forefront of *in vitro* assays for developmental toxicity testing.

		Reprotracker		
E3 Ligase	Compound	**Cardiomyoctes**	**Hepatocytes**	**Neural rosettes**
CRBN	Thalidomide			
	Lenalidomide			
	Iberdomide			
	Pomalidomide			
	Bavdegalutamide			
MDM2	Nutlin3			
VHL	ARV771			

In Vivo			
Rabbit	**Rat**	**Human**	**Human Cmax**
			2.4 µM
			~2 µM
n.d.	n.d.		~40 nM
		n.d.	n.d.
n.d.	n.d.	n.d.	n.d.
n.d.	n.d.	n.d.	n.d.
n.d.	n.d.	n.d.	n.d.

Negative control		**Reprotracker**		
E3 Ligase	Compound	Cardiomyoctes	Hepatocytes	Neural rosettes
VHL	(S,S,S)- AHPC hydrochloride			

In vivo			
Rabbit	Rat	Human	Human Cmax
			n.d.

Bibliography

1. Jamalpoor A, Hartvelt S, Dimopoulou M, et al. A novel human stem cell-based biomarker assay for in vitro assessment of developmental toxicity. *Birth Defects Res*. 2022;114(19):1210-1228. doi:10.1002/bdr2.2001

AIO toxafette - Vaios Fytsilis

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 passes the baton to a fellow PhD-student. This time Vaios Fytsilis, from food toxicology at Maastricht University tells us about his project.

Can you introduce yourself?
My name is Vaios Fytsilis, and I am a PhD student in food toxicology at Maastricht University. I studied chemistry and specialized in applied biochemistry in Greece, before moving to the Netherlands for my PhD studies. My first contact with toxicology was as a bachelor's intern in forensic toxicology and continued with studying the pharmacological effects of simvastatin as a treatment for triple-negative breast cancer in my master's thesis.

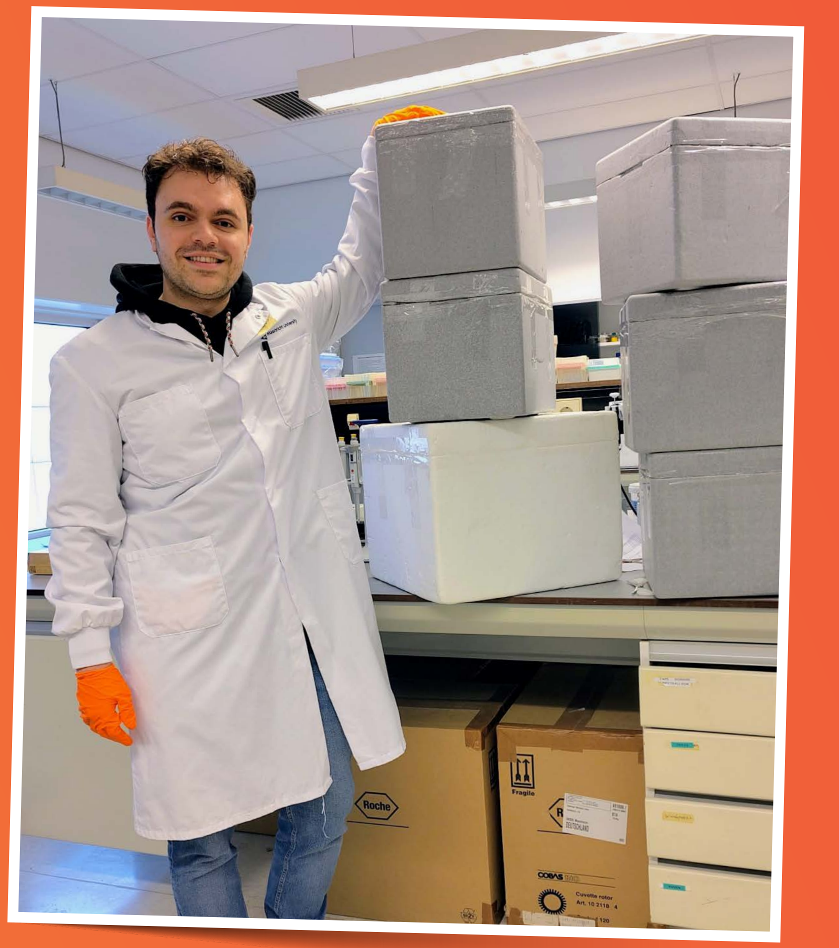
Now, I get to study the safety of dairy proteins produced through cellular agriculture, which are also known as lab-grown foods, as part of the Protein Transition 2.0 consortium. My goal is to advance and develop new approach methodologies for the safety assessment of Novel and GMO-derived foods, produced through cellular agriculture. My project focuses on protein-related adverse effects and also touches upon contaminants in the food processing chain.

How would you explain the subject of your research to a layperson?
Eating certain foods can sometimes make people sick. This can be due to various reasons, like food allergies or high levels of chemical substances that should not be there. I study to understand how and why food can make people sick. Ultimately, I work to create tests that could reliably predict whether a certain new food is likely to make someone sick before it can reach the supermarket shelves.

How is your research related to the field of toxicology, and why did you choose this subject?
My research falls under the wide scope of food toxicology which can relate to many toxicological subdisciplines. When assessing the safety of a food product there are several types of toxicity to be considered, such as genotoxicity, immunotoxicity and endocrine disruption. The approach I have chosen pertains to next-generation risk assessment because it is somewhat new, and I find this to be very exciting with many opportunities for development.

What was your motivation for starting a PhD program?
After completing my master's thesis, I was left with a feeling of incompleteness. In my mind, the knowledge I had obtained had created more questions than it had answered. So, naturally, I wanted some control over a project where I could form research questions, design experiments to answer them, then conduct these experiments and analyze the results to get my answers. In that sense, a PhD was the only way forward for me, and I was fortunate enough to find a group and a project that would allow me this freedom to evolve my skills.

How do you see the future of your research topic? What do you hope for?
My research revolves around alternative proteins and NAMs, so I think that it's a topic that's here to stay for many years. The protein transition is being driven by the climate crisis and food insecurity while the need for NAMs is one that stems from the desire for better and more ethical testing. So, as long as these driving factors persist, people will keep making novel foods and they will need accurate tools to assess their safety.



I truly hope for a toxicological/regulatory landscape that strives to keep up with innovation in other sectors. I believe that toxicology must follow the EU-wide shift towards sustainability by adopting human-centric methods that are more controlled and accurate, and less reliant on animals and animal-derived products like fetal bovine serum. In a world dominated by the capabilities of artificial intelligence, exemplified by programs like AlphaFold, our field remains reliant on testing methods of centuries past. I hope that we can overcome this hurdle in the future, and I would like my research to be a contribution to that end.

Do you consider research communication an important aspect of your PhD and why so? If yes, to what kind of audience?
Communication of toxicological research to the public is very important. Especially in my project, where we work with “lab-grown” foods we need to be cautious because there is a certain perception around these products. We are living in a time where people have ample access to information which is often not accurate or correct. It falls to the researchers and the institutions to not only conduct risk assessments but also make sure that everyday people can be reliably informed and address their questions and doubts.

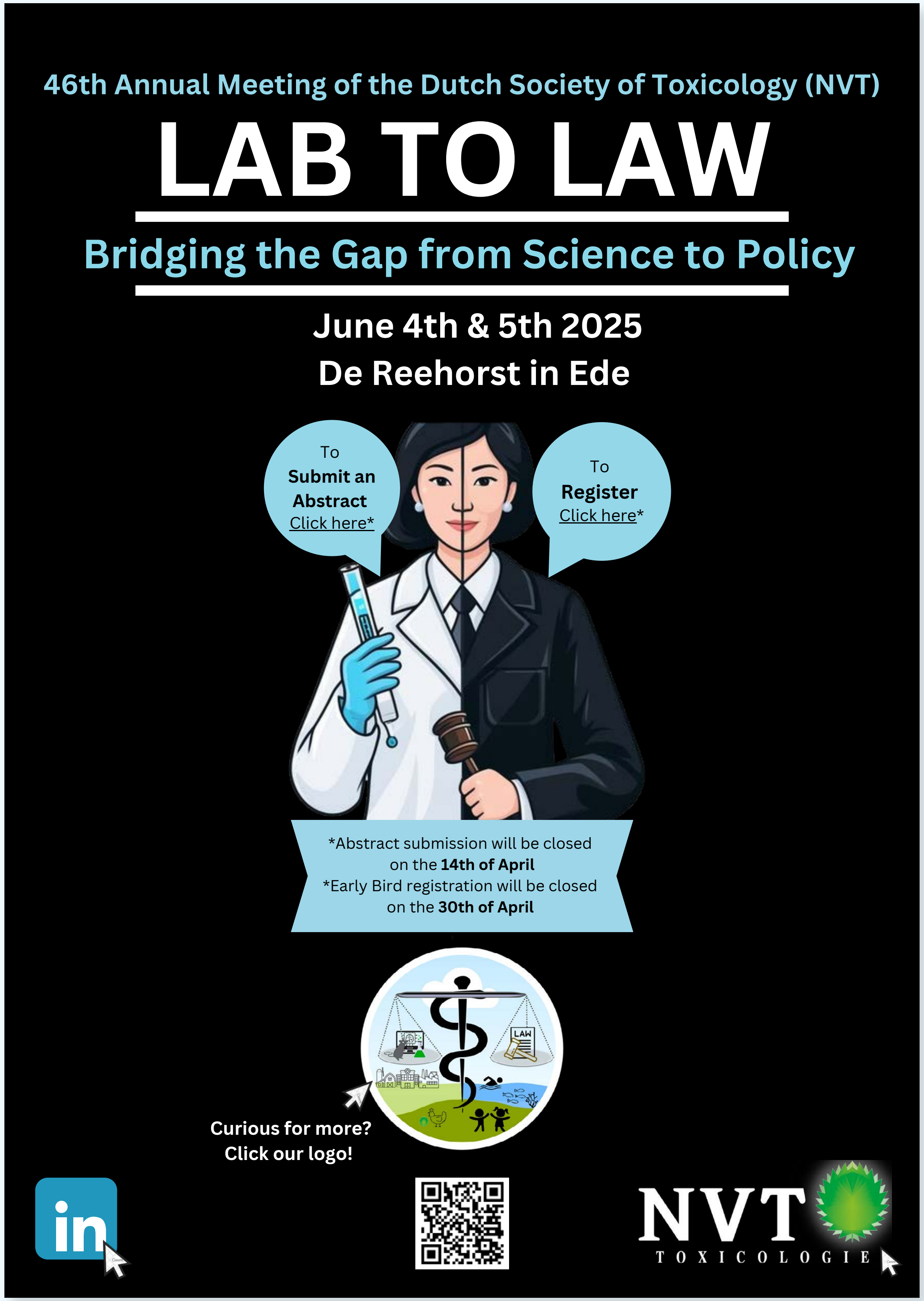
What are your thoughts on using new technologies like artificial intelligence in toxicology research? Are you using any of these technologies in your work?
Artificial intelligence specifically has already had a big impact on science, best highlighted by last year’s Nobel prizes. I believe that AI and new technologies are inevitable developments in the field, ones which we must embrace and try to utilize to our benefit because they can offer insight that we may not even have considered possible a few years ago. I do use new technologies in my work as I attempt to bridge gaps between *in vitro* and *in silico* toxicology. It might be just a dream today, but I hope that one day we will be able to conduct complete and accurate risk assessments using just one computer and a few programs.

What is the best advice that you have received as a PhD student or would like to give to another PhD student?
The best piece of advice I have to offer is “patience”. A PhD is a long project that can take much time before yielding results. Personally, I have a quote by Warren Buffet to which I turn when met with setbacks, it reads “No matter how great the talent or efforts, some things just take time, you can’t produce a baby in one month by getting nine women pregnant.”

If you could start over your studies/research project, what would you do differently?
If I could go back to the start of the project, I would tell myself to relax, take it easy. Doctoral students are put under a lot of pressure right from the beginning and I was no exception, and some of this pressure was thanks to myself, because I wanted to prove that I belong in this field and can produce results quickly. Looking back, I’d say that was unnecessary. Now I know that devoting your first year or so to developing a good study design can do wonders for your work down the stretch and save you a lot of sleepless nights. There’s been a lot of research lately showing how doctoral studies can negatively affect mental health, and I think it’s very important to address this issue.

What goals do you have regarding your career after finalization of your PhD? Would this be inside or outside academia, and why? Would you consider going abroad?
I’d really like to continue the kind of research I’m doing now. I think academia might suit me best, but wherever I end up I will keep trying to contribute to the shift towards NAMs. Having already emigrated once for better opportunities, the prospect of doing it again does not scare me. I would prefer to stay in the Netherlands, but these things are not always under one’s control.

Please answer the question from the last toxafette PhD-candidate: What do you like most about doing your PhD-research?
This is an easy one, it’s the freedom that comes with it. At any moment I can reach out to my supervisors with an idea or vice versa, and we can brainstorm about it, select the most relevant ways to explore it and go in the lab and execute. It’s also great to be able to collaborate with many people from different disciplines and that makes everything more exciting.



Upcoming Course: Current Topics in Toxicology

November 6–7, 2025

Utrecht University is offering a 1.5-day course covering recent developments in toxicology, including Omics, Particle and Fibre Toxicology, and High Throughput Screening Approaches. The course provides 3.0 CPD credits and is designed for professionals seeking to stay updated in the field. For more information and to apply, click here.

IUTOX Risk Assessment Summer School (RASS)

IUTOX is sponsoring advanced training for selected postgraduate and postdoctoral toxicologists in risk assessment through the Risk Assessment Summer Schools (RASS). This program aims to enhance skills in evaluating chemical risks and is part of IUTOX's commitment to professional development. For more information and to apply, click here.


JNST
JOURNAL OF THE NETHERLANDS
SOCIETY OF TOXICOLOGY

Review

Fluoridation Under Fire: Health Risks or Benefits to Public Health?

Barae Jomaa[1]

Affiliations: [1]Colonial Chemical EU B.V., Johan Cruijff Boulevard 65, 1101 DL Amsterdam, The Netherlands
Correspondence: Barae Jomaa, Colonial Chemical EU B.V., Johan Cruijff Boulevard 65, 1101 DL Amsterdam, The Netherlands. E-mail: barae.jomaa@ colonialchem.com

Abstract
Fluoridation of public water supplies, aimed at reducing tooth decay, has been a contentious issue for decades. While its effectiveness in improving dental health is acknowledged, there is growing debate over its necessity. The U.S. Environmental Protection Agency (EPA) has announced a review of new scientific findings, particularly following a 2024 National Toxicology Program report suggesting that fluoride levels above 1.5 mg/L may lower IQ in children. Policy responses vary internationally: the U.K. plans to expand fluoridation, while Ireland currently has the highest coverage in Europe. Despite diminishing benefits from fluoridated water as fluoride toothpaste has become widespread, data still indicates a reduction in dental cavities, with socioeconomic factors playing a larger role in oral health outcomes. The risks of dental fluorosis and potential developmental neurotoxicity at high fluoride levels are also concerns. Even more, the ethical issue of public water fluoridation overriding personal choice is central to the debate, particularly when alternatives like fluoride toothpaste are widely available. The complex relationship between fluoride levels, public health, and individual autonomy continues to fuel the need for further research.

Keywords
Fluoridation, Fluoride toxicity, Public health, Dental fluorosis, Drinking water standards, Mass medication ethics

1. Introduction

Fluoridation is the process of adding fluoride to public water supplies in order to reduce tooth decay. While this strategy is effective, there has been a longstanding debate regarding its necessity. The U.S. Public Health Service previously recommended an optimal fluoride level of 0.7 to 1.2 mg/L, but later revised this downward to 0.7 mg/L. Based on 2022 figures, 62.8% of the U.S. population receives fluoridated water (1). The U.S. Health Secretary Robert F. Kennedy Jr. called for an end to the practice altogether in the United States following its recent ban in the state of Utah. The ban was enacted due to concerns about potential health risks and the ethics of mass medication without individual consent (2).

Amid the ongoing debate, the U.S. Environmental Protection Agency (EPA) announced that it will conduct a comprehensive review of new scientific findings on the potential health risks of fluoride added to public drinking water. This decision was prompted by an August 2024 report from the National Toxicology Program, which suggests that fluoride levels above 1.5 milligrams per litre could be associated with lower IQ in children. The EPA aims to assess these findings and conduct additional studies to update its health effects assessment and potentially revise the fluoride drinking water standard (3).

Worldwide, fluoridation practices vary significantly. While countries like the United States, Australia, and Ireland have widespread water fluoridation programs, most European nations have opted against this practice. Only Ireland and the United Kingdom currently add fluoride to public water supplies in Europe, with the majority of European countries choosing alternative approaches to dental health.

2. Discussion

While most European nations have opted against water fluoridation, the United Kingdom is taking a different approach by deciding to expand its program, which has been in place since the 1960s (4). Looking at coverage rates more specifically, Ireland stands out in Europe with 71% of its population receiving fluoridated water, compared to 10% in the United Kingdom (5–7). Fluoride concentrations also vary between countries: Ireland targets 0.7 mg/L with an optimal level between 0.6–0.8 mg/L (5) while the UK aims for around 1.0 mg/L with an upper limit of 1.5 mg/L (8). Spain, which had region-specific fluoridation programs, has stopped the practice altogether with the Basque country having phased out artificial fluoridation of public water supplies in 2021. The decision was based on ethical concerns over its mandatory nature, particularly given that children already benefit from free dental care programs, and given the widespread use of fluoride toothpaste (9–11). This contrasts with the United States, where 62.8% of the population has access to fluoridated water, with a national target level of 0.7 mg/L.

Naturally occurring fluoride in drinking water varies around the globe, Africa has the highest groundwater fluoride levels, followed by Australia/Oceania and South America, with Asia and North America at lower levels, and Europe being the least affected (12).

While the effectiveness of fluoridation in reducing dental cavities is widely accepted, an updated Cochrane review shows that the dental health benefits of water fluoridation have diminished since fluoride toothpaste became widely available in the 1970s. While water fluoridation might improve oral health marginally, it does not address broader issues like sugar consumption or oral hygiene (13). A questions and answers page by the European Commission sheds further doubts on fluoridation of public water services by stating that “there is no obvious advantage in favour of water fluoridation compared with topical application, that is via toothpaste, mouthwash or gel” (14).

Nonetheless, fluoridation does decrease dental cavities as measured by decayed, missing and filled teeth (DMFT), as can be seen by comparing DMFT scores in parts of Ireland with fluoridated water and those without (figure 1). Interestingly, countries with higher GDP per capita have comparable DMFT scores despite the moderate difference that can be associated with fluoridation. A larger difference exists between countries with higher GDP per capita and those with lower GDP per capita, such as those in Eastern Europe (figures 1 and 2). This indicates that socioeconomic factors may play a more important role than the fluoridation of public water supplies. Moreover, historical data indicate that DMFT scores have also generally improved over time regardless of public water fluoridation. This trend has occurred in parallel with a steadily rising standard of living across the EU (15).

Figure 1: DMFT score (decayed, missing and filled teeth) for permanent teeth among 12-year-olds in EU countries in addition to, for comparison, the United Kingdom, USA, Canada, Australia and New Zealand. Eastern Europe: Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia. Western Europe: Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Italy, Luxembourg, Malta, Netherlands, Portugal, Spain, Sweden. North America (40-70% fluoridated): USA (ca. 70% fluoridated), Canada (ca. 40% fluoridated). Australia & New Zealand (50-90% fluoridated): Australia (ca. 90% fluoridated), New Zealand (ca. 50% fluoridated). Data retrieved from the Oral Health ″Country/Area Profile Programme″ (CAPP) database, Malmö University (16).

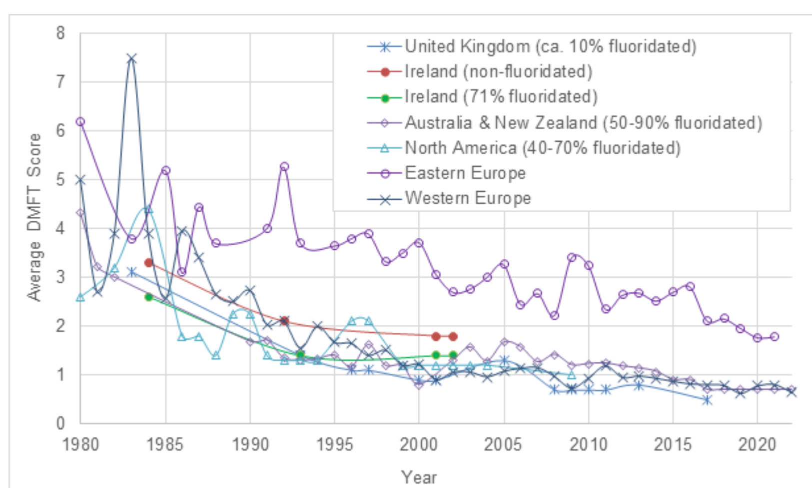
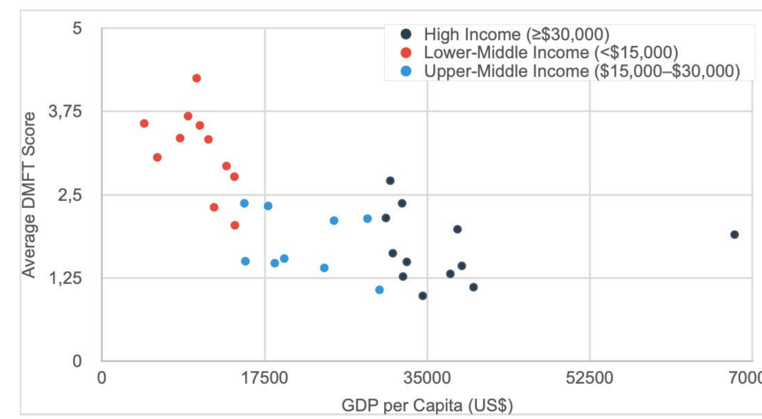


Figure 2: Average DMFT scores per country from the CAPP database plotted against average World Bank estimates for GDP per capita for the period 1980-2022 (17). Pearson Correlation Coefficient: -0.637 (moderate-to-strong negative correlation). Income groupings are based on modified GDP per capita thresholds (US$) to better reflect relative economic differences between Eastern Europe, Western Europe, North America, Australia and New Zealand: lower-middle (<$15,000), upper-middle ($15,000–$30,000), and high income (≥$30,000).



The World Health Organization (WHO) recommends a maximum of 1.5 mg/L for drinking water, a value that is higher than the typical 0.5–1.0 mg/L recommended for artificial fluoridation of water supplies (18). Concentrations exceeding this limit are associated with an increased risk of dental fluorosis, particularly in children under the age of eight. Dental fluorosis is a cosmetic condition characterized by white spots, and in more severe cases, brown staining and pitting of the enamel, the hard, outer surface of the tooth that protects it from decay. Chronic fluoride intake above 6 mg per day can result in debilitating skeletal fluorosis.

The EU Scientific Committee on Health and Environmental Risks (SCHER) reviewed the health effects of fluoride following systemic exposure through drinking water. Besides the wellestablished risk of dental and skeletal fluorosis, the committee cited epidemiological studies suggesting carcinogenicity, developmental neurotoxicity, and reproductive toxicity. However, when evaluated using a weight-of-evidence approach, the committee could not support these findings (19).

In 2024, the US National Toxicology Program (NTP) conducted a systematic review examining fluoride exposure and its potential effects on neurodevelopment and cognition. The review found, with moderate confidence, that concentrations of fluoride in drinking water above 1.5 mg/L are associated with reduced IQ in children. This finding is based primarily on epidemiological studies conducted outside the United States. The review also referred to a meta-analysis that reported a significant decrease in IQ of 1.63 points per 1-mg/L increase in urinary fluoride. The evidence was insufficient to assess whether lower fluoride levels, such as the 0.7 mg/L recommended for U.S. community water systems, have any impact on children's IQ. No adverse effects on adult cognitive function were identified. Importantly, the review highlights that the observed association does not establish causation and that further research is needed, particularly at lower exposure levels (20).

Perhaps the most poignant point raised by opponents of fluoridation relates to the freedom of choice. They argue that fluoridation violates individual choice by medicating water supplies without consent. This raises ethical questions about balancing public health benefits against personal autonomy, particularly when alternatives like fluoride toothpaste are widely available. A report by the Dutch National Institute for Public Health and Environment (RIVM) looking into cost-effective preventive interventions summed it up by stating that "fluoridation of drinking water would conflict with the freedom to choose for natural drinking water. This principle of freedom of choice is considered as an important basic principle in the Netherlands."

3. Conclusion

While fluoridation of public water supplies has proven effective in reducing dental cavities, its necessity and ethical implications remain a topic of significant debate. The growing body of scientific evidence, including concerns over potential health risks such as reduced IQ in children at higher fluoride levels, has prompted calls for re-evaluation of current practices. Furthermore, the availability of alternatives like fluoride toothpaste and the role of socioeconomic factors in dental health suggest that fluoridation may no longer be as crucial as it once was. The ongoing discussions surrounding public health, individual choice, and the balance between these interests highlight the complexity of the issue. Moving forward, more research will be essential in determining the future of water fluoridation policies, ensuring that public health benefits are maximized while respecting personal autonomy.

References:

1. CDC. Community Water Fluoridation. 2024 [cited 2025 Apr 21]. 2022 Water Fluoridation Statistics. Available from: https://www.cdc.gov/fluoridation/php/statistics/2022-water-fluoridation-statistics.html
2. RFK Jr. calls for end of fluoride in water, after Utah ban - CBS News [Internet]. 2025 [cited 2025 Apr 21]. Available from: https://www.cbsnews.com/news/rfk-jr-end-fluoride-water-utah-ban/
3. US EPA O. EPA Will Expeditiously Review New Science on Fluoride in Drinking Water [Internet]. 2025 [cited 2025 Apr 21]. Available from: https://www.epa.gov/newsreleases/epa-will-expeditiously-review-new-science-fluoride-drinking-water
4. Water fluoridation expansion given green light. BDJ In Pract. 2025 Apr;38(4):102–102.
5. Cronin J, Moore S, Harding M, Whelton H, Woods N. A cost-effectiveness analysis of community water fluoridation for schoolchildren. BMC Oral Health. 2021 Mar 25;21(1):158.
6. Powell N. Ireland reviews water fluoridation. CMAJ. 2014 Jul 8;186(10):E343–4.
7. Bardsley A, Eason C, Elwood J, Seymour G, Thomson W, Wilson N, et al. Health Effects of Water Fluoridation:A review of the scientific evidence. 2014.
8. UK Office for Health Improvement & Disparities. Water fluoridation health monitoring report 2022. 2022 Mar 21;
9. Agua TN del. El flúor en el agua en España: Un cambio en la práctica y consideraciones actuales [Internet]. Tratamiento Natural del Agua. 2024 [cited 2025 May 13]. Available from: https://aguanatural.com/blog/fluor-agua-en-espana/
10. Pérez Silva A, Aparecido Cury J, Serna Muñoz C, Cabello Malagón I, Martinez Beneyto Y, Ortiz Ruiz AJ, et al. La concentración de fluoruro en las aguas consumidas en la Región de Murcia no es suficiente para prevenir la caries dental. Enfermería Global. 2021;20(61):122–38.
11. Basque Government. Decreto por el que se deroga el decreto 49/1988, de 1 de marzo, sobre fluoración de aguas potables de consumo público [Internet]. 2021 [cited 2025 May 13]. Available from: https://www.legegunea.euskadi.eus/documentacion-relevancia-juridica/decreto-por-el-que-se-deroga-el-decreto-49/1988-de-1-de-marzo-sobre-fluoracion-de-aguas-potables-de-consumo-publico/webleg00-contfich/es/
12. Podgorski J, Berg M. Global analysis and prediction of fluoride in groundwater. Nat Commun. 2022 Aug 1;13(1):4232.
13. Iheozor-Ejiofor Z, Walsh T, Lewis SR, Riley P, Boyers D, Clarkson JE, et al. Water fluoridation for the prevention of dental caries - Iheozor-Ejiofor, Z - 2024 | Cochrane Library. [cited 2025 Apr 21]; Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.

CD010856.pub3/full
14. Questions on water fluoridation [Internet]. [cited 2025 Apr 21]. Available from: https://ec.europa.eu/health/scientific_committees/opinions_layman/fluoridation/en/index.htm
15. Standard of living in European Union countries. Ekonomia i Prawo Economics and Law. 2023;22(2):369–83.
16. Dental caries data - CAPP - Malmö University. xlsx | Powered by Box [Internet]. [cited 2025 Apr 23]. Available from: https://mau.app.box.com/s/bgaspqxzg6y0nwtnqz10kadiu8ugnevb
17. World Bank Open Data [Internet]. [cited 2025 Apr 23]. World Bank Open Data. Available from: https://data.worldbank.org
18. World Health Organization. Guidelines for drinking-water quality: fourth edition incorporating first addendum [Internet]. 4th ed., 1st add. Geneva: World Health Organization; 2017 [cited 2025 May 13]. 541 p. Available from: https://iris.who.int/handle/10665/254637
19. Directorate-General for Health and Consumers (European Commission). Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water [Internet]. Publications Office of the European Union; 2010 [cited 2025 Apr 23]. Available from: https://data.europa.eu/doi/10.2772/38897
20. National Toxicology Program (NTP). NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopment and Cognition: A Systematic Review [Internet]. 111 TW Alexander Dr, Durham, NC 27709: National Institute of Environmental Health Science; 2024 [cited 2025 Apr 23]. Available from: https://ntp.niehs.nih.gov/go/mgraph08abs

TERUG NAAR INHOUD

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.