TCDD
TOXICOLOGIE

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SPECIAL THEME

Pleasure in Poison, the Thin Line Between Use and Abuse

- RECREATIONAL USE OF PERFORMANCE-ENHANCING DRUGS (PEDS) IN THE NETHERLANDS: IF YOU CAN'T BEAT 'EM, CHEAT 'EM!
- TEENS AND RECREATIONAL DRUGS: WHAT IS THE TREND LATELY?
- PSYCHEDELICS FOR PSYCHIATRY: WHO BENEFITS MOST AND WHEN?
- HOW NEW WEIGHT LOSS DRUGS ARE CHANGING THE GAME

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Colofon

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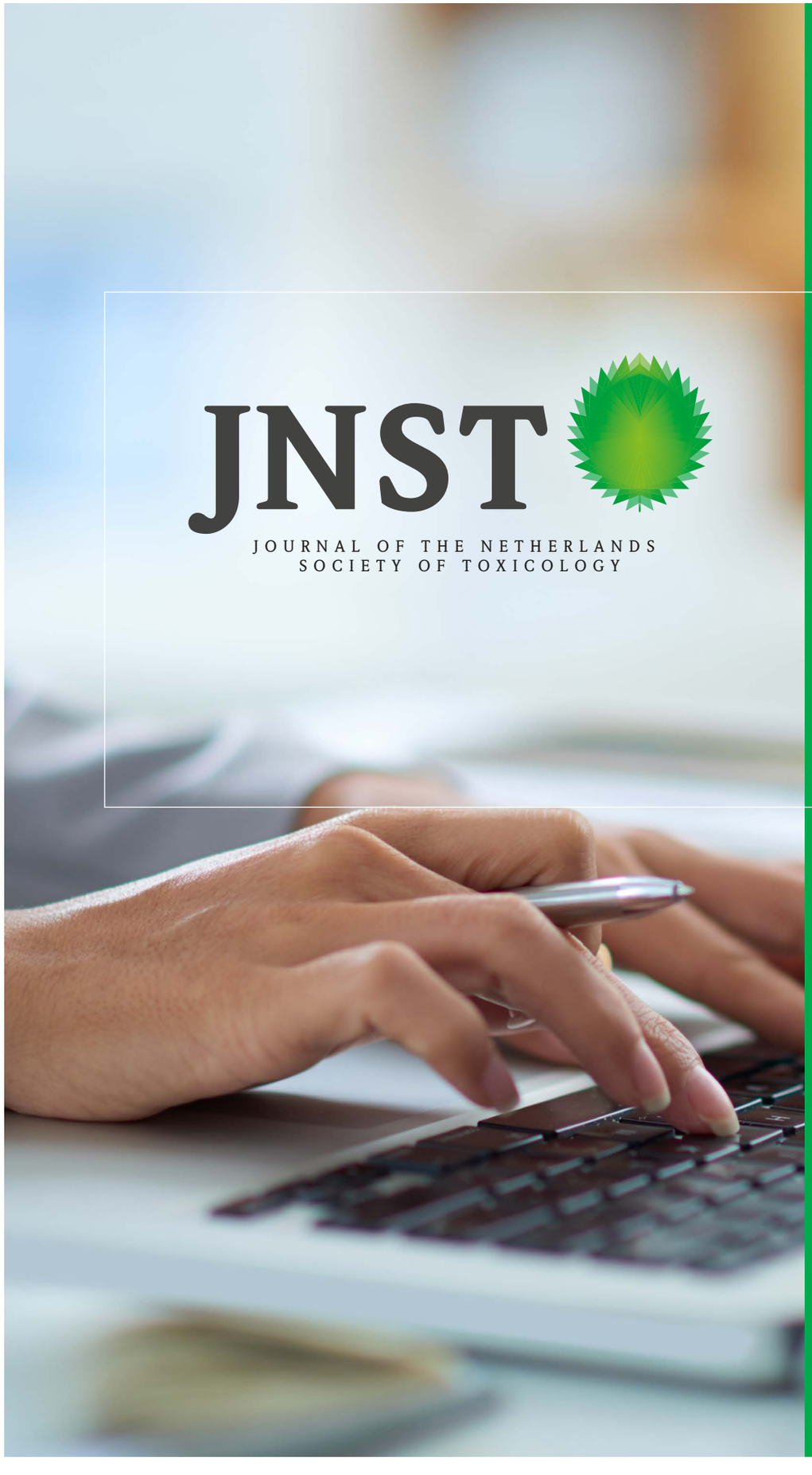

JNST

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TERUG NAAR INHOUD

Editorial

This issue of the TCDD is all about drugs. We often divide drugs into pharmaceuticals and recreational drugs. Pharmaceuticals are used to treat illnesses and are often prescribed by a doctor. Recreational drugs are often illicit drugs that are used for effects that people like or crave. But are they actually that different? On the one hand, illicit drugs such as psychedelics have beneficial effects that could be harnessed to treat mental illnesses. On the other, pharmaceuticals such as pain killers or ADHD medication are abused for effects that people like or crave. These effects may be the ones intended by the manufacturer, but they may also be off target side effects. So, the main difference between them is the rules that apply. In this issue we dive into the latest trend of teenage recreational drug use, ketamine and psychedelics for depression, the application of weight loss drugs and Performance Enhancing Drugs.

Furthermore, in the section “What’s Next?”, Pauline Herst writes about “A Day in the Life of a Toxicologist” and “Toxicology in the media” discusses Quats in household products. As usual we also have a “Promopraatje” by Marta Nazzari and a “Toxafette” by Tom Roos. And if that is not enough, the *JNST journal*, features my own peer-reviewed article: “Psilocybin Therapy for Depression: A Review of Current Molecular Knowledge”.

We hope you have as much fun reading this issue as we had in creating it.

Sincerely,

Marcha Verheijen

Photo by Jess Bailey on Unsplash

IN MEMORIAM - Dr. Ingeborg Kooter

It is with profound sadness that weannounce the passing of Dr. Ingeborg Kooter, a distinguished scientist in the field of inhalation toxicology, who bravely battled her illness until March 26, 2024. Despite knowing that Ingeborg's illness was incurable, her passing came sooner than expected and hoped for.

Ingeborg was a highly valued member of the Dutch Society of Toxicology and a pioneer in researching the health effects of environmental pollutants, notably air pollution from particulate matter. As a Principal Scientist at TNO within the Environmental Modelling, Sensing & Analysis group, part of the Energy & Materials Transition unit, she made significant contributions. She also held a part-time appointment in the Department of Pharmacology and Toxicology, Maastricht University, where she dedicated herself to guiding PhD candidates and was on the path towards a part-time professorship - a goal she, unfortunately, was unable to achieve.

Ingeborg excelled in developing and applying her expertise. With her enthusiasm and perseverance, she was extremely skilled in identifying new opportunities, combining knowledge, building strong multidisciplinary collaborations, and practically applying her scientific research.

She was an active participant in the annual meetings of our society, making numerous friends in the toxicological field, both nationally and internationally. In recent years, she was an active member of the *Registratiecommissie Toxicologie* and a driving force behind many projects related to pulmonary exposures, such as to microplastics, and was very active in the MOMENTUM consortium. Her passing leaves a significant emptiness in the field of particle inhalation toxicology.

Ingeborg will be remembered not only for her professional contributions and her ability to inspire and engage others in her work but also for who she was as a person: kind, warm, open, and interested. We are deeply grateful to have known her and for all her contributions to the toxicological field and our society. She will be greatly missed.

On behalf of the Board of the NvT

Prof dr Frederik-Jan van Schooten, vice-chair

SECTIE
GENEESMIDDELENTOXICOLOGIE

New PET course 'Pharmaceutical Toxicology'

10-14 of June, Androclus Building, Utrecht

The learning objectives of this course is to get an overview of drug toxicology, understand the impact of drug quality on safety, how to translate animal study results to humans, obtain knowledge on which toxicological studies are needed to conduct a First-In-Human study, submit a Market Authorisation Application (MAA), take into account special patient populations and specific medications and understand how to weigh a risk-benefit analysis. The course consists of interactive lectures and will refer for some topics to other PET-courses that are more detailed where applicable (e.g., Environmental Risk Assessment (ERA), reproduction toxicology, carcinogenicity, organ toxicology). The last part of the afternoon of each course day consists of active classes in small groups in which case studies are discussed. The course will be concluded with a presentation and a written exam. Participants should have knowledge of general toxicology to be able to fully profit from this course.

For more information, please see this link. For course-related inquiries, please contact Dr. C. L. E. Siezen (cl.siezen@cbg-meb.nl) Dr. Y. Ponstein (yolanda@wxy.nl). For general inquiries please contact the PET Office.

SECTIE ARBEIDSTOXICOLOGIE

Omgaan met Reproductietoxische en Hormoonverstorende Stoffen:

Navigeren tussen Theorie, Nieuwe Regelgeving en Praktijk

Verslag middagsymposium NVT-sectie Arbeidstoxicologie i.s.m. NVT-sectie Risicobeoordeling en de Contactgroep Gezondheid & Chemie; 28 maart 2024, Eindhoven.

Kelly Caris-Bergs[1] en Jeroen Terwoert[2]

De regelgeving voor blootstelling aan reproductietoxische stoffen op de werkplek gaat binnenkort ingrijpend veranderen. Reproductietoxische stoffen zijn sinds kort opgenomen in de Europese Carcinogens & Mutagens Directive (CMD 2022/431), en de Nederlandse overheid moet de nieuwe regels in het Arbeidsomstandighedenbesluit opnemen. Daarnaast is recent ook steeds meer aandacht ontstaan voor zogenaamde hormoonverstorende stoffen, en worden in het kader van de Europese stoffenwetgeving REACH testmethoden en criteria voor de classificatie ontwikkeld. De aandacht voor reproductietoxische en hormoonverstorende stoffen is verder aangewakkerd door onder meer de problematiek rond PFAS/PFOA, en door een casus in de lycrafabriek van Du Pont (15 ex-werkneemsters die het bedrijf hebben aangeklaagd, nadat zij allen een of meer miskramen hadden gehad). Dit vormde voldoende reden om eens aandacht te besteden aan deze categorieën stoffen.

Ilse Wijnands-Scheperkeuter, beleidsmedewerker bij het ministerie van Sociale Zaken en Werkgelegenheid (SZW), begon de middag met een uiteenzetting over de inhoud van de huidige en de gewijzigde regelgeving. Reproductietoxische stoffen zijn schadelijk voor de voortplanting of het nageslacht, via invloed op de fertiliteit, de ontwikkeling van het kind, of de borstvoeding. Op grond van de Europese CLP regelgeving kunnen stoffen geclassificeerd worden als bewezen (klasse 1A en 1B), of verdacht (klasse 2) reproductietoxisch. Tweemaal per jaar publiceert SZW de geactualiseerde versie van de 'CMR-lijst'[3], waarin de stoffen opgenomen worden die ofwel op EU-niveau, ofwel op nationaal niveau door de Gezondheidsraad zijn geclassificeerd. Daarnaast hebben bedrijven die een stof op de markt brengen de verplichting om deze zelf te classificeren, in het kader van de Europese stoffenregelgeving REACH, indien nog geen Europese of nationaal geharmoniseerde classificatie voorhanden is (met H-zinnen H360, 361 of 362). Dit betreft het grootste deel van de stoffen die op de markt zijn. Voor kankerverwekkende en mutagene stoffen geldt al dat er een zware inspanningsplicht op de werkgever rust om deze te vervangen waar dat technisch uitvoerbaar is, of anders de blootstelling te minimaliseren. Onder meer op dit punt zal de wijziging van de EU-richtlijn nu ook tot verplichtingen voor reproductietoxische stoffen leiden. Voor klasse 1A en 1B reproductietoxische stoffen komen als extra verplichtingen onder de Europese richtlijn:

- Een verbod op recirculatie via ventilatielucht;
- Een vervangings- en minimalisatieplicht; behalve voor R-stoffen waarvoor een veilig niveau van blootstelling (drempelwaarde) bewezen is;
- Registratie van de blootstelling van werknemer, met koppeling op naam. Anders dan sommigen denken, is dit ook ‘toegestaan’ vanuit de AVG-regelgeving.

Wanneer niet bekend is of voor een stof een drempelwaarde kan worden vastgesteld, zal in de Nederlandse implementatie van de EU-richtlijn de minimalisatieplicht gelden voor die stof. Hier gaat Nederland iets verder dan de EU-richtlijn voorschrijft, net als bij de registratie van de blootstelling van werknemers. De gegevens hiervan moeten minimaal 40 jaar bewaard worden, in plaats van 5 jaar. De reden hiervoor is dat men het gelijk wil trekken met de bewaartermijn van blootstellingsregistratie voor kankerverwekkende stoffen, om verwarring te voorkomen.

De implementatie van de gewijzigde EU-richtlijn in de Nederlandse regelgeving zal binnen enkele maanden geregeld zijn. Voor klasse 2 reproductietoxische stoffen blijven overigens de verplichtingen gelden zoals die tot nu toe al in het Arbobesluit stonden.

Een volgende wijziging van de EU-richtlijn, die in maart 2026 geïmplementeerd moet zijn, zal onder meer een verlaging van de grenswaarden voor lood en isocyanaten inhouden, waarbij ook voor lood voortaan een niet-drempelwaarde effect wordt aangenomen. Verder zullen ook *processen* waarbij mutagene stoffen kunnen ontstaan in de richtlijn worden opgenomen.

Tenslotte wijdde Ilse nog enkele woorden aan hormoonverstorende stoffen. Deze maken nu nog geen onderdeel uit van de EU-richtlijn. Het gaat om stoffen die door interactie met het hormoonstelsel een effect op het lichaam kunnen veroorzaken. Ook hier wordt onderscheid gemaakt tussen bewezen en verdacht hormoonverstorende stoffen. In een komende revisie van de (CLP-) regelgeving voor classificatie, worden testmethoden en criteria voor hormoonverstorende stoffen opgenomen. De validatie van testmethoden vormt momenteel nog wel een uitdaging. Hormoonverstorende stoffen zullen niet worden toegevoegd aan de CMR-lijst, omdat voor deze stoffen geen aanvullende verplichtingen zullen gelden, boven die voor ‘normale’ stoffen.

Ilse sloot af met een oproep: iedereen die deel zou willen uitmaken van een netwerk dat meedenkt over regelgeving voor gevaarlijke stoffen kan zich aanmelden bij het Ministerie SZW.

Vanuit de zaal werd gevraagd waarom voor verdacht kankerverwekkende en mutagene stoffen niet het aantal blootgestelde werknemers geregistreerd hoeft te worden en voor verdacht reproductietoxische stoffen wel?

Dit vindt men bij SZW ook niet logisch, maar het kan niet zomaar veranderd worden als het niet in de EU-richtlijn staat.

Ook worden vragen gesteld over de reikwijdte van de registratieverplichting. Deze kunnen echter het best door praktijkdeskundigen worden beantwoord.

De vraag of er voor hormoonverstorende stoffen H-zinnen komen, kan bevestigend worden beantwoord, nl. H380 en H381.

Aldert Piersma, reproductietoxicoloog bij het Rijksinstituut voor Volksgezondheid en Milieu (RIVM), ging in zijn presentatie nader in op de toxicologie van hormoonverstorende stoffen. De beroemde publicatie Silent Spring van Rachel Carson, schudde de wereld in 1962 wakker en beschreef effecten van onder meer DDT op vogels, waaronder mogelijke effecten op de reproductie. De publicatie Our stolen future uit 1996 bracht voor het eerst de hypothese dat mogelijk sprake kon zijn van een hormoonverstorend mechanisme. Een bekende, maar enigszins omstreden studie uit 1992 leek vast te stellen dat de spermakwaliteit tussen 1930 en 1990 continu daalde. De kwaliteit van deze studie werd echter betwijfeld, onder meer in verband met de gedurende deze 60 jaar ontstane verschillen in de behandeling van de monsters en in de telmethodieken. Ook was niet duidelijk wat de oorzakelijke verklaring voor de daling van de spermakwaliteit zou kunnen zijn, hoewel een mogelijke relatie werd gesuggereerd met de algemene toename in de productie en het gebruik van ‘chemische stoffen’. Het RIVM zelf heeft in 1996 een eerste studie uitgevoerd, waarin is gekeken naar de blootstelling aan een reeks endogene (‘eigen’) en exogene (‘van buiten af’) hormonen en mogelijke hormoonverstoorders. Het bleek dat de geschatte blootstelling aan hormoonverstoorders via het milieu zeer gering was, zeker vergeleken met de blootstelling aan zowel endogene hormonen als hormonen via bijvoorbeeld anticonceptie, die (zeer) vele ordegroottes hoger lag. Als follow-up op de Weybridge conferentie in 1996 heeft de WHO in 2002 een eerste definitie geformuleerd voor hormoonverstorende stoffen, die als een mijlpaal gezien kan worden: “*An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism or its progeny, or (sub) populations*”. Kernelementen in deze definitie zijn het veroorzaken van negatieve effecten, en dat dit - gezien de complexiteit van alle mogelijke interacties - plaatsvindt in een intact organisme (dus niet in bijvoorbeeld een celkweek). In OECD[4]-verband is vervolgens een teststrategie ontwikkeld, waarin op basis van bewijskracht vijf niveaus worden onderscheiden, lopend van de eerste aanwijzingen vanuit fysisch-chemische eigenschappen tot complexe in vivo tests. Hierbij wordt onderzoek dat zich beperkt tot de niveaus 1 en 2 als onvoldoende beschouwd om een definitieve beoordeling te kunnen doen.

Een belangrijk aspect in de beoordeling van mogelijke hormoonverstoorders is het maken van een onderscheid tussen daadwerkelijke schadelijke (‘adverse’) effecten en subtiele beïnvloeding die kan worden opgevangen door het

lichaam (‘adaptive’). Het lichaam streeft immers voortdurend naar homeostase, en kan externe beïnvloeding tot op een zeker niveau opvangen en corrigeren. Schadelijke effecten kunnen optreden als de capaciteit om de homeostase te handhaven overschreden wordt. Het onderzoeken van endocriene parameters is pas relatief recent aan bestaande testprotocollen toegevoegd, en het vormt in het algemeen nog een uitdaging om causale relaties tussen (subtiele) endocrience beïnvloeding en daadwerkelijk schadelijke effecten aan te tonen. Met een verwijzing naar het alom bekende adagium van Paracelsus, stelde Aldert dat de mogelijkheid om steeds lagere concentraties aan stoffen aan te tonen in het lichaam, soms leidt tot te veel zorg, onder de onjuiste aanname dat ‘hazard’ gelijk staat aan ‘risk’. Ter illustratie werd een voorbeeld van Stof X aangehaald, die als hormoonverstoorder werkt op het antidiuretisch hormoon (ADH), dat de uitscheiding van vocht, en daarmee de elektrolytenbalans in het bloed reguleert. Een te hoge inname van deze Stof X remt het ADH, en zorgt in extreme gevallen voor coma, en mogelijk de dood. Vele aanwezigen (maar lang niet alle) hadden inmiddels uit het verhaal opgemaakt wat deze mysterieuze Stof X is: water! De LD50 ligt nogal hoog, op 100 gr/kg/dag (ofwel: ~ 7 liter, voor een persoon van 70 kg.). Dit lijkt een extreem voorbeeld, maar ook in de gebruikelijke toxiciteitstest worden soms erg hoge doseringen toegepast, waardoor de vraag kan rijzen of dit nog reëel is, en of in de tests niet ook (meer) naar de potentie van de stof gekeken moet worden, in plaats van uitsluitend naar hazard.

Een van de deelnemers vroeg zich af of het wel terecht is om hormoonverstoring als apart eindpunt in toxiciteitstest op te nemen, of dat het meer gezien moet worden als één van de mechanismen die leiden tot reproductietoxische effecten. Daar is iets voor te zeggen, of in ieder geval, het is van belang om het achterliggende mechanisme te bestuderen indien de reproductietoxische eigenschappen van stoffen worden beoordeeld.

Een andere opmerking betrof de mogelijkheid dat een individuele stof wellicht uitsluitend een subtiel hormoonontregelend effect heeft dat nog door het lichaam kan worden opgevangen en gemoduleerd, maar dat dit vervolgens wel de capaciteit van het lichaam kan beperken om verdere verstoringen nog op te vangen.

Ingrid Oirbons is arbeidshygiënist bij Rockwool en heeft daarnaast vele jaren ervaring opgedaan vanuit arbodiensten en binnen industriële bedrijven. Het uitgangspunt is dat blootstelling aan gevaarlijke stoffen beheerst dient te zijn voor alle werknemers. En dat er mogelijk aanvullende actie nodig is als wordt gewerkt met stoffen die gevaarlijk zijn voor (het tot stand komen van een) zwangerschap, het ongeboren kind of de zuigeling. Haar ervaring leert dat beslissingen in relatie tot het werken met gevaarlijke stoffen en zwangerschap veelal worden genomen op basis van het gevaar en niet op basis van het risico. Veel bedrijven hanteren het voorzorgsprincipe waarmee zwangeren geheel worden vrijgesteld van werkzaamheden met carcinogene, mutagene en reproductietoxische (CMR-) stoffen. Deze aanpak is uiteraard prima maar kan in de praktijk tot praktische problemen leiden. Aan de hand van enkele voorbeelden uit de praktijk licht ze toe hoe er door het uitvoeren van aanvullende Risico- Inventarisatie en Evaluatie (RI&E) Zwangeren meer mogelijkheden zijn. Hierin is het van belang enerzijds te kijken naar CMR stoffen die altijd verboden zijn voor zwangeren vanuit de wetgeving. Anderzijds om na te gaan welke werkzaamheden met CMR-stoffen voor extra risico voor zwangeren zorgen. Een drietal documenten die hierbij kunnen ondersteunen zijn:

- Handreiking Arbomaatregelen Zwangerschap & Arbeid van de SER, 2018
- AI-blad 12 Zwangerschap en werk, maart 2023
- Richtlijn zwangerschap postpartumperiode en werk NVAB, herziene versie 2018

Artikel 4.108 van het Arbeidsomstandighedenbesluit schrijft voor dat zwangeren niet mogen worden blootgesteld aan genotoxische stoffen oftewel mutagene en carcinogene stoffen zonder veilige drempelwaarde. Voor welke stoffen dit geldt is terug te vinden in Arbeidsomstandighedenregeling bijlage XIII, lijst B1. Voor reproductietoxische stoffen geldt dat zwangeren niet mogen worden blootgesteld aan lood(verbindingen). Op dit moment geldt er voor overige R-stoffen géén wettelijk verbod voor zwangeren. De meeste R-stoffen hebben een veilige drempelwaarde. In de aanstaande nieuwe wetgeving worden voor bewezen (en dus niet verdachte) R-stoffen nog extra voorschriften opgenomen. Zo dient voor bewezen R-stoffen zonder veilige drempelwaarde gestreefd te worden naar een zo laag mogelijke blootstelling van werknemers en is het advies om zwangeren vrij te stellen van werkzaamheden met deze stoffen. Voor bewezen R-stoffen met een veilige drempelwaarde is blootstelling van werknemers toegestaan mits deze lager is dan de veilige grenswaarde. Het R-effect moet dan wel meegenomen zijn in de afleiding van de grenswaarde. In dat geval is er ook geen extra risico voor zwangeren. In Arbeidsomstandigheden regeling bijlage XIII, lijst B3 worden R-stoffen met bijbehorende grenswaarde benoemd. In de toekomst wordt hier ook een kolom aan toegevoegd waarin wordt aangegeven of er sprake is van een drempelwaarde. Maar momenteel is daar deze informatie nog niet vandaan te halen.

Maar hoe dan nu nog om te gaan met R-stoffen waarvan niet bekend is of ze een drempelwaarde hebben? Één mogelijkheid is alle R-stoffen te behandelen alsof ze geen drempelwaarde hebben en dus te streven naar nulblootstelling. Een andere optie is zelf wetenschappelijke bronnen te raadplegen. Te denken valt aan stukken van de Gezondheidsraad, SCOEL/RAC, DFG en het ECHA REACH dossier. Dit vergt echter meer specialistische kennis van stoffen en de gevaren die ermee gepaard gaan.

Reproductietoxische stoffen kunnen een invloed hebben op het ongeboren kind (H360d, H361d), op de vruchtbaarheid

(van mannen en/of vrouwen) (H360f, H361f) en/of van invloed zijn op de zuigeling via borstvoeding (H362). In de nadere RI&E Zwangeren is het dus belangrijk onderscheid te maken om te weten voor welke groep medewerkers de stoffen extra relevant zijn (zwangere werknemers, werknemers met een kinderwens, werknemers die borstvoeding geven).

De meeste R-stoffen hebben een veilige drempelwaarde wat inhoudt dat bij blootstelling onder een bepaalde concentratie er geen reproductietoxisch effect te verwachten is. Maar stoffen met een R-effect kennen vaak ook andere gezondheidseffecten. Bij het vaststellen van een gezondheidskundige grenswaarde wordt gekeken naar het meest kritische effect. Oftewel het effect dat als eerste wordt veroorzaakt bij blootstelling aan een bepaalde concentratie. Als een grenswaarde tegen dat effect beschermt, beschermt het ook tegen effecten waarvoor een hogere concentratie nodig is. Het is belangrijk om te controleren of in het vaststellen van de grenswaarde ook het reproductietoxische effect is meegenomen. Dit blijkt in de praktijk namelijk niet altijd het geval. Dat heeft op zijn beurt weer gevolgen voor de nadere RI&E Zwangeren. Hierbij worden als voorbeeld de stoffen Tolueen en Xyleen aangehaald. Beide stoffen zijn geclassificeerd als verdacht gevaar voor het ongeboren kind en dus relevant voor zwangere werknemers. Voor Tolueen is in het brondocument van de publieke grenswaarde duidelijk beschreven dat de effecten op het ongeboren kind pas optreden bij blootstelling aan een concentratie boven de grenswaarde. Voor Xyleen is er onvoldoende informatie beschikbaar of het R-effect is meegenomen in het vaststellen van de grenswaarde. Omdat niet duidelijk is bij welke concentratie er geen negatieve effecten voor het ongeboren kind zijn zullen zwangeren vrijgesteld worden van blootstelling. n-Hexaan is een stof die ervan wordt verdacht effect te hebben op de mannelijke vruchtbaarheid. Dit effect is meegenomen in het vaststellen van de publieke grenswaarde. Met andere woorden: wanneer mannen worden blootgesteld aan concentraties lager dan de grenswaarde zijn ze ook voldoende beschermd tegen het R-effect van n-Hexaan.

In relatie tot de nieuwe wetgeving schetst Ingrid een voorbeeld van koolmonoxide (CO). CO is geclassificeerd als een bewezen R-stof met effect op het ongeboren kind. Uit het praktijkvoorbeeld blijkt dat het type werkplek en de groep blootgestelde werknemers ook nog heel relevant kan zijn in hoeverre het uitvoeren van een nadere RI&E zwangeren op het R-effect van een stof zinvol is. Omdat momenteel de drempelwaarde voor het R-effect van CO op het ongeboren kind niet bekend is zouden zwangeren uit voorzorg vrijgesteld moeten worden van blootstelling. De nieuwe wetgeving maakt geen onderscheid in de relevantie van het R-effect voor de werksituatie. Dus geldt een nulblootstelling (minimalisatieverplichting) in dit geval ook voor een werkplek waar geen zwangeren worden blootgesteld(?)

Herman Bartstra is bedrijfsarts en klinisch arbeidsgeneeskundige bij het Nederlands Centrum voor Beroepsziekten (NCvB) en de Polikliniek Mens en Arbeid (PMA), beiden onderdeel van het Amsterdam UMC. In samenwerking met zijn collega Teus Brand heeft hij een presentatie verzorgd over de medische ethische aspecten van R-stoffen op de werkvloer. Aan de hand van enkele casussen daagt hij het publiek uit mee te denken wat voor beleid als medicus te hanteren. Rondom vruchtbaarheid en zwangerschap komen veel emoties kijken. Daarnaast zijn werkgevers vaak bang voor het schenden van de privacy van de werknemers. Het voorzorgsprincipe wordt vaak gehanteerd maar is niet altijd nodig. De SER Handreiking arbomaatregelen Zwangerschap & Arbeid omschrijft het RAAK-principe:

- R: Risico's wegnemen binnen eigen functie en eigen werkplek
- A: Aanpassing van het werk/werk en rusttijden
- A: Ander werk
- K: Keerpuntbenadering: vrijstellen verrichten arbeid

Informatie blijkt vaak moeilijk te vinden voor personen die bij een casus uitkomen. Dat zijn niet alleen de werknemer, werkgever en bedrijfsarts maar kunnen bijvoorbeeld ook een huisarts of verloskundige zijn. De algemene RI&E is een eerste belangrijke start. Een verdiepende RI&E levert meer informatie maar is vaak niet voorhanden. Deze wordt veelal pas gemaakt zodra een werknemer meldt zwanger te zijn, er vruchtbaarheidsproblematiek is of een werknemer borstvoeding wil geven. De FNV heeft de app 'Werk en Zwangerschap' ontwikkeld waarin gewezen wordt op mogelijke risico's in op het werk in relatie tot een zwangerschap. Want naast gevaarlijke stoffen zijn er andere gevaren die in geval van een zwangerschap voor extra risico kunnen zorgen (o.a. geluid en biologische risico's).

In de presentatie komt ook de studie 'Healty work in pregnancy' van Monique van Beukering aan bod. Uit deze studie blijkt dat ruim de helft van de zwangere vrouwen niet volgens de wettelijke regels en richtlijnen werken. Dit geldt in diverse beroepen en branches. Er is dus nog veel winst te behalen. Voor vragen kunnen zorgprofessionals maar ook leidinggevende en werknemers terecht bij de NCvB helpdesk https://www.beroepsziekten.nl/ncvb/helpdesk

Paneldiscussie

In de paneldiscussie wordt gevraagd hoe om te gaan met stoffen zonder eigenaar (bijvoorbeeld lasrook en dieselmotoremissie). Deze stoffen worden minder gereguleerd vanuit de wetgeving maar kunnen ook relevante R-effecten hebben. Het is dus van belang deze stoffen ook mee te nemen in de nadere RI&E Gevaarlijke stoffen en Zwangerschap. Aangezien de exacte stofsamenstelling en concentraties niet altijd bekend zijn en/of kunnen variëren wordt ook hier vaak het voorzorgsprincipe gehanteerd.

Ook wordt opgemerkt dat werknemers meestal pas na enkele weken weten zwanger te zijn en daarna meestal nog enkele maanden wachten voordat de zwangerschap aan de werkgever wordt gemeld. Dit maakt dat het ongeboren kind mogelijk al meerdere maanden worden blootgesteld aan stoffen met een

R-effect terwijl juist die eerste maanden van de ontwikkeling extra kwetsbaar zijn. Dit benadrukt het belang van het al op voorhand bekend zijn met de extra risico's die bij een werkgever een rol kunnen spelen voor werknemers met een kinderwens, zwangere werknemers en/of werknemers die borstvoeding geven. Door een aanvullende RI&E op te stellen voor deze groepen werknemers kunnen deze risico's in kaart worden gebracht. Dit stelt de werkgever ook in staat om werknemers al voor aanvang van de werkzaamheden op de hoogte te brengen van mogelijke risico's. Op die manier zijn de werknemers ook voorgelicht om weloverwogen keuzes te maken over een (aanstaande) kinderwens/zwangerschap/geven van borstvoeding.

[1] Nederlandse Voedsel en Waren Autoriteit (NVWA), Bureau Risicobeoordeling en Onderzoek (BuRO) & NVT, sectie Arbeidstoxicologie

[2] Nederlandse Arbeidsinspectie; Kenniscentrum

[3] SZW-lijst van kankerverwekkende stoffen en processen, mutagene of voor de voortplanting giftige stoffen

[4] Organisation for Economic Co-operation and Development

REGISTRATIE CIE

Inschrijving register

Voorletters	Achternaam	Datum inschrijving	Datum uischrijving
J.J.	Nugteren-van Lonkhuyzen	26-03-2024	26-03-2029
V.M.P.	de Bruijn	26-03-2024	26-03-2029
S.	Fragki	26-03-2024	26-03-2029
J.J.	Dommershuijzen	26-03-2024	26-03-2029

Recreational use of performance-enhancing drugs (PEDs) in the Netherlands:

if you can't beat 'em, cheat 'em!

By *Damiën van Berlo*

The word "doping" may have its origin in the Dutch language: it could refer to the practice of dipping ("dopen") something in a liquid substance that enhances performance in some sense. Sounds like dipping your cookie in your coffee… An alternative explanation that is sometimes given, is that it is derived from a stimulating beverage (called "dop" by Dutch settlers), that is consumed by members of the African Kaffir tribe during religious ceremonies (Conti, 2010). So there is a Dutch connection: and actually, and for me surprisingly, the Dutch appear to be quite fond of their "augmented candy" jar. But there will be more on that later.

Prompt: "A curling athlete on steroids sweeping the ice"
(AI-generated image using Gencraft). Look at that 'roid roar!

Use of doping, or performance-enhancing drugs (PEDs), is widely known to occur quite commonly in professional sports (this includes horse and greyhound racing; but for the current piece, the focus will be on use in humans). In fact, PED use has been occurring since ancient times; chariot racers were reported to use herbal infusions for strength enhancement (*Kumar, 2010*). The endurance walker Abraham Wood claimed to have use laudanum, containing opiates, to keep him awake for 24 h (*Novich et al., 1964*). In the sport of endurance cycling, where participants had to cycle for as long as possible during 6 days, nitroglycerine was provided to the participants to improve their breathing (*Novich et al., 1964*). One can imagine that the performance boost must have been *explosive*...

In particular, athletes competing in disciplines that rely heavily on athletic attributes, such as endurance, strength or speed, can greatly benefit from pharmacological enhancement. Weightlifters, runners, gymnasts, cyclists for instance can see their own performance improved to a large extent when using PEDs; for a sport like curling, benefits will be much lower. It would be interesting to see a curling contestant frantically sweeping with his/her broom after heavy PED use, though; let's ask AI for some help.

Even if the impact of PED use is reduced for sports like snooker or darts, there can be benefits when something like a mild muscle relaxant is taken to reduce muscular tension and avoid shaking of the hands. Or something that reduces anxiety because of the pressure related to performing in the spotlight.

Of course, PED use is generally prohibited and is considered as "cheating" by most professional sports associations. Such organisations go to great lengths to convince the general public that no cheating occurs in "their" sport because of rigorous testing procedures. One can imagine the importance for the reputation of the sport: the spectators should believe that these are hardworking athletes that achieve great things by practice, talent and discipline.

So how often are PEDs used? The World Anti-Doping Agency has investigated this in a 2017 randomized-response survey. We know that around 1-2% of all blood and urine samples tested annually, test positively for PEDs. In this survey, 2,167 athletes competing at the sporting events (the 13th International Association of Athletics Federations Word Championships in Athletics (WCA) in Daegu, South Korea in August 2011 and

the 12th Quadrennial Pan-Arab Games (PAG) in Doha, Qatar in December 2011) were questioned with anonymity guaranteed to all athletes. Of these athletes, 43.6% (WCA) and 57.1% (PAG) admitted to use of doping in the year previous to the event (*Ulrich et al., 2017*). So this would be around 50% on average, roughly. Please remember: these athletes admitted to using, the expectation should be that the true numbers are significantly higher. It is no easy thing to admit to cheating. What these data also show, is that it is very easy to evade PED testing, only a small fraction gets caught. Many tests are performed after previous announcement, so athletes know when they should be clean. And the positive test from Ben Johnson in 1988 at the Summer Olympics in Seoul, which led to him admitting that he had in fact used a number of PEDs, would be considered a negative nowadays because the acceptable level in blood has been increased. *In hushed voice* …is it possible that sports associations have financial and PR interests, do not want to see their heroes disgraced and like to see records broken by ever-improving athletes for more press coverage and sponsorship income…?

To be fair, even those athletes that choose to cheat, *still* need enormous effort to get to the top. PEDs are no replacement for hard work, there is no success without some blood, sweat and tears. That is regardless of whether those body liquids contain trace amounts of PEDs or their metabolites.

So what kind of substances are we talking about, when we discuss PEDs? The most common PED categories are:

Anabolic-androgenic steroids; these increase lean muscle mass, bone growth and physical strength and can make you recover better from strenuous exercise. They include methandrostenolone, stanozolol, nandrolone, clenbuterol and human growth hormone; most anabolic steroids mimic the effect of testosterone and dihydrotestosterone. A substance specifically developed for doping purposes is tetrahydrogestrionone (THG), which was undetectable

for years and provided cheaters with a free ride to bulging muscles. Side effects include the development of masculine traits for females: excessive body hair, baldness and low voice. For males, it can lead to gynaecomastia (breast tissue development), testicular shrinkage, impotence and lower sperm production. Gender-aspecific effects include increased aggressiveness (“roid rage”), liver damage, acne, disruption, depression and suicidal tendencies.

Stimulants, that reduce (the sensation of) fatigue, increase activity, improve motor coordination. These include cocaine, amphetamine, modafinil and ephedrine. Target the central nervous system. Not all stimulants are considered as doping, caffeine for instance is allowed. Side effects include insomnia, anxiety, weight loss, dehydration, tremors and increased risk of stroke andheart attack.

Relaxants, such as beta blockers (e.g., propranolol, atenolol, exprenolol). These substances can reduce shaking in concentration sports such as archery, darts, golf or snooker. And maybe even curling… Adverse effects are plentiful and include nausea, diarrhea, bronchospasm, dyspnea, cold extremities, hypotension, heart failure, fatigue, dizziness, alopecia, abnormal vision, hallucination, insomnia, nightmares and sexual dysfunction, among others. It’s a good thing the beta blockers reduce anxiety induced by all of these health problems....

Diuretics, including xanthines, thiazides and vasopressin antagonists: promote urination, which can mask use of other types of doping because they are eliminated quicker, and because the urine volume is increased, they are diluted as well. Also used for more rapid weight loss in sports like boxing and wrestling, where the athlete needs to meet stringent body weight standards. Adverse effects include hypovolemia (abnormally low extracellular fluid level), hypokalemia (low kalium levels, leading to tiredness and constipation) and hyponatremia (associated with nausea, poor balance, headaches) and metabolic alkalosis or acidosis.

Erythropoietin and blood doping; erythropoietin stimulates erythrocyte formation while blood doping involves including injecting one’s own red blood cells. Both result in higher red blood cell counts and thus better oxygen uptake and transport. The use of EPO was approved in 1989 as a treatment for anemia, and it was added to the doping list (and banned) since the early 1990s, but the first detection test was not available until the 2000 summer Olympics. Side effects include an increased of myocardial infarction, leukemia, stroke and thromboembolism.

For professional athletes, it is obvious that the benefit of using PEDs is potentially tremendous. In contrast, benefits for amateurs that do not have the potential to win trophies and medals (plus wealth by sponsorship deals etc.) is far less. Which is where we get to the surprising bit: the available data suggest that recreational use of PEDs is increasing even if the side effects are severe and potentially life-threatening. An important disctinction between professional and recreational use, is that recreational use in principle is allowed. But because many PEDs are actually medicines, the trade and production outside of the regular

channels (in compliance with the Dutch “Geneesmiddelenwet”) is prohibited (*Van Leiden et al., 2020*).

According to a recent investigation by the Mulier Institute, around 25% of recreational strength athletes (who practice weight lifting, powerlifting, bodybuilding, Crossfit, calisthenics or just common fitness) use PEDs. For martial arts (kickboxing, boxing, thai boxing, mixed martial arts, jiu jitsu, wrestling, karate, taekwondo and karate), this is even higher at around 47% (*Mulier institute, 2023*). During this investigation, 2200 people were surveyed who performed weightlifting or martial arts at least once or twice a week. Most of the PED use involved anabolic steroids (22% of strength athletes, 38% of martial artists). This means that in the Netherlands alone, around 400,000 people who regularly exercise at a gym and 80,000 people who practice martial arts are using anabolic steroids (*Mulier institute, 2023*). Huge numbers for such a small country. What might also be remarkable (to me it is, at least), is that although men use anabolic steroids more often, this difference was sometimes small. This means that use among female recreational athletes can be almost as common. Another interesting observation is that PED use is higher among younger people compared to elder people, even if the former usually having more to lose in terms of fertility and healthy life years than the latter. Indeed, another study also found that younger people have a more positive attitude towards PED use than older people (*Huiberts and Balk, 2022*).

Older investigations of PED use among recreational athletes found lower percentages: in one study PED use among gym-goers was 8.2% on average (*Stubbe et al., 2009*) and in another it was reported that 9% of recreational athletes had at some point in their life used PEDs (*Hilkens et al., 2021*). There are some differences however, because in the recent Mulier institute study, the population consisted of recreational athletes who exercise/ perform sports *regularly*. In other countries percentages on PED use are likely to be different, for instance in the US there is historical evidence that 8-12% of *all high school males* were using anabolic steroids (*Goldman, 1992*). And data from Russia, former Eastern Germany or China will probably look even more dramatic.

Still, it looks as though recreational PED use in the Netherlands might be increasing; this could be related to the role of social media in present-day society. “Gym bro” and “fitgirl” type influencers are increasingly prevalent on Instagram and Youtube; the more muscular and fit they appear, the more followers (and thus, income and attention) they often attract. Probably, the conclusion is readily drawn that those achieving the best results will be capable of providing the best advice. The fittest, most muscular influencers will most likely be on significant amounts of PEDs to achieve their physique. That is simply because one achieves significantly better results with PEDs than without; so, it makes a lot of sense that the most impressive physiques are PED-enhanced. Of course, the overwhelming majority of such influencers vehemently denies PED use.

If the use in the Netherlands is increasing; could it be that side effects for some reason are less prevalent? Well, in a recent Dutch study investigating side effects of PEDs, all users experienced positive effects on muscular development but also all experienced negative side effects. These included excessive perspiration, acne, gynaecomastia, reduced sperm production, increased blood pressure and decreased cardiac function (*Smit et al., 2022*). Low term effects on fertility and cardiovascular disease are still not completely clear, but the chance of adversity after long term usage is not good. If makes you wonder: could increasing PED use play some role in the well-known reduction of human fertility that is observed world-wide?

Well, as a father of two young kids who practice karate, I will be sure to thoroughly inform them about the risks of PEDs especially if they would ever reach competitive level (right now their karate class is mostly playful). Of course, at that point they could probably kick my behind if they disagree…

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Teens and Recreational Drugs:

What Is the Trend Lately?

By *Héloïse Proquin*

With the arrival of new synthetic drugs and the opioid crisis in the US, one can ask if these are not becoming more trendy than the other (illicit) drugs available on the market. Recently, the European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA) published a report named "European Drug Report 2023: Trends and Developments" where they monitor the drugs and their consequences on the European population.

The use of nitrous oxide among young people

Over the last years, in Europe, there have been signs of an increase in the use of nitrous oxide through inhalation, also known as laughing gas. It produces a rapid and short-lived rush of euphoria, happiness or excitement. Other effects can include: dissociation of the mind from the body (a sense of floating) changes in thoughts, feelings and perceptions[1].

However, the intensive and chronic use of nitrous oxide has been linked to health harms including burns, lung injuries, and poisonings. Additionally, in some cases of prolonged exposure, nerve damage from vitamin B12 deficiency. Currently, regulatory approaches to the sale and use of this substance vary between countries.

Increased diversity in the illicit synthetic recreational drugs

Research suggests that amphetamine remains the most commonly used synthetic drug. However, there is increasing diversity in the drug market in this area with drugs such as methamphetamine and synthetic cathinones such as 3-MMC and 3-CMC. Consumers may view different drugs as functionally similar and be willing to try new products based on their availability in the market. These different dugs may also be available in similar-looking powders or pills, consumers may sometimes be unaware of what they are consuming.

Consequently, people who use drugs may be at greater risk of adverse health outcomes, including poisonings, acute and chronic mental health problems, infectious diseases and deaths, through consuming, possibly unknowingly, higher-potency or more-novel substances and engaging in high-risk behaviours.

Drug-induced death in the EU

The first figure shows the age distribution of the drug-induced death reported in the EU, Norway and Türkiye. The results indicate that the majority of drug-induced deaths are in the age category 25-44 years old. The second figure shows that the majority of these drug-induced death are males except in the category >64 years old.

These figures demonstrate that the young people are not the age category the most at risk for overdose.

Figure 1. Age distribution of drug-induced deaths reported in the European Union, Norway and Türkiye in 2021 (percent)

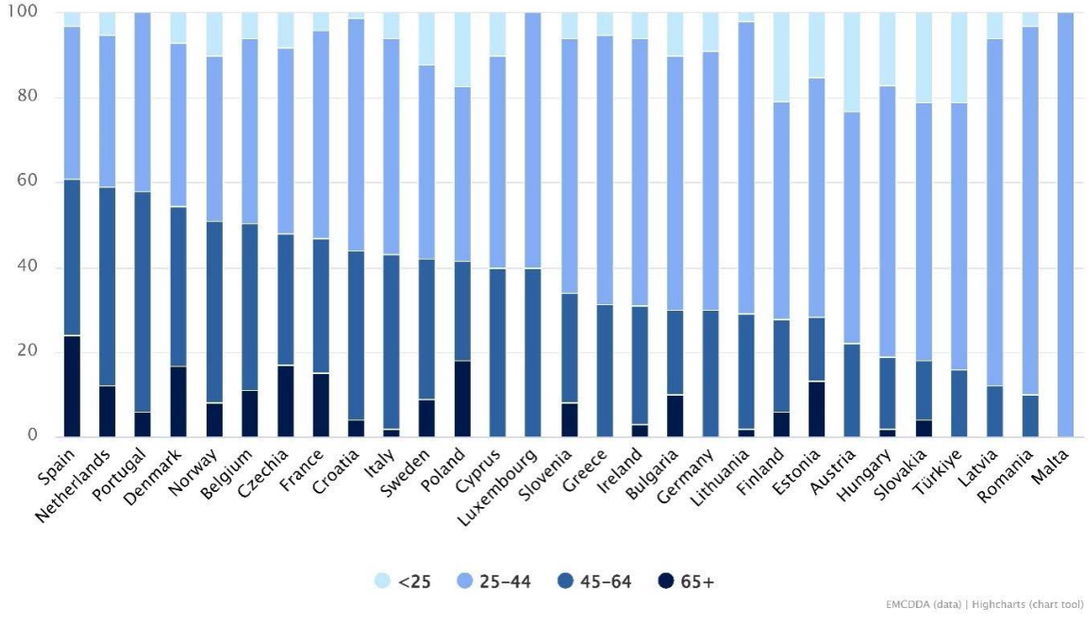
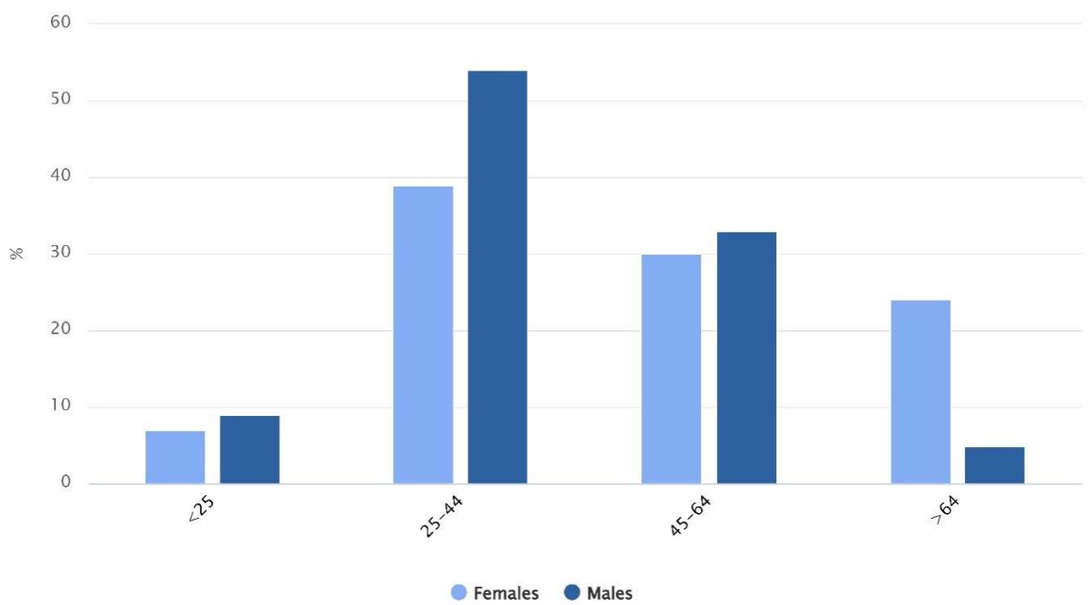


Figure 2. Drug-induced deaths in the European Union: age at death, 2021 or most recent available data (percent)



The role of polydrug use in drug-induced mortality

Opioids, usually in combination with other substances, remain the substances most commonly implicated in drug-induced deaths. However, the role played by heroin in overall rates of death appears to be decreasing in some countries but always in combination with other drugs such as other opioids and medications. Deaths where synthetic drugs are implicated is rising in some countries being more common in younger age range and is often alongside opioids. Additionally, the role benzodiazepines play in drug-induced deaths is not sufficiently understood. Non-controlled and new benzodiazepines are available in Europe; these substances may have important consequences for health, especially when consumed in combination with other drugs like the new synthetic opioid metonitazene and bromazolam, a new benzodiazepine.

They are often very cheap and may be used by young people in combination with alcohol, sometimes resulting in potentially serious health reactions or aberrant behaviour. They have also been linked to increasing the risk of opioid overdose death and the proportion of overdose deaths involving benzodiazepines increased in some countries.

What about the most common (illicit) drugs?

Alcohol use remains high among adolescents in Europe, with an average of over three-quarters (79%) of school students having used alcohol in their lifetime[3].

Among the illicit drugs, cannabis (use has been legalized in Germany, Luxembourg and Malta for ages 18 or over) is the most frequently used illicit drug by adolescents in Europe, representing a constant prevalence of 16% since 2015. Use of other illicit drugs is less common, with a prevalence of 0.7-9.2%[4].

While the use of illicit drugs remains high among young people in Europe, with around 1 in 3 people aged 18-24 using illicit drugs, alcohol is still the most widely used substance[1].

The misuse of prescription drugs, such as pain relievers, is also a concern given the higher prevalence in use, compared to illicit drugs. In Spain, based on a recent study, 2.52% of 12-17 year olds are misusing prescription drugs[5]. Additionally, lifetime prevalence of tranquilizer/sedative and painkiller misuse among European adolescents aged 15-16 was 6.6% and 4%, respectively. As a category, prescription drugs misuse, has become the second most abused among illegal drugs in young people ages 12-17 in Europe, behind only marijuana[5].

Conclusions

To conclude, the evidence suggests that while European teenagers do use a range of recreational drugs, alcohol remains the most widely used substance among this age group. Marijuana is the most commonly used illicit drug, but its use is still lower than alcohol. Other illicit drug use rates are relatively low, though prescription drug misuse is also a concern. There currently appears to be insufficient evidence showing that restrictions on underage alcohol use cause teenagers to substitute drug use. The lack of clear causality is supported by the finding that the vast majority of adolescents in Europe have consumed alcohol, despite the restrictions. Rather than a reaction to prohibition, the reasons teenagers use drugs and alcohol may be more complex, involving factors like peer pressure, mental health issues, and a desire to experiment or rebel[6].

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[6] https://drugfree.org/article/why-teens-drink-and-experiment-with-drugs/

Psychedelics for Psychiatry:

Who benefits most and when?

By *Aedan O'Shea*

Since the turn of the century, there has been an exponential increase in Psychedelic drug research Internationally, while The Netherlands serves as a major contributor and European hub. Drugs such as LSD, MDMA (Ecstasy), and Psilocybin, the active ingredient in Magic Mushrooms, are frequently being studied as potential treatments for Psychiatric conditions, especially depressive illnesses. This modern resurgence in the field of Psychedelic research, after many years of strict regulation, has been coined 'The Psychedelic Renaissance'. As we see a clearer picture being painted before our eyes, fresh insights are accompanied by new obstacles in their medicalisation.

One major barrier is to adequately identify patients who would benefit most from Psychedelic medicine. Although Psychedelics have shown efficacy in treating a range of neuropsychiatric conditions, such as Post-Traumatic Stress Disorder (PTSD) and Major Depressive Disorder (MDD), they may not serve as ubiquitous treatment tools. This is because PTSD and MDD, much like many psychiatric conditions, exhibit significant heterogeneity amongst patients. Currently, the Diagnostic and Statistical Manual of Mental Disorders (DSM) is used for Symptomatic diagnosis of the mentioned conditions, even though patients may possess different neurobiology. Consequentially, traditional treatment approaches are insufficient for many patients. In the case of MDD, drugs acting as Selective-Serotonin Reuptake Inhibitors (SSRIs) are often the first line treatment, but over 1/3 of patients do not have a clinically significant response and for those who do, several weeks are needed for the drug to elicit an effect. Overall, less than half of patients treated with current pharmacological methods reach complete remission.

On July 1st last year, Australia became the first country to regulate MDMA and Psilocybin as medications, prescribed

TERUG NAAR INHOUD

by approved psychiatrists. However, Psilocybin can only be prescribed to patients who have not responded to other available treatments.

To better understand and leverage the therapeutic effect of Psychedelic drugs, a novel approach to human proof-of-concept studies is necessary. Therefore, focusing on core symptoms shared amongst conditions that have a well-defined neurobiological origin is likely a suitable approach. For example; Cognitive flexibility is impaired in MDD and other psychiatric disorders which benefit from psychedelic medicine. Such an impairment often results in patients adopting a negativity bias, due to focus on negatively perceived cues, which then results in cognitive rigidity and depressive rumination. It's hypothesized that psychedelics reduce negativity bias in depressed patients by restoring deficits in a cognitive process called "pattern separation", ultimately increasing psychological and cognitive flexibility. The process of pattern separation relies on the rate of neurogenesis in a specific brain region, the Subgranular Zone of the Hippocampus, which is impaired in MDD. Additionally, Psychedelics have been shown to increase neurogenesis in the Hippocampus and neuroplasticity in the medial Prefrontal cortex, regions associated with emotional processing, presumably contributing to their therapeutic effect.

But now you may ask; how can the neurobiological effect of Psychedelic drugs be physically monitored, and related to behavioural changes?
Exosomes are lipid-encapsulated Extracellular Vesicles with a diameter of 30-150nm, which are released by a variety of cells and contain proteins, lipids, mRNA, and miRNAs. Primarily acting as intercellular communication vectors, these parcels of useful scientific information are small enough to cross the Blood-Brain-Barrier (BBB) and therefore can grant insight to cellular and molecular mechanisms of the brain in physiological and pathological states when used as blood-based biomarkers.

Exosomes originating from cells in the brain can be isolated via immunoaffinity-based methods due to markers on their surface membrane and if necessary, the neural cell type of origin; Neuron, astrocyte, oligodendrocyte, or microglia can be specified.

Much like circulating miRNA (cimRNA) changes in Exosome miRNA have proven useful in monitoring pharmacological treatments and could **bring cellular resolution** to determining the molecular mechanisms of drugs or other agents. In the context of Toxicology, assessing the miRNA in Exosomes may be preferable to cimRNA, as the latter is susceptible to degradation and interference from other blood components while Exosomes have a ribonuclease-resistant phospholipid bilayer which increases the stability of their contained miRNA.

My PhD project at Maastricht University aims to employ brain-derived exosomes as blood-based biomarkers of Psychedelic drug exposure. To do this, blood samples will be retrieved during ongoing clinical studies of psychedelics. I will then isolate the Brain Derived Exosomes by Immunoaffinity based methods, before sequencing the miRNAs they contain to perform differential expression analysis in conjunction with behavioural data collected during the clinical studies. Through this project, we hope to bring further understanding to the molecular mechanisms of psychedelics and add to the ever-expanding repertoire of research in this fascinating space.

How New Weight Loss Drugs are Changing the Game

When major breakthroughs occur in medicine, they can have a profound impact. Take the latest development in the medical field: a new set of drugs intended to address obesity. Drugs like Ozempic, Wegovy, Mounjaro, and Retatrutide could revolutionize our general approach to weight loss.

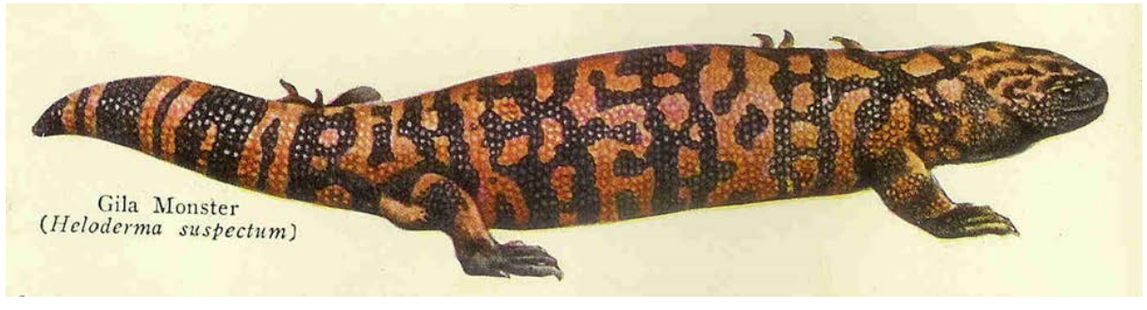
By *Carolien Schophuizen*

Many people struggle with it on a daily basis. For years, finding effective treatments has been challenging. The journey to developing effective obesity drugs was not simple, it involved a series of accidental discoveries. Researchers discovered that when the brain is exposed to a hormone called glucagon-like peptide 1 (GLP-1) [13], in unusually high levels, it has a positive effect on weight loss [11, 12, 14, 17, 18]. The exact reasons behind this are still being investigated. However, the pivotal moment came from an unexpected source: the venomous Gila monster. Researchers discovered a variant of GLP-1 in its saliva that had long-lasting effects, laying the groundwork for drug development [16].

The presence of GLP-1 in the Gila monster's saliva serves as a natural adaptation to its physiological needs. GLP-1 is a hormone primarily produced in the gut of mammals, including humans, where it plays a crucial role in regulating blood sugar levels after meals by stimulating insulin release and inhibiting glucagon secretion. In the case of the Gila monster, researchers believe that the presence of GLP-1 in its saliva may aid in its digestive processes. When the Gila monster consumes food, the GLP-1 in its saliva could potentially help regulate blood sugar levels and aid in the digestion of its prey. [10]

Another hormone involved in weight regulation is GIP [2, 15], or glucose-dependent insulinotropic peptide. Like GLP-1, GIP is released from the gut in response to food intake and plays a role in insulin secretion and blood sugar regulation. Researchers have discovered that combining GLP-1 with GIP can lead to even more significant weight loss effects than using GLP-1 alone. [8]

The quest for better drugs led to the creation of medications like Victoza (liraglutide), Ozempic and Wegovy (semaglutide) which are glucagon-like peptide-1 receptor agonists (GLP-1 RAs). [9] These drugs help with managing blood sugar levels in diabetes, but also show promise in tackling obesity. Recent breakthroughs, like combining GLP-1 with GIP, have led to even more promising results. Mounjaro, for example, is a diabetes drug developed by Lilly that combines GLP-1 with GIP. Early studies suggest that this combination could lead to significant weight loss, with some patients experiencing a median weight reduction in the range of 20%. [19]



Similarly, retatrutide, another experimental drug, seems to elicit effective weight loss in early testing phases. [7] These findings are ground-breaking, and the exact mechanisms behind these drugs' effectiveness are still being investigated.

The Risks of Off-Label Use

While the idea of losing excess weight with the help of medications like Ozempic might sound great, recent concerns have cast a shadow over their safety, particularly when used off-label for weight loss.

In July, the European Medicines Agency raised alarms regarding potential mental health side effects associated with Ozempic, including disturbing thoughts of self-harm and suicide. This revelation came amidst growing reports of patients experiencing anxiety, depression, or suicidal ideation while taking drugs containing the active ingredient Semaglutide, such as Ozempic. [4]

The FDA Adverse Event Reporting System (FAERS) has received many reports in which such mental health concerns among

patients using Semaglutide-based medications like Ozempic were mentioned. While these reports are important for individuals to voice their experiences and alert regulatory authorities to potential risks, they do not automatically confirm a causal relationship between the medication and the observed side effects. [3]

Ozempic, originally approved by the FDA for type 2 diabetes management, has surged in popularity, particularly on social media platforms, where influencers and celebrities have championed its weight loss benefits. [6] However, its instructions for use did not mention mental health side effects. In contrast, Wegovy, another FDA-approved weight loss drug containing Semaglutide but in a higher dose, explicitly acknowledges these risks in its labeling. [5]

The occurrence of mental health concerns raises questions: Are these adverse effects a mere coincidence or a direct consequence of the drug's action? While the correlation between Ozempic and mental health issues cannot be dismissed, definitive causation remains elusive. It's essential to approach these reports with caution. FAERS submissions are not verified, and duplications are possible, undermining their reliability as standalone evidence. They serve as a catalyst for further investigation rather than conclusive proof of causality. [2]

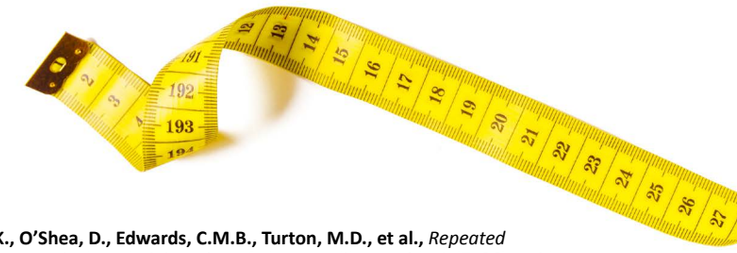
While Wegovy's association with depression highlights the potential link between Semaglutide and mental health, additional rigorous research is required to validate this statement. Only through comprehensive investigation can we ascertain the true extent of the risks associated with off-label use of Ozempic and similar medications.

Weight loss drugs and designer analogues

Weight loss drugs and designer analogues present their own set of challenges due to their regulatory status and potential health risks. One significant issue arises from the fact that new designer versions of approved medications fall into a regulatory grey area. These designer analogues are not automatically regulated. Primarily, health authorities are unaware of these designer analogues, rendering them unrecognized as medicines. Additionally, since these designer analogues are not known to the general scientific community, their safety and toxicity cannot be assessed. Moreover, concerning labelling requirements, manufacturers may assert that a designer analogue is derived from one of the declared natural ingredients, further complicating regulatory oversight.

The RIVM Report 370030002/2009 highlights concerning trends in health risks associated with illegal weight-loss medicines and supplements from 2002 to 2007. [18] Consumers are misled by mislabelled supplements, and counterfeit medicines proliferate outside official distribution channels. A notable incident in Japan in 2002, where a herbal tea containing a designer analogue of fenfluramine (n-nitroso-fenfluramine) led to poisonings and fatalities, underscores the global concern regarding product safety. [1]

Weight loss drugs and designer analogues pose regulatory and health challenges that will require attention, especially when new drugs gain massive popularity. Addressing the regulatory grey area and escalating health risks associated with these products is essential to safeguarding public health.



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First human trial shows ‘wonder’ material can be developed safely

A revolutionary nanomaterial with huge potential to tackle multiple global challenges could be developed further without acute risk to human health, research suggests. Carefully controlled inhalation of a specific type of graphene – the world’s thinnest, super strong and super flexible material – has no short-term adverse effects on lung or cardiovascular function, the study results show. The first controlled exposure clinical trial in people was carried out using thin, ultra-pure graphene oxide – a water-compatible form of the material.

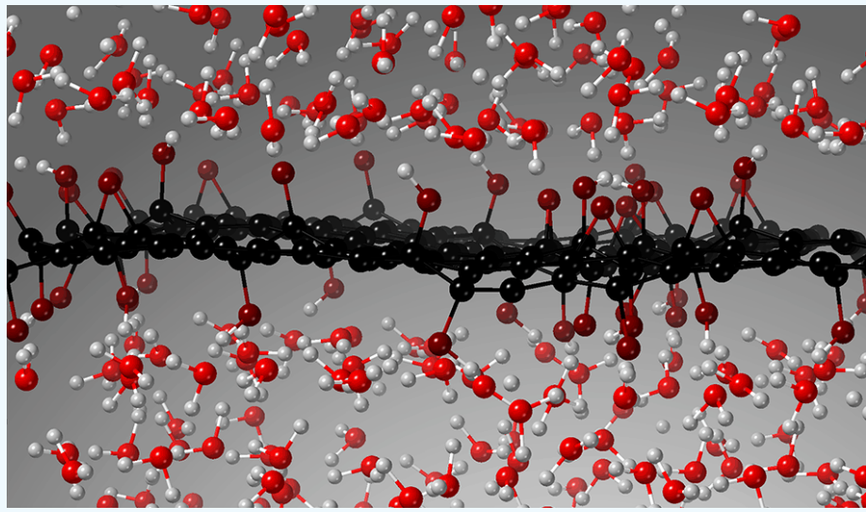
The following text is an overview by the University of Edinburgh of a study published in the journal Nature Nanotechnology: https://www.nature.com/articles/s41565-023-01572-3 .

***Dr. Flemming R. Cassee,** Chief Science Officer, RIVM / Professor in Inhalation Toxicology, Utrecht University is a co-author.*

Researchers say further work is needed to find out whether higher doses of this graphene oxide material or other forms of graphene would have a different effect. The team is also keen to establish whether longer exposure to the material, which is thousands of times thinner than a human hair, would carry additional health risks. The work was a multi center effort that from the Dutch side included the National Institute for Public Health and the Environment (RIVM) and the study itself was performed at the Royal Infirmary in University of Edinburgh’s Centre for Cardiovascular Science with Dr Mark Miller as the PI.

There has been a surge of interest in developing graphene – a material first isolated by scientists in 2004 and which has been hailed as a ‘wonder’ material. Possible applications include electronics, phone screens, clothing, paints and water purification. Graphene is actively being explored around the world to assist with targeted therapeutics against cancer and other health conditions, and also in the form of implantable devices and sensors. Before medical use, however, all nanomaterials need to be tested for any potential adverse effects. Researchers from the Universities of Edinburgh and Manchester recruited 14 volunteers to take part in the study under carefully controlled exposure and clinical monitoring conditions. The volunteers breathed the material through a face mask for two hours while cycling in a purpose-designed mobile exposure chamber brought to Edinburgh from the National Public Health Institute in the Netherlands. Effects on lung function, blood pressure, blood clotting and inflammation in the blood were measured – before the exposure and at two-hour intervals. A few weeks later, the volunteers were asked to return to the clinic for repeated controlled exposures to a different size of graphene oxide, or clean air for comparison. There were no adverse effects on lung function, blood pressure or the majority of other biological parameters looked at. researchers noticed a slight suggestion that inhalation of the material may influence the way the blood clots, but they stress this effect was very small.

Dr Mark Miller, of the University of Edinburgh’s Centre for Cardiovascular Science, said: “Nanomaterials such as graphene hold such great promise, but we must ensure they are manufactured in a way that is safe before they can be used more widely in our lives. “Being able to explore the safety of this unique material in human volunteers is a huge step forward in our understanding of how graphene could affect the body. With careful design we can safely make the most of nanotechnology.” Professor Kostas Kostarelos, of the University of Manchester and the Catalan Institute of Nanoscience and Nanotechnology (ICN2) in Barcelona, said: “This is the first-ever controlled study involving healthy people to demonstrate that very pure forms of graphene oxide – of a specific size distribution and surface character – can be further developed in a way that would minimize the risk to human health. “It has taken us more than 10 years to develop the knowledge to carry out this research, from a materials and biological science point of view, but also from the clinical capacity to carry out such controlled studies safely by assembling some of the world’s leading experts in this field.”



Graphene oxide in liquid water
By Marie-Laure Bocquet, under Creative Commons Attribution 4.0 International License.

A Closer Look at QACs and Organophosphate Flame Retardants

By *Barae Jomaa*

In recent years, the safety of common household chemicals has come under scrutiny. A study[1] has highlighted the potential neurological risks associated with two such chemicals: quaternary ammonium compounds (QACs) and organophosphate flame retardants. The study generated significant attention and grabbed headlines in the media[2–4].

QACs are a common ingredient in many household products, including disinfectants and body washes. Organophosphate flame retardants, on the other hand, are often found in electronics and furniture. Despite their ubiquity, these chemicals may pose health risks.

The study suggests that QACs can cause the death of oligodendrocytes, a type of brain cell vital for nerve protection. Similarly, organophosphate flame retardants may inhibit the maturation of these cells. These findings have raised concerns about the potential link between exposure to these chemicals and neurological disorders such as autism and multiple sclerosis.

However, the industry has responded to these concerns with reassurances about the safety and regulatory compliance of these chemicals. The American Cleaning Institute, which represents manufacturers like Clorox and Procter & Gamble, emphasizes the crucial role these chemicals play in public health.

Despite these assurances, the study's findings underscore the need for further research into the potential health impacts of common household chemicals. As consumers, it is essential to stay informed about the products we use daily and the potential risks they may pose to our health.

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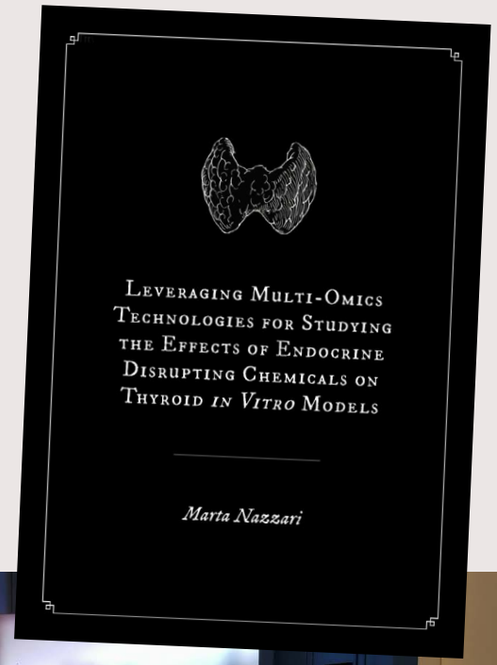
Omics in *In Vitro* Toxicology: Unlocking Mechanisms of Endocrine Disruption

— Insights from My Doctoral Thesis

By *Marta Nazzari*

On Wednesday 10th April 2024 I defended my PhD thesis titled “Leveraging Multi-Omics Technologies for Studying the Effects of Endocrine Disrupting Chemicals on Thyroid *In Vitro* Models” at Maastricht University. If we were to summarize what it was about in a few words, it would be the following: I applied bioinformatics to study *in vitro* thyroid toxicology.



The work done in the thesis was part of SCREENED, a Horizon2020 project focused on developing novel 3D *in vitro* thyroid models and using these models for assessing toxicological responses caused by endocrine disrupting compounds (EDCs). EDCs which are a broad category of anthropic or natural compounds that can interfere with the functioning of endocrine systems and cause an adverse effect.

In my thesis, I took a bioinformatics approach to answer a toxicological problem, a path not often taken by traditional toxicology. Indeed, what is relevant for thyroid risk assessment is evaluating some specific parameters that are indicative of thyroid functionality disruption. For example, in its guidelines, the Organization for Economic Co-operation and Development (OECD), recommends assessing changes in thyroid hormone (TH) and thyroid stimulating hormone (TSH) serum levels, direct effects on thyroid histology as well as alterations in development and maturation. As the reader can notice, they are all physiological parameters: this is because the only currently approved tests for assessing thyroid disruption are *in vivo*, and do not provide any information about the mechanism underlying the observed perturbation.

One could ask oneself: is mechanistic information necessary then, if we only need to be able to see whether thyroid hormone levels are really altered? My simple answer is yes. And that’s when the use of *in vitro* models really comes through. Gaining mechanistic insight can be useful in several circumstances, and greatly facilitated using omics, since you get information on the whole transcriptome, proteome or genome asset of a cell or cell population. For example, you could observe a disruption that is the consequence of interference with a more “common” cellular pathway, which involves genes whose expression is not thyroid-specific, but for which the thyrocytes (the main thyroid cell type, responsible for synthesizing the TH) have a particular sensitivity. Alternatively, omics can be employed in the context of Adverse Outcome Pathways (AOPs): they can help connect changes in gene or protein expression to an adverse effect irrespective of the compound that is being studied, being AOPs, they are cell and compound agnostic. This could be applied, for example, to the categorization of compounds: if their action can be traced back to a known Molecular Initiating Event (MIE) and eventual Adverse Outcome (AO), they could be classified as toxic or not, and could be an alternative to read-across methods.

To give an example of how omics can be used in toxicology, I can provide some examples from my thesis: in the chapter titled “Multiomics Analysis of the Effects of Endocrine Disrupting Chemicals on Mouse Embryonic Stem Cell-Derived Thyroid Organoid”, we generated a mRNA, miRNA and protein dataset of mouse embryonic stem cell-derived thyroid follicles exposed to 16 different EDCs. We combined the three datasets to identify if changes in genes or miRNA expression could be predictive of the levels of target proteins and to derive Random Forest classification models using the levels of expressions of the three to determine whether a sample belongs to any of the EDC classes analyzed.

In our manuscript “Investigation of the Effects of Phthalates on *In Vitro* Thyroid Models with RNA-Seq and ATAC-Seq”, we studied the effects of four phthalates, observing a common upregulation of the fatty acid metabolism pathway, and a downregulation of pathways involving signaling molecules like RHO GTPases, TGFb and tyrosine kinases and extracellular matrix organization.

In the chapter “Impact of Endocrine Disrupting Chemicals and Sex Hormones on Human ESC-Derived Thyroid Follicles Using Single Cell Transcriptomics” (preprint and under review), we used single-cell RNA-Seq to dissect the response of the thyrocyte population to benzo[a]pyrene or PCB153 under the influence of sex hormones combinations representative of human males and females of reproductive age, as a possible way of highlighting some differences in the thyroid physiology observed between the two sexes.

To summarize, we showcased how omics technologies can be used in toxicology experiments to elucidate the cell response to toxic chemicals and provided hypotheses to be further tested with targeted experiments. SCREENED started developing a model and tested it, laying the basis to eventually lead to the use of *in vitro* models for endocrine disruption testing.

AIO toxafette - Tom Roos

In the toxafette, Ph.D. students specializing in toxicology exchange insights gained from their research projects. Each edition features a fresh participant who responds to a set of inquiries before passing the torch to another doctoral candidate. In this instance, Tom Roos, PhD candidate at Utrecht University.

Can you introduce yourself?
Hello! My name is Tom. I obtained my bachelor’s and master’s degrees in Biomedical Sciences (BMS) at the Radboud University in Nijmegen, the city where I was born and currently still live. Right after obtaining my master’s degree, I started my PhD at the IRAS Pharmacology group at Utrecht University back in March 2022, where I currently work on the EU-project ALTERNATIVE which is focused on cardiotoxicity assessment.

How would you explain the subject of your research to a layperson?
Heart disease is a leading global cause of death. Recent research indicates that certain environmental chemicals can worsen heart problems. However, many chemicals have not been adequately tested for long-term effects on the heart before they were placed on the market. The European ALTERNATIVE project is developing a non-animal testing method that can assess how certain chemicals affect the heart, i.e. cause cardiotoxicity. This involves growing artificial pieces of heart tissue in a bioreactor in the lab and applying chemicals of interest to see what happens. By combining this artificial heart with computational methods, we can test the cardiotoxic potential of these chemicals without having to use animals.

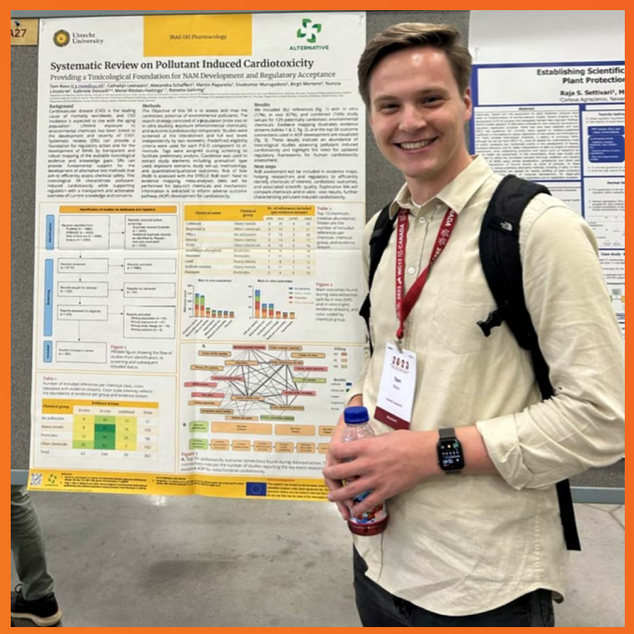
My research involves a systematic literature review of scientific studies to understand which and how chemicals can cause cardiotoxicity. This informs policymakers and promotes non-animal testing methods for cardiotoxicity by providing a clear overview of the available toxicological evidence. Furthermore, we are developing mathematical models which can predict the fate of chemicals in the human body by using physiological principles of the human body. With these models, we can calculate how much exposure to a chemical is needed to cause heart problems, and, together with the literature review, this information can be used to prioritize and screen certain chemicals for cardiotoxicity assessment in the platform.

How is your research related to the field of toxicology, and why did you choose this subject?
From a toxicological perspective, exposure to certain pollutants such as heavy metals and pesticides may exacerbate cardiovascular disease development and progression, especially when accounting for chronic exposure. However, not much is currently known about the extent to which certain chemicals can affect the heart in the long term, and testing methods to assess this are lacking.

I mainly chose this project as it was focused on computational toxicology. I have always liked doing the subsequent data analysis more than the actual lab work, so this was a clear sign for me to stay away from the more lab-focused positions. My current position allows me to further develop my main interests in computational toxicology by analyzing and potentializing the lab data that we receive from our partners within the project. In summary, this project allows me to combine my main interests in toxicology and pharmacology (computational modelling) with a subject that is super relevant and all around us (heart disease).

What was your motivation for starting a Ph.D. program?
During my master's degree, I specialized in pharmacology and toxicology, which I highly enjoyed. However, after finishing my master's degree, I felt that I still had a lot to learn and wanted to delve deeper into the different aspects of (computational) toxicology and pharmacology. I also enjoyed doing research during my internships at Radboud University and at the RIVM, so a Ph.D. program was the perfect next step. I feel that a PhD position provides a great opportunity to professionally and personally develop as a young scientist, and I'm happy with my choice.

How do you see the future of your research topic (follow-up research / social impact)? What do you hope for?
I hope to contribute to an adequate testing paradigm for chemical cardiotoxicity while reducing unnecessary animal testing. I also feel that there is a shift towards a more computational centered approach in toxicology, as more tools are becoming available to potentialize the huge amounts of data that are produced in this field. In the end, it would be great if I could contribute a small piece of the puzzle towards a reduction in animal testing while helping the development of computational tools in toxicology.



Can you explain how different subjects or areas relate to your research, and why this connection matters?

The main goal of the ALTERNATIVE project is to develop an Integrated Approach to Testing and Assessment (IATA) for cardiotoxicity by using new approach methodologies (NAMs). Many other (European) projects are focused on developing IATAs and NAMs for certain target organs, tissues, systems or phenotypes, and many aspects involved in the development of IATAs and NAMs are similar between these projects. Therefore, we are collaborating within a Green Deal Cluster with sister projects including PROMISCES, LifeSaver, SCENARIOS, PANORAMIX and ZeroPM. The goal of this collaboration is to learn from each other's experiences, towards regulatory acceptance of these alternative methods.

How do you ensure that others can replicate your experiments and achieve the same results?
By using open-source software (R) for our computational models and publishing the full source code alongside our papers, we can make sure that everyone can test and reuse our models and adjust them to their own liking. We've also published the protocol of our systematic review in an open-access journal ahead of performing the actual systematic review, so that the methodology and research questions were clear, transparent and peer reviewed before starting screening, data extraction and subsequent analyses. Furthermore, we're adhering to the FAIR principles in our project, ensuring that all output, products, reports and publications are available to the public.

What are your thoughts on using new technologies like artificial intelligence in toxicology research? Are you using any of these technologies in your work?
I think that AI is well suited to handle the complexity and large volumes of data associated with modern toxicology research, and that there are a lot of possible use cases for AI in toxicology. We are using machine learning methods that can parameterize our physiologically based kinetic (PBK) models for chemicals with limited information. Similarly, machine learning models can be trained on existing datasets of chemicals and their toxicity profiles to predict the toxic potential of new chemical entities, accelerating chemical screening and selection. I think these are powerful tools that can potentially be helpful in certain scenarios but should always be handled with care and evaluated by experts.

Does the project meet your expectations, why or why not?
The project exceeds my expectations! I think cardiotoxicity is a really exciting and (in case of environmental chemicals) emerging field within toxicology. I also like the link with pharmacology, veterinary science, and the international nature of the project. The project allows me to contribute to the animal free testing paradigm for chemicals while cooperating with partners all over Europe!

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?

Right now, I am highly enjoying my position in academia and feel that there is still a lot of unfinished work before I can think of something else. I like taking things one step at a time, so we'll have to see what the future holds.

Please answer the question from the last toxafette PhD-candidate: What do you think is needed for a future where all animal toxicity studies are replaced with computational toxicity studies?
Although it is exciting to think about an animal free testing future, I think we have to be realistic in acknowledging there's still a long road ahead. However, computational methods are essential tools in the transition towards alternative methods. Currently, computational methods can already make toxicology much more efficient, reducing animal testing by predicting some of the toxicological endpoints that can easily be captured with non-animal methods. More emphasis could be placed on these methods (including computational tools) for a future in which animal toxicity studies can be reduced (and eventually hopefully replaced).

A Day in the Life of a Toxicologist

How I use toxicology to manage regulatory requirements

By *Pauline Herst, Ctgb*

How I use toxicology to assess the health risks in response to plant protection products

The task of the Dutch Board for the Authorisation of Plant Protection Products and Biocides (Ctgb) is to assess whether plant protection products and biocidal products are safe for humans, animals and the environment in accordance with international agreements and criteria laid down in legislation.

Based on this assessment, the Ctgb decides whether products can be sold and used in the Netherlands. Our scientific assessment work is subject to many European regulations, European directives and national laws, including the Plant Protection Products and Biocidal Products Act (Wgb).

How did you end up at Ctgb?

I conducted my doctoral studies at the department of Animal Sciences of Laval University in Quebec City, Canada. There, I studied the multigenerational burden of *in utero* exposure to Arctic pollutants on the sperm epigenome and how Vitamin B9 supplementation could act as a shield across generations using a rat model. Aside my thesis, I also studied the impact of Arctic pollutants on fat metabolism of wild Norwegian Polar bear mothers and her cubs. It was an interesting mix of molecular biology, reproductive biology and environmental toxicology. After my PhD, I chose to gain experience in industry and worked as a medical researcher for a start-up biotech company in Vienna, Austria. This company aimed to develop an at-home diagnostic tool to measure various blood markers like ferritin, thyroid stimulating hormone and the Anti-Müller hormone. Although the work and team were great, I missed scientific depth and so decided to look for other jobs which also involved toxicology and ended up working as a Scientific Risk Assessor for Team Human Toxicology Plant Protection Products at Ctgb.

What does your team do?

In a nutshell, Team Human Toxicology Plant Protection Products evaluates the safety of both active substances and products. The use of plant protection products may result in human exposure occurring via different routes: oral, dermal and respiratory. It is therefore important that the intrinsic human toxicological properties of each active substance and product can be evaluated and established. The information on the toxic effects and kinetics of a substance is mainly based on the results of experimental toxicological research performed with various laboratory animal species. Besides toxicity data on the active substance, data on metabolites may also be required if human exposure to such metabolites occurs. Each study is summarized separately in the toxicological summary and, if possible, the relevant endpoint dose descriptor is derived such as the 'No Observed Adverse Effect Level' (NOAEL) for repeated dose toxicity studies and reproductive toxicity studies, LD50 for acute toxicity studies etc. This evaluation is conducted for each study and for each sub-aspect in a toxicologically-based endpoint, and finally this results in the toxicological profile of a substance. After approval of an active substance at the EU level, the dose descriptors of toxicological endpoints that are derived from the submitted research then form the basis of the risk evaluation for products for operator, worker, bystander and resident, and for consumers. These evaluations, as a whole, are carried out in close collaboration with other EU Member States and EFSA. For example, we often participate in EFSA Expert meetings to discuss data gaps with experts of other EU Member States. Also, the active substance assessment includes a proposal for classification and labelling, which will be submitted to ECHA by RIVM.

What makes your job interesting?

There are many aspects that make the job interesting! Let's start with the complexity of the evaluation which requires

you to deep dive into the toxicity of an active substance/mixture. Examples of data requirements that we evaluate according to the respective guidance include: absorption/distribution/metabolism/excretion, acute toxicity, repeated dose toxicity, genotoxicity, long-term/carcinogenicity, neurotoxicity, developmental and reproductive toxicity as well as endocrine disruption studies. This variety, and knowing that no dossier is the same, makes the work very interesting. All dossiers have their own particularities. It is also very motivating when everything comes together and you can perform the actual risk assessment for the operator, worker and residents/bystanders or can set up the classification of the mixture. Besides learning more about your own discipline, you also learn from other disciplines. Besides human toxicology, the Ctgb covers the evaluation for chemistry, efficacy, residues and consumer exposure, environmental fate and behaviour and ecotoxicology. Together we use scientific knowledge, expert judgement and (inter)national regulations to make well-founded and transparent decisions about the safety of an active substance or mixture. Apart from the above, the world of plant protection products regulation is an ever-evolving field. Products, guidelines and science change. Nowadays more and more green plant protection products are submitted which require different data requirements than their chemical cousins.

Lastly, the work that you do as a scientific risk accessor in human toxicology directly contributes to the safety and health of society.

Flemming Cassee Honored with Career Achievement Award at SOT

At the Society of Toxicology (USA) annual conference in Salt Lake City, Flemming Cassee (RIVM) received a Career Achievement Award in Inhalation and Respiratory Toxicology on March 13. This award is given to a senior investigator whose work represents outstanding achievement in the field of respiratory/respiratory toxicology and considers breadth and depth of scientific contributions, influence on the education/training/mentoring of young scientists in the field, leadership and service to the field, and influence on regulatory/public health decisions.

Flemming started his career in science by studying biology at Utrecht University in the Netherlands, from 1985 - 1990, with a major in toxicology. He subsequenty worked on a project on combined exposures to aldehydes under the supervision of the late Prof. Victor Feron of the TNO institutes in the Netherlands. He was most inspired by people like Jack Harkema, Kevin Morgan, Henry Heck, Mercedes Casanova and James Bond J and in 1995 Flemming obtained his PhD degree from the Utrecht University and immediately after, he was appointed as a researcher at the National Institute for Public Health and the Environment (RIVM), the Netherlands to study the causal relationship between various fractions of particulate matter and health effects, primarily by performing rodent inhalation studies, initially supervised by Leendert van Bree and Peter Rombout. After a few years at RIVM he took over the role of head of the department of Inhalation Toxicology.

While conducting the inhalation studies with secondary inorganic particulate matter he also became familiar with particle dosimetry as a tool to extrapolate findings from experimental studies to humans in order to link toxicology and epidemiology. This led to the development of the multiple-path

particle dosimetry model, mainly developed by, at that time, CIIT colleagues Ravi Subramaniam, Bahman Asgharian and Fred Miller and Flemming together with his RIVM colleagues made sure that a user-friendly interface was developed and that the model became freely available. By now, MPPD is a commonly used model that recently also received approval from the US EPA, pushed hard by Annie Jarabek. Inspired by Gunter Oberdorster and Wolfgang Kreyling, he always emphasized the need for dosimetry and understanding the biologically effective and retained dose rather than only looking at concentrations.

In 1998, he started to work with one of the first ambient fine particle concentrators developed at the Harvard School of Public Health by Costas Sioutas and Petros Koutrakis. His group was the first to install it in a mobile laboratory, recognized that air pollution differs depending on the location - and the campus of RIVM was not the most polluted area in the Netherlands. Exposing animals near freeways was never done before. Here he also took the initiative to harmonize the various study designs with colleagues that also used concentrators for both the animal as well as human exposures. At the same he started to use high volume cascade samplers to collect PM fractions across Europe, as part of EU funded projects. This resulted in more insight in source specific health effects. Flemming was not only doing research, but he also participated in review panels such as those for the PM centers sponsored by the US EPA, and was advisor at WHO Europe working on documents to inform policy makers. His papers *Black carbon as an additional indicator of the adverse health effects* in Environmental Health Perspectives and *Particulate matter beyond mass: Recent health evidence on the role of fractions, chemical constituents and sources of emission* in Inhalation Toxicology have been cited well over 300 times. He has co-authored > 224 papers and with an H factor of 71 his work has been appreciated by many researchers across the world.

He also has been the editor-in-chief of Particle and Fibre Toxicology for more than 10 years and under his leadership this journal reached a very high impact factor among the toxicological journals. He also is associate editor of Inhalation Toxicology.

While inhalation toxicology primarily focuses on effects on the respiratory system, Flemming went beyond this and, in collaboration with investigators at the Edinburgh University, the first human controlled exposure studies were done with a focus on cardiovascular responses. This has led to several very well cited papers in which not only effects of diesels exhaust was explored but also the beneficial effects of using particle traps and catalytic converters. Their study, using gold particles to demonstrate particle translocation to plaques in blood vessels, was very well received and most recently they showed that certain graphene oxides can be very well tolerated up to 200 µg/m^3 for 2 hr by healthy volunteers.

Like the US EPA, RIVM is very much dependent on political willingness to invest in air pollution research and since the Netherlands was reaching EU standards, funding declined. This resulted in a partial shift around 2005 towards nanotechnology, after all, this is still about being exposed to particles, but now these are engineered. Since then, he has been a partner in a number of projects funded by the European Commission to establish which factors influence particle toxicity and, more recently, how these can be modified according to safe-by-design principles. The lessons learned from inhalation toxicology were also applied in the revision of OECD inhalation toxicity testing guidelines in which he played a major role.

Meanwhile his work on air pollution continued with studies on microorganisms in particulate matter, effects on the brain and also studies in which translocation of very small inhaled particles from the placenta into the fetus was studies including the implications for fetal development. Here again, his interest in particle dosimetry became evident as in a recent paper he co-authored where carbon particles were identified in fetal tissues.

Flemming also contributed to a WHO paper titled *Dietary and inhalation exposure to nano- and microplastic particles and potential implications for human health,* showing is broader interest in particle toxicology.

At present his air pollution research focuses on wood smoke and non-tail pipe emissions. Apart from this, he became professor in Inhalation Toxicology in 2012, at the Institute for Risk Assessment Sciences of Utrecht University and he also is Chief Science Officer at the RIVM, coordinating the internal research program which has a much wider scope than toxicology.

Society of Toxicology Annual Meeting

March 10-14, Salt Lake City, USA

TRAVELER:
Irene Gosselink, Maastricht University

The NVT travel grant supported my visit to the largest toxicology meeting worldwide (5000+ attendees), the SOT Annual meeting. My abstract, entitled 'Assessing toxicity of amorphous micro- and nano-plastics on bronchial epithelial cells using air-liquid interface models' was accepted for an oral presentation. Microplastics have been reported both in indoor and outdoor air and these particles have been found in all areas of the lung, making it clear that inhalation is a major exposure route to micro -and nano-plastics. However, knowledge of the toxicological impact of micro- and nanoplastics on the human airway and lung epithelium is limited, and almost exclusively based on submerged *in vitro* experiments with spherical polystyrene.

Our study aims to study the toxicity of well-characterized environmentally relevant microplastics on bronchial epithelial cells, using relevant culture models. Therefore, we include several submerged and air liquid interface cell cultures, among which cultures of fully differentiated primary bronchial epithelial cells. We looked at diverse outcomes, including cytotoxicity and inflammation. In our study, we found that smaller-sized nanoplastics, specifically nylon particles, were exhibiting higher toxic effects on bronchial epithelial cells than microplastics. In addition to size, also polymer type, doses, as well as differences in experimental models lead to different outcomes in micro- and nanoplastics toxicity research.

Presenting my research during the platform session about micro- and nanoplastics was a very valuable experience that contributed to the development of my scientific presentation skills. Our work received a lot of attention during this well visited session and I had great discussions afterwards about particle deposition, variations in cell culture systems and potential collaborations in the field of respiratory toxicology and micro- and nanoplastics research.

My "take home message" from this conference would be that it is crucial to validate and characterize the cell cultures used for toxicity testing very well, as this is critical for data interpretation.

Although being crucial for research development, conferences have an impact on the carbon footprint and waste production. To reduce single-use plastics and reduce microplastics exposure, I would like to challenge everyone to bring their own reusable cup to scientific conferences (like the NVT meeting this year).

I would like to thank the NVT to support my visit to the SOT 2024. It was a great opportunity to present my data and meet experts in the field of respiratory toxicology.

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RESEARCH ARTICLE

Marcha C.T. Verheijen

Psilocybin Therapy for Depression: A Review of Current Molecular Knowledge

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Research Article

Psilocybin Therapy for Depression: A Review of Current Molecular Knowledge

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Abstract

Depression, affecting over 264 million people globally, presents significant treatment challenges, often due to the limited efficacy and adverse effects of traditional antidepressants and the accessibility issues associated with psychotherapy. Recent advancements in psychedelic-assisted therapy, particularly using psilocybin, a naturally occurring compound found in "magic mushrooms", shows promising potential for treating major depressive disorder (MDD) and treatment-resistant depression (TRD). This review explores the historical context, clinical trial outcomes, and the biological mechanisms underlying psilocybin's effects. Clinical studies from 2016 to 2023 indicate that psilocybin, in combination with psychological support, significantly reduces depressive symptoms, with benefits lasting up to several months after a single dose treatment. The molecular action of psilocybin involves its conversion to psilocin, which interacts with serotonin receptors, notably the 5-HT2A receptor, influencing neurotransmitter systems and promoting anti-inflammatory responses and neuroplasticity. The review also discusses the safety profile of psilocybin, highlighting its low risk for dependency and minimal adverse effects compared to traditional treatments. Finally, the therapeutic advantages of psilocybin over conventional antidepressants are evaluated, emphasizing its rapid and sustained antidepressant effects, which contribute to its potential as a groundbreaking treatment for depression.

Keywords

Psilocybin; Therapy; Depression; Molecular mechanisms.

1 Introduction

Depression affects over 264 million people worldwide and is primarily treated with antidepressants like SSRIs (Selective Serotonin Reuptake Inhibitors), NRIs (Norepinephrine Reuptake Inhibitor), or SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors) targeting serotonergic mechanisms, and/or through psychotherapy [1, 2]. However, antidepressants often have a moderate success rate and can cause side effects such as sexual dysfunction and emotional blunting [3, 4]. Moreover, they require long periods to take effect and multiple courses of treatment are necessary [1, 2]. Psychotherapy may be inaccessible due to high costs and long wait-lists and often demands high motivation levels, which can be challenging for depressed patients [1, 5]. When patients do not respond to two adequate treatments with conventional antidepressants, their condition is classified as Treatment-Resistant Depression (TRD) [6]. This occurs in approximately one third of depressed patients [7], highlighting the urgent need for innovative treatments beyond the traditional methods.

Psilocybin is a naturally occurring psychedelic compound found in the Psilocybe genus of mushrooms, often referred to as "magic mushrooms" [2]. As a classic psychedelic, psilocybin belongs to the tryptamine class, structurally similar to serotonin [8]. It has been used for centuries by indigenous populations for religious ceremonies [9]. After Albert Hofmann and colleagues [10] managed to isolate the active compound psilocybin from the mushrooms in 1958, it became highly researched. These studies, although not up to modern scientific standards, indicated promising outcomes, with 80% of patients showing improvement [1, 8]. Around this same time, there was a global increase in recreational use of psychedelics (mostly LSD). Concerns over the unpredictable psychological effects and the sensationalized media portrayal of negative incidents involving psychedelics further fueled public fear and moral panic [11]. This resulted in the U.S. Controlled Substances Act of 1970, which classified psychedelics as Schedule I drugs, making research into their beneficial effects complicated.

2 Results from recent clinical trials

Despite psilocybin's illegal status, obstacles to research have loosened over time. Recent studies have sparked renewed interest in psilocybin, particularly for treating mood disorders [6, 8]. Notably, groundbreaking research in 2016 [12, 13] demonstrated that psychedelic-assisted psychotherapy is highly effective in treating depression. These studies marked a crucial resurgence of interest in psilocybin as a viable therapeutic option [9].

From 2016 to 2023, a series of clinical trials have underscored the effectiveness of psilocybin therapy in managing major depressive disorder (MDD) and treatment-resistant depression (TRD). These trials administered psilocybin in conjunction with psychological support from trained therapists [6, 13–17]. Results have consistently shown that a single dose of psilocybin can lead to statistically and clinically significant reductions in depressive symptoms, alleviating depression severity, anxiety, and functional outcomes, and notably decreasing the number of lost or ineffective days. These benefits have been observed to last for the duration of the studies, typically 6 to 12 weeks. Moreover, a long-term follow-up study, conducted 4.5 years post-treatment, indicated that 60-80% of participants sustained significant antidepressant responses, with 71-100% reporting that the psilocybin-assisted therapy contributed to positive life changes [17]. The promising results from clinical studies on psilocybin led to further research aimed at elucidating the mechanisms underlying its potential therapeutic effects [9].

3 Metabolism of psilocybin

Psilocybin is a prodrug, meaning it must be converted into its active form, psilocin, to be effective (Fig. 1). This conversion involves a dephosphorylation reaction, catalyzed by alkaline phosphatases. The reaction primarily occurs in the intestines, although it also takes place to a lesser extent in the stomach, kidneys, and blood [2]. Once converted to psilocin, it induces a hallucinogenic phase lasting between 2 to 6 hours, characterized by a range of subjective effects including visual hallucinations, euphoria, a loss of sense-of-self, and spiritual experiences [2, 9]. Psilocin undergoes further metabolism in the liver, primarily through demethylation and oxidative deamination by enzymes such as monoamine oxidase and aldehyde dehydrogenase. This metabolic process gradually reduces the hallucinogenic effects [2].

4 Psilocybin action through serotonin receptor 5-HT2A

Psilocybin closely resembles the structure of serotonin (5-hydroxytryptamine, 5-HT) [8] (Fig. 1). Despite psilocybin being a prodrug with pharmacologically negligible

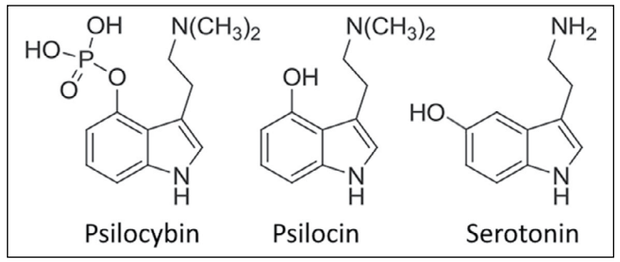

Fig. 1: Chemical structures of psilocybin, psilocin and serotonin. After psilocybin is metabolized to its active form Psilocin, it shows a close resemblance with serotonin [18]

effects itself, its active metabolite, psilocin, engages with multiple receptors. Psilocin binds with moderate affinity to the 5-HT1A, 5-HT1B, 5-HT2A, and 5-HT2C receptors, as well as to the histamine H1 receptor. It shows higher affinities to the 5-HT2B and 5-HT7 receptors. This multi-target interaction contributes to the complex therapeutic effects observed in the treatment of depression [9].

Serotonin receptors are implicated in numerous physiological functions, including vision, immune response, and neurotransmitter signaling, highlighting their extensive influence across body systems. The acute subjective effects of psilocybin include visual hallucinations, altered perception, and emotional experiences often described as mystical or spiritual. These effects are mediated primarily through the activation of the 5-HT2A receptors, which are prominently expressed in the visual cortex. Psilocybin's interaction with these receptors leads to profound sensory and perceptual changes, supported by physiological responses such as changes in heart rate, blood pressure, and temperature, reflecting the receptor's widespread influence [9].

Activation of the 5-HT2A receptor by psilocybin is critical for its hallucinogenic effects. This was confirmed through studies employing 5-HT2A receptor antagonists like ketanserin that have shown that blocking this receptor significantly attenuates the psychedelic effects [19]. 5-HT2A receptor activation triggers a series of downstream effects mediated by secondary messenger systems, leading to alterations in gene expression and protein activity that are characteristic of psilocybin's acute impacts [2]. Interestingly, the antidepressant effects of psilocybin are not solely dependent on 5-HT2A receptor activation. Experiments using psilocybin in conjunction with ketanserin demonstrated that other serotonin receptors also contribute to its antidepressant properties [19]. This indicates that psilocybin's therapeutic effects may involve a broader array of receptor interactions, including but not limited to 5-HT2B and 5-HT2C, and potentially non-serotonergic pathways as well [19]. Therefore, while current literature mostly focusses on 5-HT2A receptor dependent mechanisms, 5-HT2A receptor independent signaling pathways also exist [9]. Furthermore, continuous activation of 5-HT2A by psilocybin leads to receptor downregulation, a process likely involved in the desensitization mechanisms that underlie long-term therapeutic effects, because previous studies have suggested that overexpression of 5-HT2A receptors is present in patients with MDD, with expression correlating positively to the severity and duration of depression [2].

5 Anti-inflammatory effect

Next to 5-HT2A receptor's role in the hallucinogenic effects of psilocybin, it is essential to explore another aspect —its influence on inflammatory processes. Chronic low-grade inflammation is increasingly recognized as a significant factor in the pathogenesis of mood disorders such as depression [1]. This inflammation is characterized by elevated levels of pro-inflammatory cytokines like IL-1α, IL-1β, IL-6, and TNF-α, along with acute-phase proteins such as C-reactive protein (CRP). These markers are not only elevated due to psychosocial stressors but also play a role in the onset and maintenance of depressive disorders [2, 20].

Psilocybin's agonism at the 5-HT2A receptor leads initially to a reduction in TNF-α, a key pro-inflammatory cytokine. The inhibition of TNF-α is crucial because it can induce IL-6 synthesis through the activation of the NFκB and MAPK pathways, particularly phosphorylation of p38 MAPK [2]. IL-6, in turn, is a direct inducer of CRP synthesis in the liver, which is considered an important circulating biomarker of inflammation in clinical practice. Studies indicate an immediate reduction in TNF-α levels following psilocybin administration, with these levels returning to baseline within seven days. However, the levels of IL-6 and CRP remain reduced, suggesting a long-term anti-inflammatory effect. This persistent reduction correlates with sustained improvements in mood and prosocial behavior [20].

TNF-α is not only a critical mediator of systemic inflammation but also a potent inducer of the kynurenine pathway. This pathway metabolizes tryptophan into kynurenine, diverting it from serotonin synthesis, which can lead to reduced serotonin availability and contribute to depressive symptoms. More critically, certain metabolites within the kynurenine pathway, such as quinolinic acid, are neurotoxic and have been implicated in neurodegeneration and the pathophysiology of depression. By modulating this pathway, psilocybin may reduce harmful kynurenine metabolites and neuroinflammation, thereby potentially alleviating symptoms of depression [1].

6 Neuroplasticity

Neuronal atrophy in the prefrontal cortex (PFC) is a significant feature of many stress-related neuropsychiatric disorders, including depression. Psilocybin has demonstrated the potential to counteract these deficits by promoting structural and functional neuroplasticity in the PFC [21]. Research has shown that even a single administration of psilocybin can lead to robust and lasting changes in cortical neuron growth, significantly increasing spine density in the PFC for at least a month. Additionally, psilocybin has been shown to promote dendritic growth both in vivo and ex vivo, enhance excitatory postsynaptic potential in hippocampal neurons, and induce behavioral changes suggestive of antidepressant-like activity. These structural changes are supported by further studies demonstrating that psilocybin effectively promotes neuritogenesis, spinogenesis, and synaptogenesis in rat embryonic cortical cultures, further illustrating its profound impact on brain plasticity [9, 21].

The activation of the 5-HT2A receptor by psilocin, triggers an increased release of glutamate, which is the main excitatory neurotransmitter in the brain responsible for promoting neuronal communication and activation [9]. Furthermore, when psilocin binds to the 5-HT2A/mGlu2 receptor complex, it likely results in the inhibition of mGlu2 activity, which typically acts to suppress the synaptic release of glutamate. Therefore, its inhibition by psilocin can lead to further increase in glutamatergic transmission [2]. This glutamatergic surge is critical, as it facilitates the activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-D-aspartate) receptors, enhancing synaptic plasticity and excitatory signaling within neural networks [1].

Activation of AMPA and NMDA receptors results in an upregulation of brain-derived neurotrophic factor (BDNF), a protein that plays a key role in the survival, growth, and maintenance of neurons in the developing and adult brain [1]. BDNF then binds to tropomyosin receptor kinase B (TrkB), initiating a signal transduction cascade that leads to the activation of the mTOR (mammalian target of rapamycin) pathway, crucial for protein synthesis that support synaptic strength and plasticity, contributing to the structural changes. This pathway not only supports current synaptic function but also prepares the neuron for future connections, enhancing the brain's ability to adapt to new information or environments. Additionally, mTOR activation further increases the production of BDNF, creating an autoregulatory feedback loop that sustains activation and promotes long-lasting changes in synaptic function [21]. It was also found that psilocin itself is able to bind allosterically to the TrkB receptor, promoting its dimerization and enhancing its activation by BDNF, suggesting that this process can take place independent of 5-HT2A receptor activation [9].

BDNF-TrkB signaling initiates a cascade of intracellular signaling events that profoundly influence neuronal function and plasticity. Crucially, this includes the activation of the Ras/Mitogen-Activated Protein Kinase (Ras/MAPK) and Phosphoinositide 3-kinase (PI3K) pathways, both of which are pivotal for cell growth, survival, and synaptic plasticity [2, 21]. Additionally, TrkB activation recruits phospholipase Cγ (PLCγ) that catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol trisphosphate (IP3). This leads to increased intracellular calcium levels through the release of calcium from internal stores, further driving the activation of calcium/calmodulin-dependent protein kinases (CaMK), resulting in the activation of various transcription factors, notably the cAMP Response Element-Binding Protein (CREB). CREB plays a crucial role in modulating gene expression necessary for synaptic growth and adaptation. These pathways, stimulated by BDNF-TrkB signaling, underscore the essential role in enhancing synaptic plasticity and facilitation of late-phase Long-Term Potentiation (LTP) in hippocampal neurons [2].

Overall, the mechanisms described in this review and depicted in Figure 2 illustrate the complex and multifaceted ways in which psilocybin influences brain function and structure, particularly through its impact on the immune system and neuroplasticity. These processes, combined with additional mechanisms not covered in this review, as well as those that may be uncovered through ongoing and future research, underscore the broad spectrum of actions through which psilocybin can exert its therapeutic effects beneficial for treating mood disorders, including major depressive disorder (MDD) and treatment-resistant depression (TRD).

7 Safety of psilocybin treatments

Effective doses of psilocybin range from 1–5 g of dried mushrooms (20–40 mg of psilocybin), with effects lasting 6–8 hours [9]. It is generally well-tolerated, with common side effects including nausea and headache. Psychological effects can include anxiety and emotional distress during sessions, but no long-lasting adverse effects have been reported [8]. Psilocin acts as a partial, not complete, agonist at the 5HT2A receptor, significantly reducing the risk of serotonin syndrome. While an overdose of psilocybin is not physiologically dangerous, it can lead to risky behaviors (e.g. acting on delusions such as capability to fly) if used without supervision. The development of psychosis has not been associated with psilocybin use, though there might be a potential risk for individuals with a family history predisposing them to psychosis. Overall, expert consensus ranks psilocybin among the safest recreational drugs used [8].

8 Benefits of psilocybin treatments

Psilocybin induces a rapid-acting antidepressant effect, noticeable within days after a single dose, with long-lasting benefits that persist for at least 12 weeks. This rapid efficacy far exceeds that of traditional antidepressants, which typically require 1-4 weeks to begin showing effects [6, 8, 22]. Additionally, unlike many standard medi-

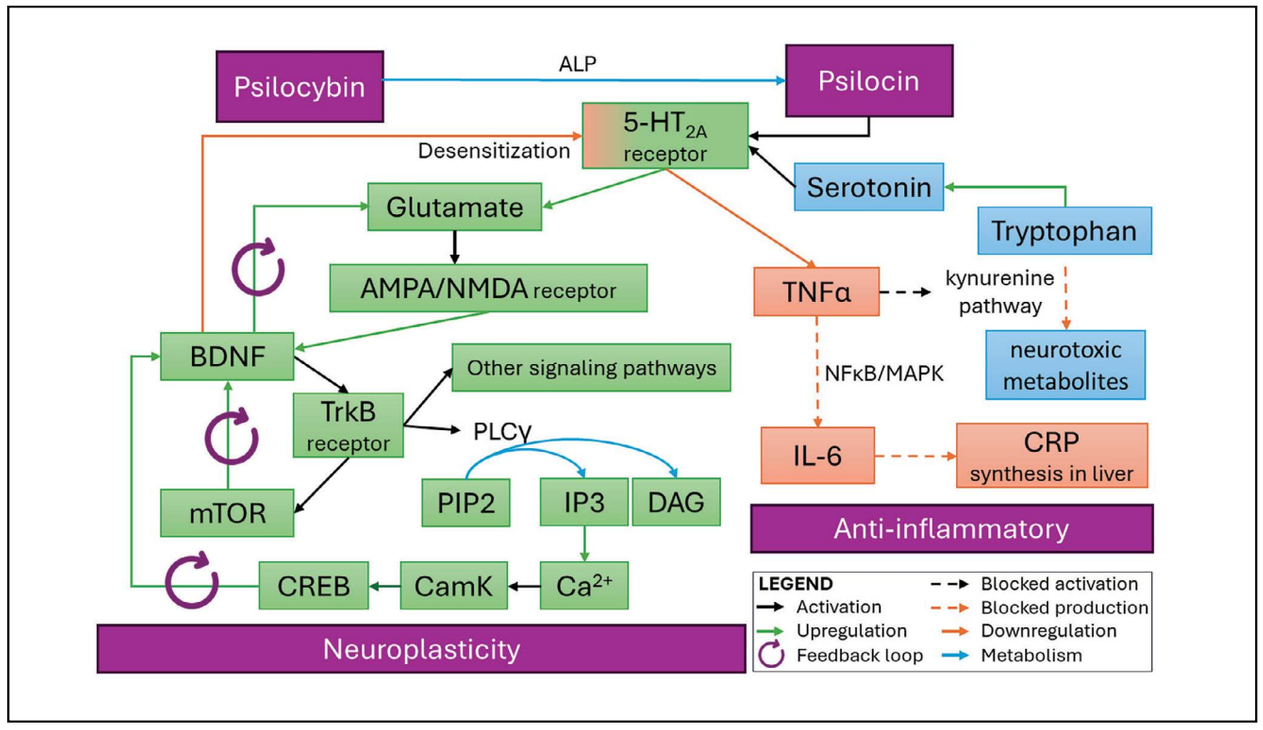

Fig. 2: Overview of molecular psilocybin effect on neuroplasticity and anti-inflammation

cations, psilocybin does not induce emotional blunting and is associated with minimal dependency issues and withdrawal symptoms, making it an appealing option for treatment [2, 8, 22].

9 Conclusion

The resurgence of interest in psilocybin as a therapeutic agent marks a significant shift in the treatment landscape for major depressive disorder (MDD) and treatment-resistant depression (TRD). Over the past few years, an accumulating body of evidence from clinical trials has demonstrated the remarkable efficacy of psilocybin-assisted therapy in alleviating depressive symptoms, often with effects lasting significantly longer than those observed with traditional antidepressants. Unlike conventional treatments, which might take weeks to show benefits and often come with undesirable side effects like emotional blunting and dependency issues, psilocybin offers a rapid onset of action and minimal side effects. Its ability to induce lasting neuroplastic changes following a single dose, coupled with its low toxicity and absence of significant physiological dangers, positions psilocybin as a promising alternative to traditional pharmacotherapy. The molecular mechanisms underlying its benefits extend beyond simple serotonin receptor modulation, involving complex interactions that promote synaptic plasticity and reduce inflammation, potentially addressing foundational biological aspects of depression.

Furthermore, the integration of psychedelic-assisted psychotherapy into mental health treatments could potentially reshape patient care strategies, offering more effective and enduring solutions for those suffering from persistent depressive symptoms with a major reduction in the amount of therapeutic session. This would benefit not only the patients, but also reduce the pressure on the health care system by reducing waitlists and therapy cost.

Ultimately, the continued exploration of psilocybin not only broadens our understanding of psychopharmacology but also enhances our ability to confront the complexities of mental health. Overall, psilocybin therapy offers hope for a brighter future in the management of depression and related mood disorders.

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