WAGENINGEN
UNIVERSITY & RESEARCH

Postbus 9101 | 6700 HB Wageningen

UITSLUITEND PER E-MAIL

[redacted]

Geachte [redacted]

Op 29 april jl. hebben wij uw verzoek om informatie ontvangen om openbaarmaking van informatie die valt onder het College van Bestuur van Wageningen University (hierna: het "College").

Uw verzoek om informatie

U verzoekt om kopieën van documenten en interne en externe correspondentie (waaronder e-mails inclusief bijlagen, sms'jes, Whatsapp-berichten of verslagen, gespreksverslagen, vergaderstukken, memo's, notities, notulen of opnames van gesprekken) te verstrekken, die betrekking hebben op de volgende zaken over de periode vanaf 1 januari 2015 tot heden:

1) Een volledig overzicht van de taken en werkzaamheden van [redacted] aan Wageningen University, waaronder, maar niet beperkt tot, de onderzoeksprojecten waar hij bij betrokken was en zijn nevenfuncties. Dit in de vorm van een lijst, of in de vorm van documenten en correspondentie waaruit al zijn taken, werkzaamheden en meldingen van nevenfuncties blijken. Per taak wenst u een korte beschrijving van de taak, de start- en einddatum, de financieringsbronnen en de samenwerkingspartners binnen en buiten de universiteit te ontvangen.
2) Alle beleidsdocumenten inzake belangenverstrengeling van Wageningen University.
3) Correspondentie over of bekendmaking van mogelijke of daadwerkelijke belangenverstrengelingen van [redacted] aan Wageningen University.
4) De overeenkomst(en) of contract(en) en correspondentie tussen Wageningen University en Shell, BP en Concawe die te maken hebben met de onderzoeken waar [redacted] aan werkte (zoals bijvoorbeeld, maar niet gelimiteerd tot de onderwerpen waarover hij heeft gepubliceerd: https://research.wur.nl/en/persons/[redacted]/publications/).
5) Correspondentie tussen medewerkers van BP en medewerkers van Wageningen University met betrekking tot onderzoek over "marine oil-snow sedimentation and flocculent accumulation".

Wageningen
University

DATUM
1 juli 2024

ONDERWERP
Besluit op uw verzoek om informatie

ONS KENMERK
2414989

POSTADRES
Postbus 9101
6700 HB

BEZOEKADRES
Wageningen Campus
Gebouw 104
Droevendaalsesteeg 4
6708 PB Wageningen

INTERNET
www.wur.nl

CONTACTPERSOON
[redacted]

E-MAIL
woo@wur.nl

Behandeling van uw verzoek
Per e-mail van 1 mei jl. hebben wij de ontvangst van uw verzoek bevestigd. Op 24 mei jl. hebben wij u bericht dat wij de behandeling van uw verzoek om informatie met twee weken verdagen, overeenkomstig artikel 4.4 lid 2 Woo.

Op 11 juni jl. ontvingen wij uw ingebrekestelling. In reactie daarop hebben wij aangegeven dat wij mogelijk met deelbesluiten kunnen werken om de afhandeling van uw verzoek te bespoedigen. In daaropvolgend telefonisch contact heeft u aangegeven dat u bij voorkeur vasthoudt aan één besluit. Nadien heeft u per e-mail d.d. 12 juni jl. schriftelijk bevestigd akkoord te gaan met een nader uitstel tot 5 juli 2024.

Naar aanleiding van uw verzoek hebben wij de informatie zoals hierboven beschreven opgevraagd binnen de organisatie van Wageningen University en vervolgens inhoudelijk getoetst op de aanwezigheid van wettelijke uitzonderingsgronden. Wij hebben informatie opgevraagd bij de genoemde medewerker, bij de leerstoelgroep waar de betreffende medewerker werkzaam is en bij de directie van AFSG, bij de leerstoelgroepen waarmee de medewerker heeft samengewerkt, bij verschillende HR-afdelingen en bij de afdeling Juridische Zaken & Contractmanagement.

Daarnaast hebben wij externe zienswijzen opgevraagd bij derde-belanghebbenden. Diens reactie op de uitvraag hebben wij meegenomen in onze uiteindelijke besluitvorming.

Besluit
Het College besluit om uw verzoek om informatie gedeeltelijk te honoreren, waarbij wij de kaders van de Woo in acht nemen. Dit betekent dat wij de door u verzochte documenten verstrekken indien en voor zover Wageningen University die informatie onder zich heeft en indien en voor zover de uitzonderingsgronden van de Wet open overheid zich niet tegen openbaarmaking van deze informatie verzetten.

In reactie op onderdeel 2 van uw verzoek verwijzen wij u graag naar de volgende beleidsdocumenten die gepubliceerd zijn op de website van Wageningen University:

- Code goed bestuur: https://www.wur.nl/en/show/de-code-goed-bestuur-universiteiten.htm
- WUR Integriteitscode: https://www.wur.nl/nl/show/integriteitscode-wageningen-ur.htm
- WUR Regeling nevenwerkzaamheden: https://www.wur.nl/nl/show/regeling-nevenwerkzaamheden-wageningen-university-research.htm
- Overzicht van nevenwerkzaamheden: https://www.wur.nl/en/show/ancillary-activitiesnevenactiveiten.htm
- WUR Anti-corruptiecode: https://www.wur.nl/nl/show/anti-corruptie-code-wageningen-university-research-nl.htm
- Nederlandse gedragscode wetenschappelijke integriteit: https://www.wur.nl/nl/show/nederlandse-gedragscode-wetenschappelijke-integriteit-2018.htm
- Richtlijnen voor het instellen van leerstoelen en (her)benoemen van hoogleraren aan Wageningen University https://www.wur.nl/en/show/policy-for-establishing-chairs-and-appointing-and-reappointing-professors-at-wageningen-university.htm

Omdat die documenten reeds openbaar zijn, verstrekken wij die niet alsnog onder dit besluit.

Toepassing van de uitzonderingsgronden

Niet alle informatie die aan uw verzoek voldoet kan openbaar worden gemaakt. Wij hebben in ieder document aangegeven op welke grond wij eventueel informatie hebben afgeschermd.

Waar de bescherming van persoonlijke levenssfeer zwaarder weegt dan het algemeen belang van openbaarheid, is de uitzonderingsgrond van artikel 5.1 lid 2, aanhef en onder e van de Wet open overheid toegepast. Concreet betekent dit dat in de documenten de namen van personen en hun contactgegevens, zoals e-mailadressen, telefoonnummers en specifieke kamernummers, zijn weggelakt. Het belang van openbaarmaking van die gegevens weegt naar het oordeel van het College niet op tegen het belang bij bescherming en eerbiediging van de persoonlijke levenssfeer van de betrokken personen. De persoonsgegevens van personen die een openbare functie bij Wageningen University bekleden, voor zover deze gegevens relevant zijn binnen het bestek van dit informatieverzoek, zijn niet weggelakt.

Daarnaast heeft het College de uitzonderingsgrond van artikel 5.1 lid 1, aanhef en onder c, van de Wet open overheid toegepast. Het gaat hier om passages in contracten waarin gegevens zijn weergegeven waaruit wetenswaardigheden kunnen worden afgeleid met betrekking tot beschermbare kennis en resultaten die door middel van geheimhouding worden beschermd, en nog te publiceren resultaten, of anderszins zeer vertrouwelijke afspraken.

Informatie en termijn voor bezwaar

Wij vertrouwen erop u hiermee voldoende te hebben geïnformeerd. Indien u vragen heeft over dit besluit kunt u contact opnemen met onze woordvoerder Vincent Koperdraat, via vincent.koperdraat@wur.nl.

U kunt binnen zes weken na de dag waarop dit bekend is gemaakt een bezwaarschrift indienen. U dient in dat geval schriftelijk uw bezwaren te richten aan het college van bestuur van Wageningen University, Postbus 9101, 6700 HB Wageningen dan wel per e-mail gericht aan woo@wur.nl.

Hoogachtend,

Dr. ir. S. Heimova
Voorzitter college van bestuur
Wageningen University

From: 5.1.2.e
Sent: dinsdag 19 december 2017 11:23
To: 5.1.2.e
Cc: 5.1.2.e @concawe.org';5.1.2.e ; Contractmanagement AFSG
Subject: RE: Agreement Concawe

Follow Up Flag: Follow up
Flag Status: Completed

Categories: actie 5.1.2.e

Dear all,

I have consulted internally with 5.1.2.e , and she assured me –as did 5.1.2.e- that there is no risk of any commercial application of the results of this research. Therefore we do not have any objection to the wording suggested by 5.1.2.e in the latest version of the contract as attached to the email of 5.1.2.e dated yesterday.

Could you please arrange a signing copy of the contract and send it to 5.1.2.e , me and to: contractmanagement.afsg@wur.nl (also in CC to this mail). Contractmanagement will arrange for the signature of WU, so 5.1.2.e can start arranging for the PhD.

Best regards,

5.1.2.e
Legal Counsel a.i.

Wageningen University & Research,
Agrotechnology & Food Sciences Group
Legal department and contractmanagement

P.O. Box 17, 6700 AA Wageningen, the Netherlands
Wageningen Campus, Building 115,
Stippeneng 2,
6708 WE Wageningen
The Netherlands

Phone: 5.1.2.e
Mail to 5.1.2.e @wur.nl
URL: www.wur.nl

From: 5.1.2.e [mailto:5.1.2.e @concawe.org]
Sent: Monday, December 18, 2017 8:32 PM
To: 5.1.2.e @wur.nl>
Cc: 5.1.2.e @wur.nl>;5.1.2.e @wur.nl>
Subject: RE: Agreement Concawe

Beste 5.1.2.e ,

Bijgevoegd het contract met een kleine wijziging van onze lawyer in the liability/indemnification text – hopelijk is dit OK van jullie kant.

Kunt u laten weten of het contract hiermee afgerond kan worden?
Dan zal 5.1.2.e morgenvroeg nog het afgeronde contract naar Lidy en u sturen voor ondertekening.

Bedankt!

Vriendelijke groeten,
5.1.2.e

[redacted], PhD, ERT
Science Executive, Health

concawe
ENVIRONMENTAL SCIENCE FOR THE EUROPEAN REFINING INDUSTRY

Boulevard du Souverain 165
B-1160 Brussels, Belgium
T. 5.1.2.e
M. 5.1.2.e
5.1.2.e @concawe.org
www.concawe.org

From: 5.1.2.e
Sent: Monday, December 18, 2017 10:28 AM
To: 5.1.2.e @wur.nl>
Cc: 5.1.2.e @wur.nl>; 5.1.2.e @wur.nl>
Subject: RE: Agreement Concawe

Beste 5.1.2.e,

Hopelijk weer helemaal hersteld..?

Bedankt voor het opvolgen – ik heb het doorgestuurd naar legal, en die zullen er vanmorgen nog naar kijken. Ik kom zsm bij u terug!

Groeten,
5.1.2.e

From: 5.1.2.e [mailto:5.1.2.e @wur.nl]
Sent: Monday, December 18, 2017 9:59 AM
To: 5.1.2.e @concawe.org>
Cc: 5.1.2.e @wur.nl>; 5.1.2.e @wur.nl>
Subject: RE: Agreement Concawe

Beste 5.1.2.e,

Door een garantie vanuit WU op te nemen zoals voorgesteld door Concawe's legal department, hoop ik nu dit punt te hebben opgelost. Zou jij mij kunnen laten weten of het contract dan nu akkoord is vanuit Concawe, dan kunnen we zo snel mogelijk het ondertekeningtraject inzetten.

Met vriendelijke groet,

5.1.2.e
Legal Counsel a.i.

Wageningen University & Research,
Agrotechnology & Food Sciences Group
Legal department and contractmanagement

P.O. Box 17, 6700 AA Wageningen, the Netherlands
Wageningen Campus, Building 115,
Stippeneng 2,
6708 WE Wageningen
The Netherlands

Phone: 5.1.2.e
Mail to: 5.1.2.e @wur.nl
URL: www.wur.nl

From: 5.1.2.e [mailto 5.1.2.e @concawe.org]
Sent: Wednesday, December 13, 2017 5:24 PM
To: 5.1.2.e @wur.nl>
Cc: 5.1.2.e @wur.nl>; 5.1.2.e @wur.nl>
Subject: RE: Agreement Concawe
Importance: High

Beste 5.1.2.e

Ik heb hier daarnet nog even contact gehad met onze Legal afdeling, en het ging volgens mij alleen nog om het punt mbt "indemnification".
Daarop kreeg ik deze feedback:

> *Concawe cannot accept the suggestion on indemnification, as WUR do not provide any undertaking that it will not infringe any third party rights (e.g. IP) in preparing the final report.*
>
> *Company indemnifies and holds WU harmless from any third-party claims, including claims regarding product liability, arising from the Research executed by WU on Company's request, the use by Company of the Research Results delivered by WU, or both.*

Hoe kunnen we dit het best zo snel mogelijk oplossen? Zou het helpen om morgen even tussen u en 5.1.2.e, onze lawyer, telefonisch contact te hebben?

Laat maar weten, dan zal ik het opzetten.

Fijne avond,
5.1.2.e

From: 5.1.2.e
Sent: Wednesday, December 13, 2017 12:40 PM
To: 5.1.2.e @wur.nl>
Cc: 5.1.2.e @wur.nl>; 5.1.2.e @wur.nl>
Subject: Re: Agreement Concawe

Beste 5.1.2.e

Ja, dit klopt - excuses voor de vertraging.

5.1.2.e zal vandaag zsm contact met u opnemen om een paar laatste open items te bespreken en hopelijk vandaag nog op te lossen.
Daarmee zouden we het contract deze week nog moeten kunnen vastleggen.

Vriendelijke groeten,
5.1.2.e

5.1.2.e, PhD, ERT
Science Executive, Health
M: +5.1.2.e

Op 13 dec. 2017 om 09:43 heeft 5.1.2.e @wur.nl> het volgende geschreven:

> Beste 5.1.2.e,
>
> Kan het kloppen dat wij nog geen finale versie hebben ontvangen? Vanwege het naderende kerst reces zouden we graag zsm het contract ontvangen in de hoop dat het nog voor het eind van dit jaar kan worden afgerond.
>
> Met vriendelijke groet,
>
> 5.1.2.e
> Legal Counsel a.i.
>
> Wageningen University & Research,
> Agrotechnology & Food Sciences Group
> Legal department and contractmanagement
>
> P.O. Box 17, 6700 AA Wageningen, the Netherlands
> Wageningen Campus, Building 115,
> Stippeneng 2,
> 6708 WE Wageningen
> The Netherlands
>
> Phone: 5.1.2.e
> Mail to: 5.1.2.e @wur.nl
> URL: www.wur.nl
>
>

From: 5.1.2.e [mailto:5.1.2.e @concawe.org]
Sent: Friday, December 08, 2017 5:56 PM
To: 5.1.2.e @wur.nl>
Cc: 5.1.2.e @wur.nl>; 5.1.2.e @wur.nl>
Subject: RE: Agreement Concawe

Beste 5.1.2.e,

Bedankt voor de feedback; ik heb dit besrpoken met ons law department, en ik hoop dat er een finale versie van het contract op Maandag naar u toekomt.

Mbt tot het tweede punt: hier staan zoveel partijen vermeld, omdat Concawe een organisatie is die bestaat uit alle petroleum bedrijven die in Europa actief zijn. Dus al het werk wat hier gedaan wordt, wordt eigenlijk gedaan door al de mensen die het bedrijf waar ze in dienst zijn representeren in Concawe.

Ik zal kijken met onze lawyer of dit eventueel anders te formuleren is, maar dit is standard tekst die door Concawe gebruikt wordt.

In ieder geval, met deze zaken denk ik dat we er wel uit moeten komen.

Een heel fijn weekend!
5.1.2.e

From: 5.1.2.e [mailto:5.1.2.e @wur.nl]
Sent: Thursday, December 07, 2017 10:33 AM
To: 5.1.2.e @concawe.org>
Cc: 5.1.2.e @wur.nl>; 5.1.2.e @wur.nl>
Subject: RE: Agreement Concawe

Beste 5.1.2.e,

Dank voor het toesturen van de aangepaste versie. Ik denk dat we er bijna uit zijn.
Twee opmerkingen nog:
Graag zouden wij de indemnification voor third party claims terugzien, zoals met track changes opgenomen in de aangehechte versie (de door u toegestuurde versie, met dus deze wijziging). Als Concawe de resultaten gaat gebruiken en wellicht ter beschikking gaat stellen aan derden, dan wil WU het risico dat die derden een claim indienen bij de WU graag afgedekt zien.

Daarnaast is het nogal ongebruikelijk dat de resultaten niet alleen gebruikt mogen worden door de contractspartij, maar door : "Concawe and Member Companies and Concawe working groups and task forces (where such groups consist of Concawe staff, staff of Concawe Member Companies and from other oil industry associations)" Dat zijn heel veel partijen. Zou u kunnen toelichten waarom dat wordt voorgesteld en waarom dat in dit geval wenselijk en redelijk is?

Met vriendelijke groet,

5.1.2.e
Legal Counsel a.i.

Wageningen University & Research,
Agrotechnology & Food Sciences Group
Legal department and contractmanagement

P.O. Box 17, 6700 AA Wageningen, the Netherlands

Wageningen Campus, Building 115,
Stippeneng 2,
6708 WE Wageningen
The Netherlands

Phone: 5.1.2.e
Mail to: 5.1.2.e @wur.nl
URL: www.wur.nl

From: 5.1.2.e [mailto:5.1.2.e @concawe.org]
Sent: Wednesday, December 06, 2017 2:02 PM
To: 5.1.2.e @wur.nl>
Cc: 5.1.2.e @wur.nl>; 5.1.2.e @wur.nl>
Subject: RE: Agreement Concawe

Beste 5.1.2.e,

Bijgevoegd is de aangepaste overeenkomst, een versie met track changes en een 'schone' versie.

Het lijkt me dat we er hiermee uit zouden moeten komen, maar ik hoor graag uw feedback.
Zoals afgesproken zouden we het morgen of Vrijdag nog telefonisch kunnen bespreken mocht dat nodig zijn om het te af te ronden.

Vriendelijke groeten,
5.1.2.e

From: 5.1.2.e [mailto:5.1.2.e @wur.nl]
Sent: Tuesday, December 05, 2017 3:19 PM
To: 5.1.2.e @concawe.org>
Cc: 5.1.2.e @wur.nl>; 5.1.2.e @wur.nl>
Subject: RE: Agreement Concawe

Beste 5.1.2.e,

Dat lijkt me prima. Ik zie haar input graag tegemoet.

Met vriendelijke groet,

5.1.2.e
Legal Counsel a.i.

Wageningen University & Research,
Agrotechnology & Food Sciences Group
Legal department and contractmanagement

P.O. Box 17, 6700 AA Wageningen, the Netherlands
Wageningen Campus, Building 115,
Stippeneng 2,
6708 WE Wageningen
The Netherlands

Phone: 5.1.2.e

Mail to: 5.1.2.e @wur.nl
URL: www.wur.nl

KvK1: Stichting Wageningen Research is located in Wageningen and registered at the Chamber of Commerce (Kamer van Koophandel) under number 09098104
KvK2: Wageningen Universiteit is located in Wageningen and registered at the Chamber of Commerce (Kamer van Koophandel) under number 09215846
www.disclaimer-uk.wur.nl

From: 5.1.2.e [mailto:5.1.2.e @concawe.org]
Sent: Tuesday, December 05, 2017 3:17 PM
To: 5.1.2.e @wur.nl>
Cc: 5.1.2.e @wur.nl>; 5.1.2.e @wur.nl>
Subject: RE: Agreement Concawe

Beste 5.1.2.e,

Bedankt voor uw feedback en beschikbaarheid.

5.1.2.e, onze lawyer, is morgen jammer genoeg niet beschikbaar. Maar ze is jullie feedback nu aan het bekijken, en ik zal voorstellen dat we haar feedback over email naar jullie terug sturen zodat jullie daar eerste even naar kunnen kijken.

We kunnen dan naar aanleiding daarvan later deze week een korte call inplannen mocht het nodig zijn.

Vriendelijke groeten,
5.1.2.e

From: 5.1.2.e [mailto:5.1.2.e @wur.nl]
Sent: Tuesday, December 05, 2017 11:46 AM
To: 5.1.2.e @concawe.org>
Cc: 5.1.2.e @wur.nl>; 5.1.2.e @wur.nl>
Subject: RE: Agreement Concawe

Geachte heer 5.1.2.e, beste 5.1.2.e,

Het lukt mij helaas vandaag niet om dit telefonisch door te nemen. Het zou wel morgen kunnen tussen 8:30 en 15 uur.

Ter voorbereiding (ook voor mijzelf) even een overzicht:

- Op 8 november bekeek ik de door Concawe toegestuurde Consultancy Agreement en voorzag die van commentaar en tekstvoorstellen. Het viel mij op dat voor een consultancy agreement was gekozen, terwijl het om een research project bleek te gaan.
- Op 9 november, nadat ik bericht had gekregen dat Concawe geen bezwaar had tegen het gebruik van een research agreement, stuurde ik per mail de door WU gehanteerde research agreement aan Concawe.
- Op 13 november ontving ik van Concawe een door Concawe opgestelde research agreement, dus niet een bewerkte versie van het WU voorstel, maar een nieuwe overeenkomst.
- Op 23 november stuurde ik mijn commentaren op de door Concawe voorgestelde research agreement aan 5.1.2.e met het verzoek een Field definitie op te nemen.

In de laatste versie van 23 november heb ik een aantal wijzigingen doorgevoerd om de door Concawe toegestuurde overeenkomst in lijn te krijgen met de research agreement die WU altijd hanteert in dergelijke onderzoeksprojecten. Het lijkt me inderdaad efficiënt

om daar met elkaar even doorheen te lopen, en te kijken of er nog punten zijn die aandacht behoeven. Hopelijk lukt het morgen elkaar te spreken.

Met vriendelijke groet,

5.1.2.e
Legal Counsel a.i.

Wageningen University & Research,
Agrotechnology & Food Sciences Group
Legal department and contractmanagement

P.O. Box 17, 6700 AA Wageningen, the Netherlands
Wageningen Campus, Building 115,
Stippeneng 2,
6708 WE Wageningen
The Netherlands

Phone: 5.1.2.e
Mail to: 5.1.2.e @wur.nl
URL: www.wur.nl

From: 5.1.2.e [mailto: 5.1.2.e @concawe.org]
Sent: Monday, December 04, 2017 4:51 PM
To: 5.1.2.e @wur.nl>
Cc: 5.1.2.e @wur.nl>
Subject: RE: Agreement Concawe

Beste mevrouw 5.1.2.e,

Zou u wellicht morgenvroeg rond half 10 een paar minuten tijd hebben om het onderstaand contract met Concawe te bespreken, samen met 5.1.2.e (onze lawyer) en mijzelf?

Vanuit onze kant is de tekst denk ik vrij makkelijk aan te passen, maar we zouden graag van jullie kant horen wat jullie graag veranderd zouden hebben aan de research agreement.

Hartelijk bedankt!
5.1.2.e

, PhD, ERT
Science Executive, Health

<image001.jpg>

Boulevard du Souverain 165
B-1160 Brussels, Belgium
T. 5.1.2.e
M. 5.1.2.e
5.1.2.e @concawe.org
www.concawe.org

<image002.jpg>

From: 5.1.2.e
Sent: Monday, November 13, 2017 3:11 PM
To: 5.1.2.e @wur.nl
Cc: 5.1.2.e @concawe.org>; 5.1.2.e @shell.com>; 5.1.2.e @wur.nl; 5.1.2.e @wur.nl
Subject: RE: Agreement Concawe

Dear 5.1.2.e

We are contacting you in view of the Research Agreement contract among Concawe and WUR.

Attached you can find a proposal from our part. Could you please review the document attached and indicate whether it is acceptable for you?

Fields highlighted in yellow should be filled-in or revised by WUR.

Thank you very much in advance for your feedback.

Kind regards,

5.1.2.e
Research Associate – Health and REACH

<image003.jpg>

Boulevard du Souverain 165
B-1160 Brussels, Belgium
T. 5.1.2.e
M. 5.1.2.e

www.concawe.org

<image004.jpg>

From: 5.1.2.e [mailto:5.1.2.e @wur.nl]
Sent: Thursday, November 09, 2017 1:07 PM
To: 5.1.2.e @concawe.org>
Cc: 5.1.2.e @concawe.org>; 5.1.2.e @wur.nl>; 5.1.2.e @shell.com>; 5.1.2.e @wur.nl>
Subject: FW: Agreement Concawe

Dear mrs 5.1.2.e and mr 5.1.2.e ,

Would you please be so kind have contact with 5.1.2.e from our contract department concerning the research agreement?

It is unfortunately not my field of expertise.

Please do not hesitate if there is anything I can help you with,

With kind regards,

5.1.2.e

Office Toxicology
5.1.2.e | Wageningen University & Reseach | Toxicology Department |
Visiting Address: Campus, Helix Building; 124 Stippeneng 4, 5.1.2.e | 6708 WE Wageningen | The Netherlands |
P.O.BOX 8000 | 6700 EA | Wageningen | The Netherlands|
T: 5.1.2.e | E-mail: office.tox@wur.nl
Not present Wednesday and Friday afternoon from 12.00 hour
<image005.png>
<image006.png>

Van: 5.1.2.e
Verzonden: donderdag 9 november 2017 12:04
Aan: 5.1.2.e @wur.nl>
Onderwerp: RE: Agreement Concawe

Hi 5.1.2.e ,

Good to hear that Concawe agrees to making this a research agreement instead of a consultancy agreement. I have tried to recover any previous research agreements between Concawe and AFSG, but couldn't find one. Therefore I have attached our standard research agreement. It might be easiest to take this agreement as a starting point.

Best regards,

5.1.2.e
Legal Counsel a.i.

Wageningen University & Research,
Agrotechnology & Food Sciences Group
Legal department and contractmanagement

P.O. Box 17, 6700 AA Wageningen, the Netherlands
Wageningen Campus, Building 115,
Stippeneng 2,
6708 WE Wageningen
The Netherlands

Phone: 5.1.2.e

Mail to: 5.1.2.e @wur.nl
URL: www.wur.nl

KvK1: Stichting Wageningen Research is located in Wageningen and registered at the Chamber of Commerce (Kamer van Koophandel) under number 09098104
KvK2: Wageningen Universiteit is located in Wageningen and registered at the Chamber of Commerce (Kamer van Koophandel) under number 09215846
www.disclaimer-uk.wur.nl

From: 5.1.2.e
Sent: Thursday, November 09, 2017 7:56 AM
To: 5.1.2.e @wur.nl>
Subject: FW: Agreement Concawe

Hoi 5.1.2.e

Deze mail kreeg ik gistermiddag!

Voor jou misschien wel prettig ;-)

Grtjs 5.1.2.e

Van: 5.1.2.e [mailto:5.1.2.e @concawe.org]
Verzonden: woensdag 8 november 2017 14:53
Aan: 5.1.2.e @shell.com>
CC: 5.1.2.e @wur.nl>
Onderwerp: RE: Agreement Concawe

Beste mevrouw 5.1.2.e ,

Ik had did vanmorgen doorgegeven aan 5.1.2.e , maar realiseer me dat hij niet op kantoor is en het misschien gemist heeft.

De naam van onze jurist is 5.1.2.e en u kunt haar bereiken op: 5.1.2.e @concawe.org

Ter verduidelijking: ik begrijp dat u een CSA gekregen heeft om te reviewen. Hierin staat vrij strikte tekst rondom het publiceren van data, IP, etc. Daarom stellen we voor een project zoals dit normaal gesproken een research agreement op (zoals al eerder gedaan met de WUR), en ik geloof dat een voorstel hiervoor later ook naar 5.1.2.e gestuurd is. Als dit de problemen geeft, dan hoor ik het graag – dit is vrij eenvoudig op te lossen, en de tekst van die agreement kunnen we ook verder bespreken.

Laat maar weten als ik u verder ergens mee kan helpen vanuit hier.

Vriendelijke groeten,
5.1.2.e

, PhD, ERT
Science Executive, Health

<image001.jpg>

Boulevard du Souverain 165
B-1160 Brussels, Belgium
T. 5.1.2.e
M. 5.1.2.e
5.1.2.e @concawe.org
www.concawe.org

<image002.jpg>

From: 5.1.2.e @shell.com [mailto:5.1.2.e @shell.com]
Sent: Wednesday, November 08, 2017 2:28 PM
To: 5.1.2.e @concawe.org>
Cc: 5.1.2.e @wur.nl
Subject: FW: Agreement Concawe

Best 5.1.2.e ik kom net van een bespreking terug uit Nijmegen dus zie uw mail nu pas.

5.1.2.e kun je dit geven aan 5.1.2.e?

Groet,
5.1.2.e

From: 5.1.2.e [mailto:5.1.2.e @wur.nl]
Sent: Wednesday, November 08, 2017 8:52 AM
To: 5.1.2.e @shell.com>
Subject: FW: Agreement Concawe

Geachte heer 5.1.2.e ,

Helaas heb ik geen telefoonnummer van u maar in de email van 5.1.2.e staat dat als er iets nodig is dat ik dan u zou kunnen mailen.

Wij zijn dringend op zoek naar het email adres van de Jurist van Concawe
Ik hoop van harte dat u mij kunt helpen.

Met vriendelijke groeten,

5.1.2.e

Office Toxicology
5.1.2.e | Wageningen University & Reseach | Toxicology Department |
Visiting Address: Campus, Helix Building; 124 Stippeneng 4, 5.1.2.e | 6708 WE Wageningen | The Netherlands |
P.O.BOX 8000 | 6700 EA | Wageningen | The Netherlands|
T: 5.1.2.e | E-mail: office.tox@wur.nl
Not present Wednesday and Friday afternoon from 12.00 hour
<image005.png>
<image006.png>

Van: 5.1.2.e
Verzonden: woensdag 8 november 2017 8:36
Aan: 5.1.2.e @wur.nl>
CC: 5.1.2.e @wur.nl>; 5.1.2.e @shell.nl'
5.1.2.e @shell.nl>; Contractmanagement AFSG <contractmanagement.afsg@wur.nl>;
5.1.2.e @wur.nl>; 5.1.2.e @wur.nl>
Onderwerp: RE: Agreement Concawe

Hi 5.1.2.e

Ik stuurde de mail naar jou omdat ik geen adres van de jurist van Concawe heb. Zou jij mijn mail kunnen doorsturen? Met mij in CC en met mijn gegevens voor dit jurist, dan kunnen we contact hebben. Alvast dank!

Met vriendelijke groet,

5.1.2.e
Legal Counsel a.i.

Wageningen University & Research,
Agrotechnology & Food Sciences Group
Legal department and contractmanagement

P.O. Box 17, 6700 AA Wageningen, the Netherlands
Wageningen Campus, Building 115,
Stippeneng 2,
6708 WE Wageningen
The Netherlands

Phone: 5.1.2.e
Mail to: 5.1.2.e @wur.nl
URL: www.wur.nl

From: 5.1.2.e
Sent: Tuesday, November 07, 2017 11:44 AM
To: 5.1.2.e @wur.nl>
Cc: 5.1.2.e @wur.nl>; 5.1.2.e @shell.nl'
5.1.2.e @shell.nl>; **Contractmanagement AFSG** <contractmanagement.afsg@wur.nl>;
5.1.2.e @wur.nl>; 5.1.2.e @wur.nl>
Subject: RE: Agreement Concawe

Hallo 5.1.2.e,

Wat ontzettend fijn dat je zo voortvarend te werk gaat. Dat stellen we zeer op prijs.

Heb je verder alle gegevens die je nodig hebt? Naam van de Jurist van Concawe? Of wil je dat ik daarachteraan ga voor je.

Als ik je met iets kan helpen, aarzel niet alsjeblieft en mail of bel!

Dank je wel,

Met vriendelijke groeten,

5.1.2.e

Office Toxicology
5.1.2.e | Wageningen University & Reseach | Toxicology Department |
Visiting Address: Campus, Helix Building; 124 Stippeneng 4, Room 4043 | 6708 WE Wageningen | The Netherlands |
P.O.BOX 8000 | 6700 EA | Wageningen | The Netherlands|
T: 5.1.2.e | E-mail: office.tox@wur.nl
Not present Wednesday and Friday afternoon from 12.00 hour
<image005.png>
<image006.png>

Van: 5.1.2.e
Verzonden: dinsdag 7 november 2017 11:38
Aan: 5.1.2.e @wur.nl>
CC: 5.1.2.e @wur.nl>; 5.1.2.e @shell.nl'
5.1.2.e @shell.nl>; Contractmanagement AFSG <contractmanagement.afsg@wur.nl>
Onderwerp: Agreement Concawe

Beste 5.1.2.e,

Zoals verzocht keek ik naar de overeenkomst met Concawe nadat ik met 5.1.2.e telefonisch had overlegd.
Uit het overleg kwam naar voren dat het op dit moment gaat om de aanstelling van 5.1.2.evoor een jaar en dat publicatie van alle resultaten het uitgangspunt is.

In de overeenkomst met Concawe viel mij op dat het is opgezet als een Consultancy Agreement. Normaliter bestaan consultancy activiteiten uit het verzamelen van reeds gepubliceerde kennis, niet uit het doen van nieuw inventief onderzoek. Daarvoor sluiten wij meestal research collaboration agreements, immers, hoewel Concawe het salaris van de onderzoeker betaalt, draagt WU ook voor een groot deel bij aan de totstandkoming van het resultaat. Zij stelt haar knowhow, faciliteiten en begeleiding ter beschikking, de reden dat Concawe ook graag met de WU samenwerkt. Het is dan wenselijk dat deze verhouding ook wordt gereflecteerd in de overeenkomst. Vooral omdat deze overeenkomst niet alleen ziet op de aanstelling van 5.1.2.e maar een raamovereenkomst is die 5 jaar loopt en waaronder meer projecten door middel van Work Orders kunnen worden gehangen.

De overeenkomst heb ik dus vrij ingrijpend gewijzigd. Wellicht is het zinvol als de jurist van Concawe en ik daarover even contact hebben, zodat ik kan toelichten waar de wijzigingen vandaan komen. Gezien het feit dat 5.1.2.ezou moeten worden aangesteld per 1 december, hoop ik op korte termijn dit overleg te kunnen hebben.

Met vriendelijke groet,

5.1.2.e
Legal Counsel a.i.

Wageningen University & Research,
Agrotechnology & Food Sciences Group
Legal department and contractmanagement

P.O. Box 17, 6700 AA Wageningen, the Netherlands
Wageningen Campus, Building 115,
Stippeneng 2,
6708 WE Wageningen
The Netherlands

Phone: 5.1.2.e
Mail to: 5.1.2.e @wur.nl
URL: www.wur.nl

From: [redacted]@fuelseurope.eu>
Sent: woensdag 8 november 2017 14:15
To: [redacted]
Cc: [redacted] (Concawe); [redacted]; Contractmanagement AFSG; [redacted]
Subject: Re: Agreement Concawe
Attachments: image001.png; image002.png; image001.jpg; image002.png; image003.png; image004.png; image005.png

Dear [redacted],
Thanks for your email. I am free all day on Friday.
Regards,
[redacted]

[redacted]
Legal Advisor
Member of the IJE
[FE_Logo_CMYK]

Bd du Souverain 165 | 1160 Brussels | Belgium<x-apple-data-detectors://3/0>
T[redacted] | M +[redacted]
[redacted]@fuelseurope.eu<mailto:[redacted]@fuelseurope.eu>
www.fuelseurope.eu<http://www.fuelseurope.eu/>

<http://www.savemorethanfuel.eu/>
[New try]<http://www.savemorethanfuel.eu/>
[cid:image002.png@01D08683.1D4E1A80]@fuelseurope |[cid:image003.png@01D08683.1D4E1A80] fuelseurope | [cid:image004.png@01D08683.1D4E1A80] fuelseurope

On 8 Nov 2017, at 09:42, [redacted]@wur.nl<mailto:[redacted]@wur.nl>> wrote:

Dear [redacted],

Below you find an email from our Contractmanagement from [redacted].
She would like to discuss the attached contract with you.

Is it possible for her to contact you?
I realise that her email is in Dutch but [redacted] can contact you in English off course.

Thank you so much,

With kind regards,

5.1.2.e

Office Toxicology
5.1.2.e | Wageningen University & Reseach | Toxicology Department | Visiting Address: Campus, Helix Building; 124 Stippeneng 4, 5.1.2.e | 6708 WE Wageningen | The Netherlands | P.O.BOX 8000 | 6700 EA | Wageningen | The Netherlands|
T: 5.1.2.e | E-mail: office.tox@wur.nl<mailto:office.tox@wur.nl>
Not present Wednesday and Friday afternoon from 12.00 hour <image001.png> <image002.png>

Reeds beoordeeld

From: 5.1.2.e
Sent: donderdag 14 december 2017 10:03
To: 5.1.2.e
Cc: 5.1.2.e @shell.com); Contractmanagement AFSG; AFSG-HR-Support
Subject: RE: OVK 17/322 RE: Agreement Concawe

Beste 5.1.2.e

Helaas is 5.1.2.e ziek en kan dus vandaag waarschijnlijk niet antwoorden.
Ik hoop dat zij zich snel beter voelt en dan dit weer kan oppakken.

Met vriendelijke groeten,

5.1.2.e

Office Toxicology
5.1.2.e | Wageningen University & Reseach | Toxicology Department |
Visiting Address: Campus, Helix Building; 124 Stippeneng 4, 5.1.2.e | 6708 WE Wageningen | The Netherlands |
P.O.BOX 8000 | 6700 EA | Wageningen | The Netherlands|
T: 5.1.2.e | E-mail: office.tox@wur.nl
Not present Wednesday and Friday afternoon from 12.00 hour

WAGENINGEN
UNIVERSITY & RESEARCH

www.wur.nl

Van: Contractmanagement AFSG
Verzonden: donderdag 14 december 2017 9:36
Aan: 5.1.2.e
CC: 5.1.2.e
Onderwerp: OVK 17/322 RE: Agreement Concawe

Hoi 5.1.2.e,

5.1.2.e is nog ziek. Het is het handigst als zij dit zelf oppakt, omdat zij goed in het dossier zit.

Wil jij 5.1.2.e hierover inlichten met een cc aan 5.1.2.e?

Alvast bedankt, groet 5.1.2.e

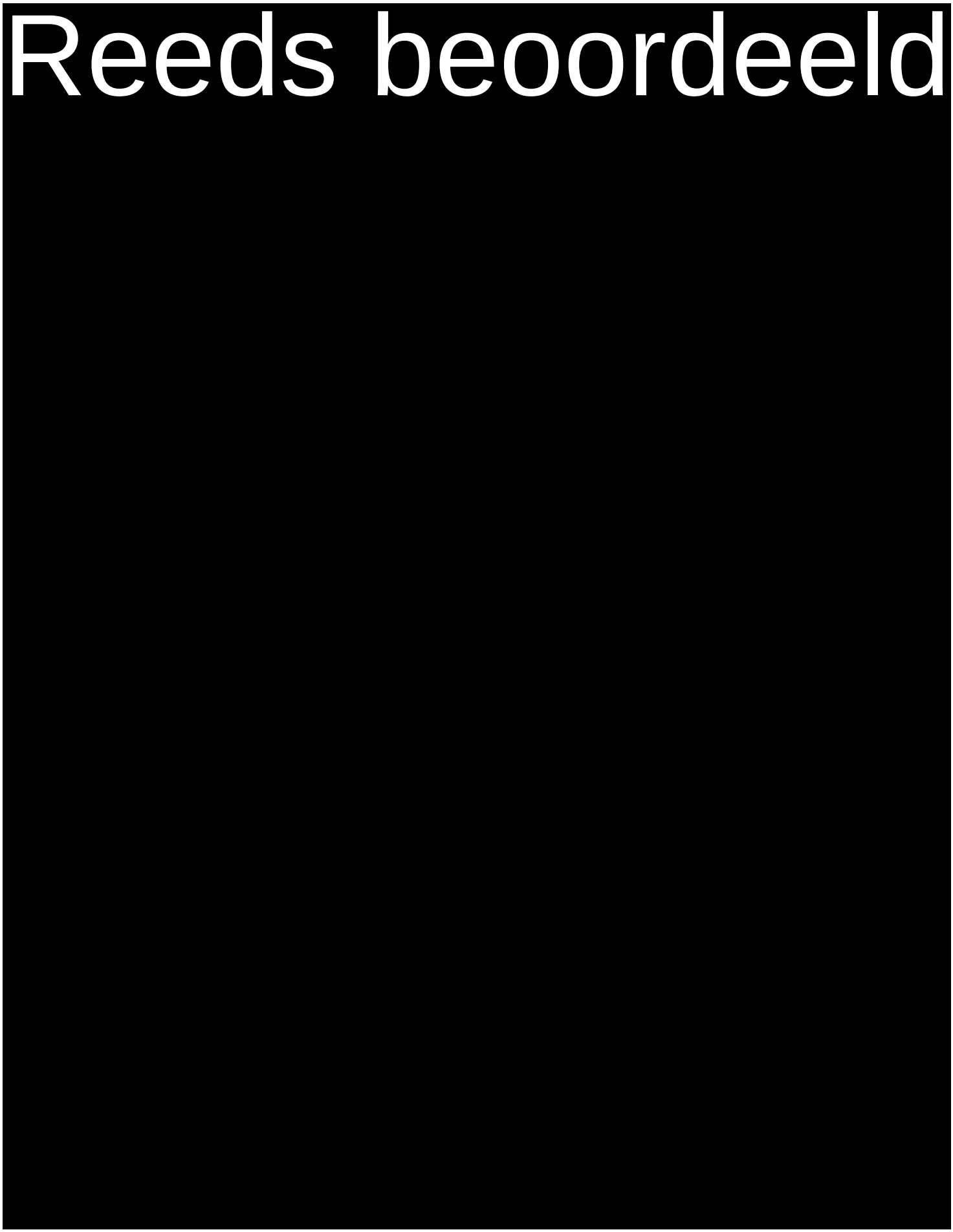
From: 5.1.2.e
Sent: donderdag 14 december 2017 8:34
To: 5.1.2.e @wur.nl>
Cc: Contractmanagement AFSG <contractmanagement.afsg@wur.nl>
Subject: FW: Agreement Concawe
Importance: High

Hey 5.1.2.e,

Ik begreep dat jij gisterochtend niet zo lekker naar huis bent gegaan.

Beterschap natuurlijk. Pak jij dit op of vraag je een van je collega’s?

Grtjs 5.1.2.e



From: 5.1.2.e @fuelseurope.eu>
Sent: woensdag 8 november 2017 14:15
To: 5.1.2.e
Cc: 5.1.2.e (Concawe); 5.1.2.e Contractmanagement AFSG; 5.1.2.e
Subject: Re: Agreement Concawe
Attachments: image001.png; image002.png; image001.jpg; image002.png; image003.png; image004.png; image005.png

Dear 5.1.2.e,
Thanks for your email. I am free all day on Friday.
Regards,
5.1.2.e

5.1.2.e
Legal Advisor
Member of the IJE
[FE_Logo_CMYK]

Bd du Souverain 165 | 1160 Brussels | Belgium<x-apple-data-detectors://3/0>
T5.1.2.e | M5.1.2.e >5.1.2.e @fuelseurope.eu<mailto:5.1.2.e @fuelseurope.eu>
www.fuelseurope.eu<http://www.fuelseurope.eu/>

<http://www.savemorethanfuel.eu/>
[New try]<http://www.savemorethanfuel.eu/>
[cid:image002.png@01D08683.1D4E1A80]@fuelseurope |[cid:image003.png@01D08683.1D4E1A80] fuelseurope |
[cid:image004.png@01D08683.1D4E1A80] fuelseurope

On 8 Nov 2017, at 09:42, Vreede, Lidy de <lidy.devreede@wur.nl<mailto:lidy.devreede@wur.nl>> wrote:

Dear mrs 5.1.2.e,

Below you find an email from our Contractmanagement from 5.1.2.e
She would like to discuss the attached contract with you.

Is it possible for her to contact you?
I realise that her email is in Dutch but 5.1.2.e can contact you in English off course.

Thank you so much,

With kind regards,

5.1.2.e

Office Toxicology
5.1.2.e | Wageningen University & Reseach | Toxicology Department | Visiting Address: Campus, Helix Building; 124 Stippeneng 4, 5.1.2.e | 6708 WE Wageningen | The Netherlands | P.O.BOX 8000 | 6700 EA | Wageningen | The Netherlands|
T: 5.1.2.e | E-mail: office.tox@wur.nl<mailto:office.tox@wur.nl>
Not present Wednesday and Friday afternoon from 12.00 hour <image001.png> <image002.png>

Reeds beoordeeld

From: Concawe <echosign@echosign.com>
Sent: maandag 8 januari 2018 13:14
To: [redacted]; Concawe _; [redacted]@concawe.org
Cc: Contractmanagement AFSG; [redacted]@shell.com; [redacted]@concawe.org
Subject: MSc research agreement_HH effects of alkylated PAH_ref. 201700093 between Concawe, [redacted]@wur.nl and [redacted]@concawe.org is Signed and Filed!
Attachments: MSc research agreement_HH effects of alkylated PAH_ref. 201700093 - signed.pdf

MSc research agreement_HH effects of alkylated PAH_ref. 201700093 between Concawe, [redacted]@wur.nl and [redacted]@concawe.org is Signed and Filed!

From: Concawe _ (Concawe)
To: [redacted]@wur.nl, Concawe _ and [redacted]@concawe.org

Cc: contractmanagement.afsg@wur.nl, [redacted]@wur.nl, [redacted]@shell.com, and [redacted]@concawe.org

Attached is a final copy of MSc research agreement_HH effects of alkylated PAH_ref. 201700093.

Copies have been automatically sent to all parties to the agreement.

You can view the document in your Adobe Sign account.

Why use Adobe Sign:

- Exchange, Sign, and File Any Document. In Seconds!
- Set-up Reminders. Instantly Share Copies with Others.
- See All of Your Documents, Anytime, Anywhere.

To ensure that you continue receiving our emails, please add echosign@echosign.com to your address book or safe list.

From: Concawe _ <echosign@echosign.com>
Sent: dinsdag 19 december 2017 17:32
To: Contractmanagement AFSG
Subject: Concawe _ has copied you on MSc research agreement_HH effects of alkylated PAH_ref. 201700093.
Attachments: MSc research agreement_HH effects of alkylated PAH_ref. 201700093 - unsigned.pdf

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: actie 5.1.2.e

Attached is Your Copy (Cc) of **MSc research agreement_HH effects of alkylated PAH_ref. 201700093**

Concawe _ has copied you on MSc research agreement_HH effects of alkylated PAH_ref. 201700093. **After all participants complete the document you will receive a final PDF copy by email.**

To: 5.1.2.e @wur.nl and 5.1.2.e @concawe.org
From: Concawe _ (Concawe)

Dear 5.1.2.e,

Please find attached the Research Agreement #1 (Msc) between Concawe and Wageningen University. Please review the document and have it signed by the person duly authorised to sign.

Please make sure that only the AUTHORIZED REPRESENTATIVE signs this agreement.

If you are not the AUTHORIZED REPRESENTATIVE, please click on "Alternative actions", which can be found the top left side of the Adobe signing page, then click the option "Someone else should sign" enter their email address in the field "Email Address", add a short message in the field "Message", and then finally click on "Delegate" to send this document to the AUTHORIZED REPRESENTATIVE for signature.

You will be notified electronically when

Concawe has signed. All parties will receive a final pdf version of the signed agreement. Please retain this for your records.

Please do not hesitate to contact us should you have any questions.

Kind regards,

Concawe Contracts Department

Click here to view this document online in your Adobe Sign account.

Why use Adobe Sign:

- Exchange, Sign, and File Any Document. In Seconds!
- Set-up Reminders. Instantly Share Copies with Others.
- See All of Your Documents, Anytime, Anywhere.

RESEARCH AGREEMENT #1 (MSc)

Ref. 201700093

BETWEEN

The European Petroleum Refiners Association AISBL, for its Concawe division, having its headquarters located at 1160 Brussels, boulevard du Souverain, 165, Belgium, represented by 5.1.2.e

Hereafter referred to as "**Concawe**"

AND

Wageningen University, having its premises located at Stippeneng 2, NL-6708 WE Wageningen, the Netherlands, hereby represented by its Managing Director, Dr R.J. Bino.

Hereafter referred to as "**University**"

AND

University and **Concawe** hereafter are jointly referred to as the "**Parties**"

PREAMBLE:

Parties intend to jointly conduct research pertaining to the study of *in vitro* metabolism and genotoxicity of naked versus alkylated PAH that may be present in mineral oils. To that end, MSc Student will conduct research at the University within the scope of his/her work on his/her master thesis. Concawe will support the MSc Student's research with a financial contribution. These funds will be managed by the University.

PROPOSAL:

Resarch Project Title: *In vitro* metabolism and genotoxicity of naked versus alkylated PAH that may be present in mineral oils.

Scope:

The aim of the present project is (1) to obtain better insight in the relative metabolic bioactivation and detoxification of naked versus alkylated PAH that may be present in mineral oils, and (2) to provide a basis for better risk assessment of MOAH using physiologically based kinetic (PBK) modelling and read-across from related non-alkylated PAHs.

DEFINITIONS

Confidential Information: means any and all Background Information and Research Results disclosed by the disclosing Party to the receiving Party and any other information (such as financial, commercial and legal information), disclosed by the disclosing Party to the receiving Party that is marked or indicated as being confidential by the disclosing Party. No information or material disclosed by the disclosing Party shall be deemed Confidential Information to the extent that the receiving Party can demonstrate that the information concerned:

- was in the possession of the receiving Party without confidentiality obligation prior to disclosure; or
- was publicly available at the time of disclosure, or subsequently has become publicly available by no wrongful act or omission of the receiving Party; or
- was developed by the receiving Party independently of the received Confidential Information; or
- was obtained from a third party and, to the best of knowledge of the receiving Party, has not originated from the disclosing Party.

Research: means research activities undertaken by the MSc Student as outlined in the Proposal.

Proposal: means the proposal for the conduct of research that is attached to this MSc Research Project Agreement as Appendix 1.

The Agreement: means this MSc Research Project Agreement and the Proposal as defined above.

Agents: means employees, the MSc Student, students and subcontractors of the respective Party.

MSc Student: means 5.1.2.e a student enrolled at University, or any other student enrolled at Wageningen University to be appointed by University

1. MSC STUDENT'S OBLIGATIONS

1.1. University will undertake to conduct the Research to the best of her abilities. She is in no way obligated to reach any scientific success or to come to any new findings.

1.2. University shall supply an efficient flow of relevant information related to the Research's progress. Such progress reports shall be provided twice per year and shall take the appropriate form as agreed by the University and Concawe including but not limited to meetings, emails and written reports.

2. UNIVERSITY'S OBLIGATIONS

2.1. The University shall bear all responsibility for the MSc Student and its Agents involved in the execution of the Agreement. It is the University's responsibility to inform their Agents and to ensure that their subcontractors inform their Agents for the express benefit of Concawe, of all the provisions of this Agreement, including but not limited to, confidentiality, ownership of intellectual property rights, related warranties of title and non-infringement, and liability.

3. CONCAWE'S OBLIGATIONS

3.1. Concawe shall supply to MSc Student and the University without charge and within a reasonable time all necessary and relevant data and information in the possession of Concawe and shall give such assistance as shall reasonably be required by MSc Student or University in the performance of the Research.

3.2. If needed, the University shall ensure that any official permits or permissions required to carry out the Research are obtained and are in force for the duration of the Research.

3.3. The University shall indemnify and hold Concawe harmless against any and all claims, demands and liability, however caused, rising out of any trespass or failure to obtain or comply with any of the permissions referred to above in carrying out the Research by the University to the extent such failure represents wilful negligence.

3.4. Concawe shall inform the MSc Student and the University in writing of any special circumstances or danger which the execution of the Research may entail.

4. FINANCIAL CONTRIBUTION AND FEE, DISBURSEMENTS

4.1. Concawe will provide a financial contribution in the amount of € 40,000 to cover the material costs and travel expenses accruing in the course of the execution of the Research by MSc Student. Concawe will pay this financial contribution to the University, which will be responsible for the administration of the funds and will in particular use these funds to reimburse expenditures made by MSc Student within the scope of Research.

4.2. Financial contribution of €40,000 will be invoiced on completion and submission of the final report in December 2018.

4.3. All payments referred to this Agreement are exclusive of Value Added Tax or other taxes or duties the amounts of which shall be paid by Concawe to the University.

4.4. All payments shall be made in Euros, except where otherwise agreed, to the University's bank 30 days end of month, which is:

Wageningen University & Research
Agrotechnology & Food Sciences Group (AFSG)

P.O. Box 8000
6700 EA Wageningen
Netherlands
ABN-AMRO Wageningen
Swiftcode: ABNANL2A
Ibancode: NL13ABNA0521072298
Reference: Concawe

Project: The "In vitro metabolism and genotoxicity of naked versus alkylated PAH that may be present in mineral oils"
Professor dr. I.M.C.M. Rietjens and Prof.dr. P. Boogaard
Division of Toxicology

The University shall quote contract reference 201700093 and details of their bank accounts on all invoices being raised under the present Agreement. Incomplete invoices will be rejected. Contractor shall invoice European Petroleum Refiners Association, Concawe division.

5. OWNERSHIP OF RESULTS

5.1. All intellectual property owned by a Party independently of the Research ("Background Intellectual Property") but used in connection therewith shall remain the exclusive property of that party. The parties shall endeavour to ensure that the relevant and necessary Background Intellectual Property is made available to the other Parties, insofar as they are entitled to do so. For the avoidance of doubt, neither party under this Agreement is granted a licence, nor transferred or assigned any rights to any Background Intellectual Property by the other party aside from those explicitly granted herein.

5.2. The copyright and all intellectual property rights in the results of the Research ("Research Results") shall belong to the University.

5.3. The University shall grant Concawe and Member Companies and Concawe working groups and task forces (where such groups consist of Concawe staff, staff of Concawe Member Companies and from other oil industry associations), a non-exclusive, irrevocable, royalty free, worldwide right and licence to use the Research Results, including, but not limited to, the use in models, the use and discussion at meetings, and for the production of documents, position papers, internal and external reports and for advocacy purposes or any similar use. The source of any material from the Research

5.4. Used in any published document or presentation will be fully acknowledged. Concawe recognizes that the University may make reference to or publish information concerning the Research, in the interests of the exchange of scientific information, in journals, theses, dissertations or other such published material.

5.5. The University shall provide Concawe prior notice of any planned publication relating to the Research Results at least 45 calendar days before the publication. Concawe shall be entitled to object to the planned publication within 30 calendar days after receipt of the notice. If no objection is made within the time limit stated above, the publication is permitted. An objection is justified if: (a) the protection of the Concawe's or a Concawe member company Background Intellectual Property would be adversely affected and/or (b) if Confidential Information is disclosed. The objection has to include a precise request for necessary modifications.

5.6. If an objection has been raised, Concawe and the University shall discuss how to overcome the justified grounds for the objection on a timely basis (for example by amendment to the planned publication and/or by protecting information before publication) and the objecting party shall not unreasonably continue the opposition if appropriate measures are taken following the discussion.

5.7. Concawe can request a publication delay of not more than 90 calendar days from the time it raises such an objection. After 90 calendar days the publication is permitted.

5.8. Neither party shall include in any dissemination activity with the other party's Background Intellectual Property without obtaining the owning party's prior written approval, unless they are already published.

6. CONFIDENTIALITY

6.1. Subject to article 5.6, the receiving Party is obliged to keep the Confidential Information in confidence and shall not – without prior written consent of the disclosing Party - disclose the Confidential Information to any third party, nor use such Confidential Information for any other purpose than the execution of this Agreement. Furthermore, the receiving Party shall take all reasonable precautions to prevent the unauthorised disclosure of the Confidential Information.

6.2. The receiving Party may only disclose Confidential Information to those employees and/or external consultants, who have a need to know such confidential information for the execution of the Research under the condition that such employees and/or external consultants are bound by appropriate (labour) agreements requiring them to treat such Confidential Information confidentially. The receiving Party shall at all times be fully responsible to the disclosing Party for the compliance with this Agreement by such employees and/or external consultants.

6.3. In the event the receiving Party is required to disclose the Confidential Information by law, regulation or court order, the receiving Party shall promptly notify the disclosing Party. The receiving Party shall disclose only that portion of the Confidential Information that is legally required and shall exercise all reasonable efforts to obtain reliable assurance that confidential treatment will be accorded to the Confidential Information.

6.4. The obligations of this Article 7 will remain in force and effect for three (3) years as of the expiration or termination date of this Agreement.

7. LIABILITY AND INSURANCE

7.1. Excepting liability arising from breach of Article 6 (Confidentiality), the aggregate liability of WU for damages to Concawe as a result of, or in connection with this Agreement is limited to an amount equal to the total fees payable by Concawe in accordance with clause 4 of this Agreement.

7.2. Neither party shall under any circumstances be liable to the other for any indirect, incidental or consequential damages (including without limitation, loss of business or profits, loss of data or loss of use of equipment), nor for any claims, costs or damages that may result, directly or indirectly, out of the use of the Research Results.

7.3. WU guarantees that to the best of its knowledge it will not infringe third party rights, including IP rights, in preparing the Research Results.

7.4. Concawe indemnifies and holds WU harmless from any third party claims, including claims regarding product liability, arising from the Research executed by WU on Concawe's request, the use by Concawe of the Research Results delivered by WU, or both. In no event shall the aggregate liability of Concawe to indemnify the WU exceed an amount equal to the total fees payable by Concawe in accordance with clause 4 of this Agreement.

7.5. In the event of damages caused by a wilful act or gross negligence ("bewuste roekeloosheid") of WU, the exclusions and limitations of liability stated above shall apply only to the extent permitted by the applicable law.

7.6. Any claims by either party in respect of this Article needs to be expressly notified to the other party as soon as possible but ultimately one (1) year after this Agreement ended, in absence of which any claim will lapse completely.

7.7. Without prejudice to the liability of the University, the University shall effect and maintain in force appropriate policies of a business liability insurance.

8. AMENDMENTS

8.1. No modification, alteration, change in, or waive of any of the terms or conditions of the Agreement, no cancellation of the Agreement, and no other contract that may be made between the parties hereto shall be valid or binding unless the same is in writing and signed by both parties.

9. ASSIGNMENT AND TRANSFER

9.1. Neither party shall assign or transfer any benefit or obligation to third party without the written consent of the other party.

9.2. Any unauthorized assignment or transfer shall be null and void.

10. INDEPENDENT ACTIVITIES

10.1. The relationship between the parties is that of independent contractors. Nothing in this Agreement shall constitute, create or give effect to a joint venture, pooling arrangement, employer/employee relationship, principal/agency relationship, partnership or other co-operative entity between the parties. Neither party shall have the right to bind the other without the other party's express prior written consent.

10.2. The University shall not be subject to orders from Concawe. Should any order be issued to the University, it shall be interpreted as a request for services.

11. SUSPENSION AND TERMINATION

11.1. Parties may terminate for convenience the Agreement subject to 60 days written notice to the other Parties.

11.2. If the University fails to comply with any of their obligations under the Agreement or, due to circumstances beyond Concawe's control, is prevented or impeded from carrying out the Work for more than 2 months, Concawe may upon not less than 30 days' notice in writing to the University:

- suspend the Agreement and cease payment to the University. Concawe shall inform the University in writing of such suspension and the reason therefore, and after the period of suspension either resume the performance of the Agreement or, if any of the reasons for suspension remain, terminate its appointment under this Agreement.
- terminate the Agreement

11.3. Termination of the Agreement howsoever arising shall not prejudice or affect the accrued rights and remedies of the Parties.

11.4. Articles 5, 6 and 7 of shall survive termination or expiry of the present Agreement.

12. FORCE MAJEURE

12.1. Neither party shall be liable to the other for failure to perform or delay in the performance of its obligations under the Agreement if such failure results wholly or partly from circumstances beyond the party's reasonable control, including but not limited to, any act of God, any acts of terrorism, failure or shortage of power supplies, flood, lightning, fire, strikes not reasonably avoidable by him, act or omission of Government, local or district authorities, public telecommunications operators and other competent authorities, war, military operations or riot providing that the other party is notified in writing of these circumstances by the affected party ("force majeure event") as soon as it becomes aware of their occurrence and that the affected party uses all reasonable endeavours to prevent, avoid, overcome or mitigate the effects of such cause. Each party shall bear all of its own claims, losses, damages, costs and expenses suffered or incurred due to such force majeure event.

12.2. If a force majeure event continues to prevent performance of this Agreement for a period of thirty (30) days, Concawe may terminate this Agreement without penalty. In such an instance both parties will agree a fair and reasonable payment for the Work properly performed prior to termination.

13. NOTICES

13.1. All notices shall be sufficiently given if delivered personally or sent by first class post to the other party and any such notice shall be deemed to have been given on the date it was personally delivered, or if sent by post 48 hours after the time it was posted.

14. GOVERNING LAW

14.1. This Agreement shall be deemed to have been made in Belgium and shall be interpreted under solely in accordance with the laws of Belgium.

15. EFFECTIVE DATE

15.1. The contract shall come into effect on the date the agreement is countersigned by all parties.

15.2. The Agreement will terminate on 31st December 2018.

16. ORDER OF PRIORITY

16.1. If there is any ambiguity, inconsistency or conflict between the terms and conditions contained in the documents forming a part of this Agreement, then the Agreement shall be construed in the following order of priority (1 takes precedence over 2):

1. the terms and conditions of the present Agreement
2. the provisions of the Proposal in Appendix 1

INTENDING TO BE LEGALLY BOUND, the parties have executed this Agreement in three original copies as of the date and place written here-below.

Executed at Brussels....., on 22 December 2017

Concawe:

5.1.2.e

5.1.2.e
Science Director

The University:

5.1.2.e

20/12/2017

Dr R.J. Bino
Managing Di

APPENDIX 1

Wageningen University MSc Student Research Proposal:

In vitro metabolism and genotoxicity of naked versus alkylated PAH that may be present in mineral oils.

Hydrocarbons may be found in food stuffs. Although some of the hydrocarbons in food are of natural origin, mineral oil residues originating from food packaging, additives, processing aids, and lubricants may also be present [1]. Based on chromatographic analyses, mineral oil residues found in food are identified as "mineral oil saturated hydrocarbons" (MOSH) and "mineral oil aromatic hydrocarbons" (MOAH) (see Figure 1).
The MOAH fraction consists mainly of substituted aromatic hydrocarbons, but may also comprise polycyclic aromatic hydrocarbons (PAHs), some of which are also known to be genotoxic carcinogens [2] (Figure 1).

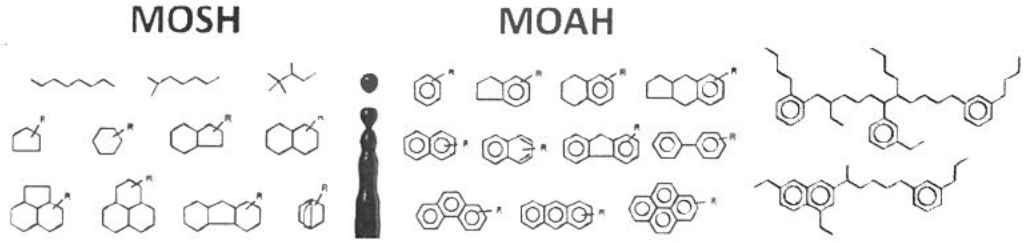


Figure 1. Chemical structure of some MOSHs and MOAHs.

The content of PAH in mineral oils is controlled by limitation of their concentration which requires their detection and quantification in samples of interest. Typically this is achieved by determination of the 16 USEPA PAH or the Grimmer PAH, which both comprise (almost) exclusively naked PAH. Recent concerns, however, arise from the detection in food stuffs of MOAHs consisting of mainly alkylated PAH which are typically not specifically quantified. Although on thermodynamic grounds it is expected that alkylated PAH will undergo oxidative metabolism on the alkyl side chains rather than on the condensed aromatic rings, facilitating their excretion rather than their bioactivation to DNA reactive metabolites, there are regulatory concerns that alkylated PAH pose a greater genotoxic hazard than naked PAH.

Aim

The aim of the present project is (1) to obtain better insight in the relative metabolic bioactivation and detoxification of naked versus alkylated PAH that may be present in mineral oils, and (2) to provide a basis for better risk assessment of MOAH using physiologically based kinetic (PBK) modelling and read-across from related non-alkylated PAHs.

Previous studies at the division of Toxicology provided the first proofs of principle that definition of parameters needed for risk assessment of compounds for which data are missing is possible when using PBK model based read-across from data for related compounds [3-5] (Figure 2). This allows modern 21st century-proof risk assessment since this novel approach contributes to the development of alternatives for animal testing, facilitating read-across from compounds for which in vivo toxicity studies are available to compounds for which these data are unavailable. In the present study this novel approach will be developed for MOAHs, using read-across from related non-alkylated polycyclic aromatic hydrocarbons (PAHs) [6].

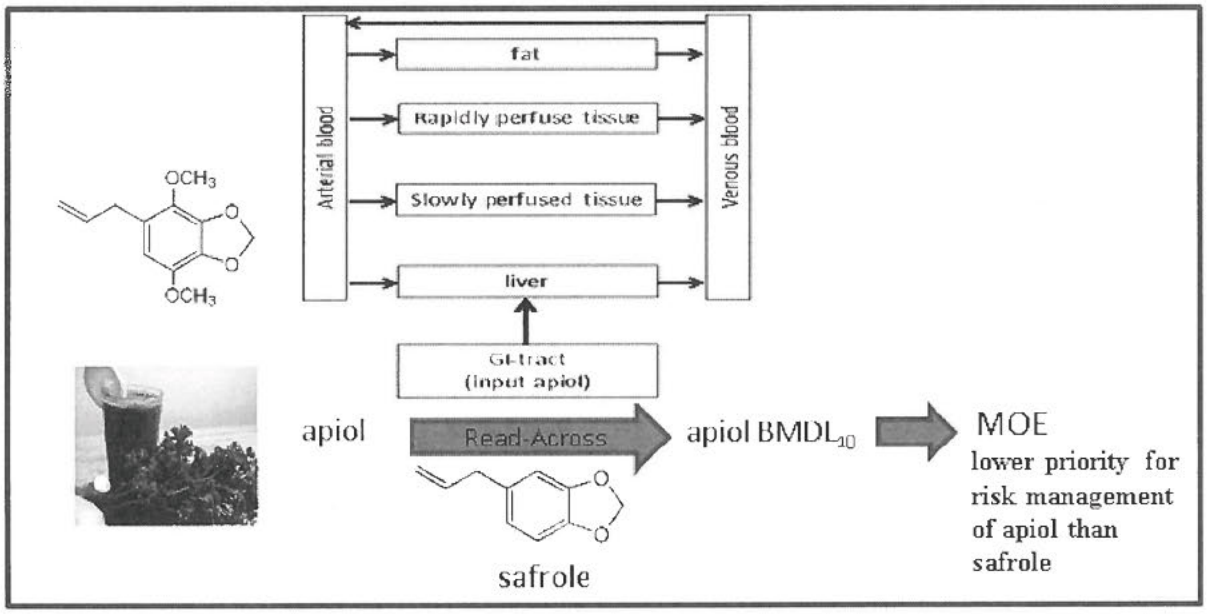


Figure 2: Example of risk assessment for a compound for which rodent tumor data are not available (apiol), based on read-across from a compound for which tumor data are available (safrole) using PBK modelling. BMDL10 = lower confidence bound of the dose level causing 10% tumor incidence above background levels, MOE = Margin of Exposure, defined as the ratio between the BMDL10 and the estimated daily intake (EDI) and indicating the priority for risk management [7]. For further details see [4].

In addition, a PBK model for mineral oil hydrocarbons present in food contact materials was recently developed which was able to predict the kinetics in a series of published kinetic studies in rats [8]. This model ~~(see Figure 3)~~ and the previously developed generic PBK model that was successfully applied to PAH [9, 10], can serve as the basis to develop PBK models for alkylated and ~~naked PAH present~~ in mineral oil.

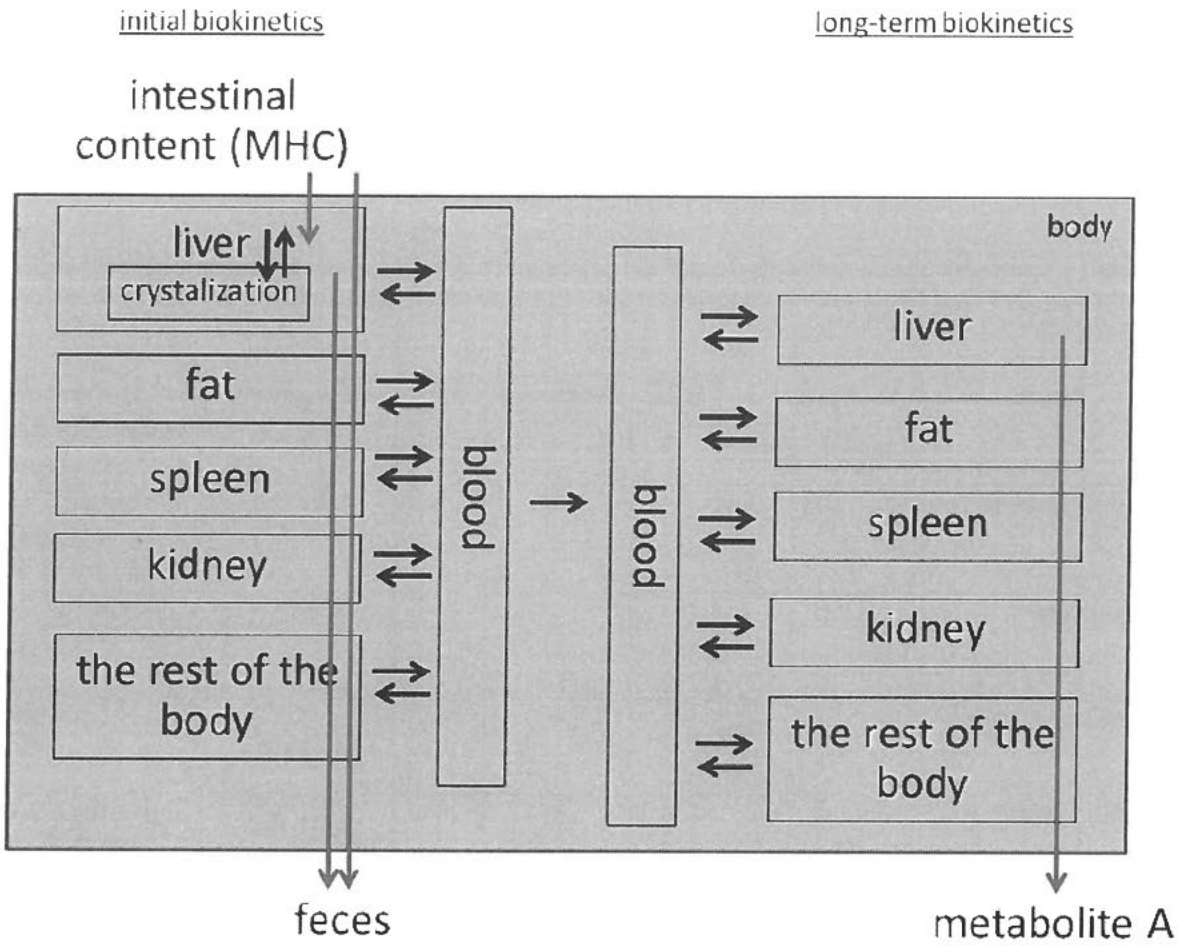


Figure 3. PBK model for mineral hydrocarbons (MHC)

Approach

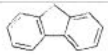
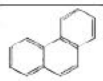
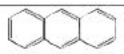
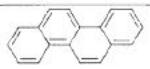
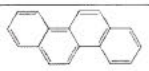
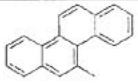
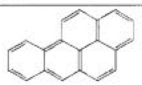
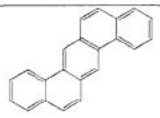
To investigate the relative balance between detoxification and bioactivation upon metabolism, the oxidative metabolism (Michaelis-Menten kinetics) and genotoxicity (γH2AX assay with the HepaRG cell line [11-13]) of naked PAH as compared to the corresponding alkylated compounds will be characterized. To this end individual PAH, their alkylated counterparts, and various mineral oil extracts will be tested.

The oxidative metabolism of a selection of PAH for which alkylated (methylated) counterparts are commercially available (see Table 1) will be tested by incubation with rat and human hepatic microsomes (with and without a metabolic activation system present) and, if possible, primary hepatocytes. The formation of hydroxylated metabolites will be measured. Attention will also be given to the nature of the alkyl chain since this may turn out an important factor influencing the metabolic pathways.

In addition, the genotoxic potency will be quantified in the so-called γH2AX assay using metabolic competent and inducible HepRG cells [14, 15]. The γH2AX assay, uses visualization by labelled antibodies of the histone H2AX that is phosphorylated to γH2AX in an attempt to repair double strand breaks (DSBs) in the DNA caused by genotoxic xenobiotics [12]. This assay has already shown able to detect genotoxicity of PAHs [12]. Moreover, it appears to be more sensitive than other genotoxicity assays such as the comet assay [16] while the human HepaRG hepatocellular carcinoma cell line represents a metabolically highly competent model comparable to cultured primary human hepatocytes [14, 15]. This HepRG cell line has high and inducible CYP450 and is expected to be highly useful in combination with the γH2AX assay to detect combined bioactivation and genotoxicity of compounds without the need for

quantifying DNA adduct) of naked PAH as compared to the corresponding alkylated compounds will be characterized.
In addition, the influence of the presence of other PAH on the metabolism and genotoxicity will be investigated by performing the same incubations as described for single PAH with actual DMSO extracts of a series of mineral oils with varying concentrations of PAH and alkylated PAH. This is of importance given that within mixtures of PAHs competition for biotransformation enzymes may influence the ultimate metabolite pattern.

Table 1 – Commercially available alkylated PAH corresponding to PAH as selected by the EU Scientific Committee for Food, the Grimmer Institute and the USA Environmental Protection Agency with cancer classification according to IARC .

Name	IARC classification	SCF	Grimmer	EPA	Structure	Commercially available alkylated congeners
Naphthalene	2B	-	-	+		1-methyl; 2-methyl; 1-ethyl; 2-ethyl; 2,7-di-t-butyl; 1-dodecyl
Fluorene	3	-	-	+		1-methyl; 2,7-di-t-butyl
Phenanthrene	3	-	+	+		3-methyl
Anthracene	3	-	+	+		2-methyl; 9-methyl; 2-ethyl; 9-phenyl-10-propyl; 2-t-butyl
Pyrene	3	-	+	+		1-methyl; 2,7-di-t-butyl
Benzo[c]phen-anthrene		-	+	-		1-methyl; 2-methyl; 4-methyl; 5-methyl
Chrysene	2B	+	+	+		1-methyl; 2-methyl; 3-methyl; 4-methyl
5-Methyl-chrysene	2B	+	-	-		
Benzo[a]pyrene	1	+	+	+		7-methyl; 8-methyl
Dibenzo[a,h]-anthracene	2A	+	+	+		3-methyl

Timeline

This project will start per December 1st 2017 and the final report will be delivered December 31st 2018 (one year).

Costs

The total costs of the project are budgeted to be 40 k€, this includes manpower (graduated MSc and several MSc students, including test materials, laboratory costs, but excluding actual mineral oils samples).

References

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11. Khoury, L., D. Zalko, and M. Audebert, Validation of high-throughput genotoxicity assay screening using gammaH2AX in-cell western assay on HepG2 cells. Environ Mol Mutagen, 2013. 54(9): p. 737-46.

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15. Guillouzo, A., et al., The human hepatoma HepaRG cells: a highly differentiated model for studies of liver metabolism and toxicity of xenobiotics. Chem Biol Interact, 2007. 168(1): p. 66-73.

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RESEARCH AGREEMENT #1 (MSc)
Ref. 201700093

BETWEEN

The European Petroleum Refiners Association AISBL, for its Concawe division, having its [redacted] located at 1160 Brussels, boulevard du Souverain, 165, Belgium, represented by [redacted]

Hereafter referred to as "Concawe"

AND

Wageningen University, having its premises located at Stippeneng 2, NL-6708 WE Wageningen, the Netherlands, hereby represented by its Managing Director, Dr R.J. Bino

Hereafter referred to as "University"

AND

University and Concawe hereafter are jointly referred to as the "Parties"

PREAMBLE:

Parties intend to jointly conduct research pertaining to the study of in vitro metabolism and genotoxicity of naked versus alkylated PAH that may be present in mineral oils. To that end, MSc Student will conduct research at the University within the scope of his/her work on his/her master thesis. Concawe will support the MSc Student's research with a financial contribution. These funds will be managed by the University.

PROPOSAL:

Research Project Title: In vitro metabolism and genotoxicity of naked versus alkylated PAH that may be present in mineral oils.

Scope:

The aim of the present project is (1) to obtain better insight in the relative metabolic bioactivation and detoxification of naked versus alkylated PAH that may be present in mineral oils, and (2) to provide a basis for better risk assessment of MOAH using physiologically based kinetic (PBK) modelling and read-across from related non-alkylated PAHs.

Concawe -Wageningen University MSc Agreement - Confidential - Page 1
Ref. 201700093

MSc research agreement_HH effects of alkylated PAH_ref. 201700093

Adobe Sign Document History 01/08/2018

Created:	12/19/2017
By:	Concawe _ [redacted]@concawe.org)
Status:	Signed
Transaction ID:	CBJCHBCAABAAIhCgPpVjhQjFQKSdIh_QBSi_E8rp2SNG

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Signed document emailed to contractmanagement.afsg@wur.nl, [redacted]@wur.nl, [redacted]@concawe.org, [redacted]@wur.nl, and 3 more
01/08/2018 - 1:14:04 PM GMT+1

From: /O=WUR/OU=CENTRAL ADMINISTRATIVE GROUP/CN=RECIPIENTS/CN=AENF002 on behalf of Contractmanagement AFSG
Sent: dinsdag 23 januari 2018 14:36
To: 5.1.2.e @concawe.org'
Subject: Concawe Research Agreement ref: 201700093 (WU ref: OVK 17/322)

Dear 5.1.2.e ,

I have received the revised copies in twofold. Thank you for that. I will replace the revised page as you suggested. Do you need the other hardcopy back with the replaced/initialled page? As for us one original is enough for our records.
Hope to hear from you soon.

Kind regards,

5.1.2.e
Contract Management AFSG

Wageningen University, dept. Agrotechnology and Food Sciences
Stippeneng 2, 6708 WE Wageningen, the Netherlands
P.O. Box 57, 6700 AB Wageningen, the Netherlands
T: 5.1.2.e
E-mail: contractmanagement.afsg@wur.nl
URL: www.wur.nl/uk

From: [redacted]@concawe.org>
Sent: maandag 8 januari 2018 15:21
To: Contractmanagement AFSG
Subject: RE: Reminder re: MSc research agreement_HH effects of alkylated PAH_ref. 201700093
Attachments: 201700093.pdf

Dear [redacted],
Please find attached the duly signed Research Agreement between Concawe and Wageningen University.
We will send you two original copies by mail today.
Kind regards,
[redacted]

[redacted]
concawe
ENVIRONMENTAL SCIENCE FOR THE EUROPEAN REFINING INDUSTRY

Boulevard du Souverain 165
B-1160 Brussels, Belgium
T. [redacted]
[redacted]@concawe.org
www.concawe.org

From: Contractmanagement AFSG [mailto:contractmanagement.afsg@wur.nl]
Sent: 08 January 2018 12:28
To: [redacted]@concawe.org>
Subject: RE: Reminder re: MSc research agreement_HH effects of alkylated PAH_ref. 201700093

Dear [redacted],

Please find attached the agreement (in twofold) and letter I have send on the 21st of December 2017. We prefer to have a fully signed original in return. When this still has not been received please let me know as soon as possible.

Kind regards,

[redacted]
Contract Management AFSG

Wageningen University, dept. Agrotechnology and Food Sciences
Stippeneng 2, 6708 WE Wageningen, the Netherlands
P.O. Box 57, 6700 AB Wageningen, the Netherlands
T: [redacted]

E-mail: contractmanagement.afsg@wur.nl
URL: www.wur.nl/uk

From: Concawe _ [mailto:echosign@echosign.com]
Sent: vrijdag 22 december 2017 15:28
To: Contractmanagement AFSG <contractmanagement.afsg@wur.nl>
Subject: Reminder re: MSc research agreement_HH effects of alkylated PAH_ref. 201700093

Email Reminder re: **MSc research agreement_HH effects of alkylated PAH_ref. 201700093**

Could you please urgently sign this contract, since this needs to be dated in 2017. If you have problems signing this electronically, please print, sign and scan a copy of the agreement, and send the scan to us by e-mail. I will then upload that copy in the Adobe Sign system to finalise the process.
Thank you!
Merry Christmas and Happy New Year.
Kind regards,
5.1.2.e

Concawe _ has requested that this reminder be sent.

Click here to login to Adobe Sign and view this document.

To ensure that you continue receiving our emails, please add echosign@echosign.com to your address book or safe list.

WAGENINGEN UR
For quality of life

P.O. Box 8000 | 6700 EA Wageningen | The Netherlands

European Petroleum Refiners AISBL
Concawe Division
165 Bd du Souverain
Brussels
Belgium

Section Toxicology

DATE
September 3, 2015

OUR REFERENCE
2015/035/5.1.2.e

POSTAL ADDRESS
P.O. Box 8000
6700 EA Wageningen
The Netherlands

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INTERNET
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www.wageningenUR.nl

CoC NUMBER
09098104

HANDLED BY
5.1.2.e

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5.1.2.e@wur.nl

Dear Attention:5.1.2.e Science Executive for Health, Concawe,

Ref: 201506110

Sponsorship letter: *Role of polycyclic aromatic compounds (PAC) in reproductive toxicity of petroleum substances*

Dear5.1.2.e

Wageningen University (WU) is willing to support the Concawe research program on Petroleum Substances as described in this letter.
Work will be done by a PhD student of the Division of Toxicology of Wageningen University (TOX-WU) over a period of 4 years starting in September 2015 and ending no later than December 2019. Concawe has expressed interest in sponsoring this work for an amount of six hundred and seventy-three thousand euros (EUR€ 673,000) covering the student's work under the supervision of 5.1.2.e 5.1.2.e (Shell Health),5.1.2.e (TOX-WU-) and5.1.2.e 5.1.2.e (TOX-WU).

By accepting Concawe's grant, Wageningen University commits to perform the research as specified in the present letter and to report to Concawe on the results on a six-monthly basis. Concawe will receive a copy of the work results upon completion, which it will be able to use freely for its own purposes.

Should the student identified in this letter become unavailable for whatever reason, Wageningen University will identify a suitable replacement and will discuss in good faith with Concawe of possible options for completing the research or returning unspent amounts.

If Concawe agrees with this proposal, please return a copy of this sponsorship letter signed for approval at your earliest convenience. The sponsorship amount

of six hundred and seventy-three thousand euros (EUR €673,000) will be invoiced to Concawe in instalments. A payment of EUR € 88,250 shall be made on the start of the contract. For each of the years 2016-2019 payment shall be half at mid-year, the other half for each year at the end of the year.

The payment schedule is as follows:

	2015	2016	2017	2018	2019	Total
Staff	31,250	62,500	62,500	62,500	31,250	250,000
Travel & Living Expenses	1,500	2,500	2,500	2,500	3,000	12,000
Consumables	23,000	25,000	25,000	25,000	23,000	111,000
RIKILT (cell lines/-omics)	25,000	60,000	60,000	60,000	25,000	230,000
Sub-total	80,750	150,000	150,000	150,000	82,250	613,000
Indirect Costs	7,500	15,000	15,000	15,000	7,500	60,000
Total	88,250	165,000	165,000	165,000	89,750	673,000

1. Student details

To be determined by [redacted]

2. Background and Justification

REACH Registrants of Petroleum Substances in the Bitumen Category have received from the European Chemical Agency a Final Decision pursuant to REACH on the Testing Proposal submitted for a prenatal development toxicity study to be undertaken on Bitumen Substances grouped in a Category. This legal Decision explicitly states that testing required does not imply that the Registrant's read across approach has been accepted, but only an analogue approach, pending that the Registrant proves his hypothesis right. Briefly, this hypothesis states that observed reproductive toxicity of some oil products is due to their content of heavy polycyclic aromatic compounds (PACs).

A research proposal has been developed by Concawe to test this hypothesis. It involves testing the hypothesis that PACs, which may be present in heavy petroleum substances, are responsible for the observed prenatal developmental toxicity observed with some of these substances, by using a battery of in vitro systems in combination with -omics technology (National Research Council, 2013).

3. Research Objectives and Tasks

This project involves testing the hypothesis that induction of prenatal developmental toxicity by heavier petroleum streams are due to the effects of PACs. These effects on prenatal developmental toxicity can be determined by applying a series of in vitro test systems such as the embryonic stem cell test (EST), the Zebra-fish Embryo test (ZET), and a range of developmental or reproduction-related cell models. These in vitro systems will be exposed to oil fractions known to contain or lack PACs. Assessment of effects in these in vitro systems will include whole genome mRNA expression analysis by RNA seq techniques. This will be followed by a bioinformatics approach that will assess both development- and reproduction-related effects as well as more general toxic effects. Detection of developmental effects will include a read-across approach in which the transcriptomics results obtained in our experiments will be compared to those published previously on developmental or reprotoxic toxicants. This will result in the identification of perturbation of relevant biological pathways. The results will be published in peer-reviewed scientific journals.

Work content:

To achieve the aims of the present project the following work packages (WPs) will be performed:

WP1: Selection of test substances (PACs, petroleum substances and GTL products).

WP2: Optimizing incubation options for the various in vitro test systems.

WP3: Quantification of the concentration-dependent in vitro developmental toxicity and gene expression profiles induced by the selected PACs, petroleum substances and GTL products in the in vitro reproductive and developmental toxicity test systems.

WP4: Quantification of the concentration-dependent in vitro gene expression profiles of the selected PACs, petroleum substances and GTL products in a series of developmental or reproduction-related cell models, and unravelling of mode of actions.

WP5: Dissemination of the results: via publications in peer-reviewed journal(s).

4. **On-site oversight on Research**

- Wageningen University: 5.1.2.e and 5.1.2.e
- Shell Health: 5.1.2.e

5. **Deliverable(s)**

- **WP1: Selection of the model PACs, model petroleum substances and GTL products; Delivery date: month 6**
  - Partners involved: Division of Toxicology of Wageningen University (TOX-WU) and the Toxicology Section of the Risk Sciences Team in Shell Health (Shell International bv) (SI-SHG/PT). Based on the selection criteria defined all partners of the project will be involved in selecting the model PACs, model petroleum substances and GTL products to be included in the other tasks (WP2,WP3 and WP4) of the project.

- **WP2: Optimizing incubation conditions for the various in vitro test systems; Delivery date: month 6**
  - Partners involved: Division of Toxicology of Wageningen University (TOX-WU) and the Toxicology Section of the Risk Sciences Team in Shell Health (Shell International, bv) (SI-SHG/PT).

- **WP3: Quantification of the concentration-dependent in vitro developmental toxicity and gene expression profiles of the selected PACs, model petroleum substances and GTL products in the selected test systems. Delivery date: month 42**
  - Partners involved: Division of Toxicology of Wageningen University (TOX-WU), the Toxicology Section of the Risk Sciences Team in Shell Health (Shell International, bv) (SI-SHG/PT) and RIKILT (WUR). The selected in vitro test systems for prenatal developmental toxicity will be performed at TOX-WU and samples for the RNA seq will be prepared and send to RIKILT for processing and analysis. Effects on steroidogenesis using the human H295R adenocarcinoma cell line will be assessed at the RIKILT.

- **WP 4: Quantification of the concentration-dependent in vitro gene expression profiles of the selected PACs, model petroleum substances and GTL products in a series of developmental or reproduction-related cell models. Delivery date: month 42**
  - Division of Toxicology of Wageningen University (TOX-WU), the Toxicology Section of the Risk Sciences Team in Shell Health (Shell

International, bv) (SI-SHG/PT) and RIKILT (WUR). The selected in vitro cell lines will be treated at TOX-WU and samples for the RNA seq will be prepared and sent to RIKILT for processing and analysis.

- **WP5: Dissemination of the results: Delivery date: month 48**
  - Partners involved: Division of Toxicology of Wageningen University (TOX-WU) and Shell International. Results will be presented at international conferences and published in scientific papers in peer reviewed journals; in addition, dissemination of the approach developed to regulatory authorities is anticipated.

    Expected publications include:
    - Effect of oil categories on gene expression and morphology in the zebra fish.
    - Effect of oil categories on gene expression and morphology in the embryonic stem cell assay.
    - Effects of oil categories on steroidogenesis using the human H295R adenocarcinoma cell line.
    - Effects of oil categories on mRNA expression in primary human Sertoli cells.
    - Effects of oil categories on mRNA expression in human Ishikawa endometrial cells.
    - Role of PACs in induction of developmental toxicity of heavier petroleum streams.

6. Publications

The Division of Toxicology of Wageningen University (TOX-WU) will have the right to publish the research results. The Division of Toxicology of Wageningen University (TOX-WU) will provide Concawe with the intended publication at least one (1) month prior to such intended publication. Concawe has a period of one (1) month to ask for amendment of the intended publication. The Division of Toxicology of Wageningen University (TOX-WU) will agree to such an amendment only if the scientific quality and integrity of the publication is not compromised. If no agreement on the requested amendment can be reached within one (1) month The Division of Toxicology of Wageningen University (TOX-WU) will postpone the publication up to a maximum of three (3) months.

7. Intellectual Property

Intellectual Property to the deliverables will belong to Concawe. Wageningen University will be granted a non-exclusive, irrevocable, royalty-free right to use these deliverables for its non-commercial research and publication purposes. Wageningen University warrants to the best of its knowledge that the work to be done hereunder shall not infringe any third party intellectual property rights and shall indemnify Concawe against any such third party claims.

8. Liability

The liability of the Division of Toxicology of Wageningen University (TOX-WU) for damages is limited to the direct damages up to a maximum of the amounts already paid by Concawe to the Division of Toxicology of Wageningen University (TOX-WU) for the research to which the damages are related.

The Division of Toxicology of Wageningen University (TOX-WU) shall in no case be liable for any indirect, incidental or consequential damages (including without limitation, lost business or profits, loss of data or loss of use of equipment).

The Division of Toxicology of Wageningen University (TOX-WU) shall not be liable toward Concawe for any claims, costs or damages that may result, directly or indirectly, out of the performed research and/or the use of the research results by Concawe or third parties which received the research results from Concawe, unless and to the extent that damage is caused by gross fault and/or due to wilful misconduct by an executive of the Division of Toxicology of Wageningen University (TOX-WU).

Any claims of Concawe in respect of this clause need to be expressly notified to Division of Toxicology of Wageningen University (TOX-WU) as soon as possible but in any case within one (1) year after this Agreement ended, in absence of which any claim will lapse completely.

9. Banking Information

All payments related to the present letter are to be made to the bank account specified below:

Name and Address of the Bank:
ABN-AMRO Wageningen
Name on Bank Account:
Wageningen University, Dept. Agrotechnology and Food Sciences

P.O.Box 17
6700 AA Wageningen

Accountnumber (IBAN): NL13ABNA521072298
SWIFT/BIC: ABNANL2A
Reference: 3909/projec[redacted]/project leader:
[redacted]

10. Termination

Concawe may terminate the Agreement subject to 6 months written notice to Wageningen University. On termination Wageningen University shall hand over to Concawe all research documents and results of the research and Concawe shall hand over to Wageningen University all sums due or committed up to the date of termination.

11. Governing Law

This Agreement shall be governed by Belgian law.

For approval

Name: Raoul Bino
Signature: [redacted]
Title: Managing director
Organisation: Wageningen University
Date: 4 Sept 2015

Name: [redacted]
Signatu[redacted]
Title: Director General
Organisation: Concawe
Date: 28/09/2015

WAGENINGEN
UNIVERSITY & RESEARCH

P.O. Box 57 | 6700 AB Wageningen | The Netherlands

European Petroleum Refiners Association AISBL
Concawe division
Attn. 5.1.2.e
Boulevard du Souverain165
1160 Brussels
BELGIUM

Dear 5.1.2.e ,

Please find enclosed three copies of the Research Agreement regarding 'Support to Concawe Health Management Group (HMG) on specific projects related to the activities of the Toxicology Sub Group of WU (TSG) as detailed in individual Work Orders'.

Would you be so kind as to initial each page, to sign the agreements and to return one fully signed copy to:

Wageningen University
Attn. 5.1.2.e – Contract Management AFSG
P.O. Box 57
6700 AB WAGENINGEN
THE NETHERLANDS

In case of any questions please feel free to contact me.

With kind regards,

5.1.2.e
Contract Management AFSG

Enclosure

DATE
December 21, 2017

SUBJECT
Research agreement for signing

YOUR REFERENCE
201700093

OUR REFERENCE
OVK 17/322

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100years
1918 — 2018

concawe
ENVIRONMENTAL SCIENCE FOR THE EUROPEAN REFINING INDUSTRY

The Managing Director
Wageningen University
PO Box 8000
6700 EA Wageningem
The Netherlands

1 April 2016

Dear Mr. Bino,

Ref: 201506110

Re: Addendum to Sponsorship agreement between The European Petroleum Refiners Association AISBL ('Concawe") and Wageningen University ("Wageningen") dated 28 September 2015

As you are aware, on 28 September 2015 Concawe and Wageningen signed an agreement ("the Agreement") whereby Wageningen agreed to carry out research on the role of polycyclic aromatic compounds in reproductive toxicity of petroleum substances.

Article 4 of the agreement stipulates that 5.1.2.e shall provide on-site oversight on research. As 5.1.2.e also has a special assignment at Wageningen, in order to prevent a conflict of interest arising, this addendum is to clarify that in the execution of this contract, 5.1.2.e 5.1.2.e shall act on behalf of Wageningen University only and therefore shall not act on behalf of or represent Concawe. Instead, 5.1.2.e of Concawe, will represent Concawe on this project.

In light of the foregoing, the parties hereby agree to amend the second line of Article 4 of the agreement as follows:

4. On-site oversight on research

- Concawe : 5.1.2.e acting solely on behalf of Wageningen University, shall be responsible for onsite oversight and research. 5.1.2.e 5.1.2.e for Concawe shall represent Concawe on this project and shall have overall accountability for the project and shall be responsible, for monitoring progress and agreeing future direction with 5.1.2.e of the project on behalf of Concawe."

All the other terms and conditions of the agreement shall remain in force except those that are modified herein.

The present letter shall be annexed to the Agreement as Addendum 1.

Executed at Brussels, on 28 April 2016.

For and on behalf of Concawe

5.1.2.e

Signature:

Name: 5.1.2.e
Title: 5.1.2.e

For and on behalf of Wageningen University

5.1.2.e

Signature:

Name: 5.1.2.e
Title: Director Operations

Special Chair:

Environmental health and human biomonitoring of contaminants.

General information

Name Chair:
Environmental health and human biomonitoring of contaminants.

Requested by:
5.1.2.e
Shell Global Solutions International
Amsterdam, Netherlands

Proposed embedding at:
Wageningen Universiteit and Research Center, Unit Agrotechnology and Food.
Chair Toxicology, 5.1.2.e
Address: Helix, Stippeneng 4, Wageningen

Name candidate:
5.1.2.e
Senior Toxicologist
Shell Health
Shell International bv
Carel van Bylandtlaan 30
2596HR Den Haag

CV candidate
A curriculum vitae, publication list and citation analysis of 5.1.2.e are provided separately.

Functioning of the proposed special chair:
The proposal is to set up a special chair for 0.2 FTE (one day per week), financed by Shell and located at the Chair of Toxicology Wageningen University. The aim is to contribute to the current education- and research programme of Wageningen University, as well as to supervise PhD- and MSc-students.

1. Motivation of the applicant in relation to the interests of Wageningen University.

Man-made chemicals are part of our society. Exposure to some of these substances may cause adverse health effects. This applies to humans but also to other organisms in our environment.
For adequate control of the risks of chemical substances in our food and the environment we need reliable human and environmental health risk assessments. In particular the potential health effects of combinations of exposures to different chemicals need to be assessed as there are significant societal concerns about multiple concurrent exposures as they may occur in day-to-day life.

An important category of complex chemical products to which we are exposed on a regular basis is formed by petroleum products. Petroleum products are produced and used on a very large scale in Europe and other parts of the world. Petroleum substances form, with an annual production of > 900 million tons, about 30% of the total volume of chemicals on the European Union market. Petroleum products are not only used as fuels and lubricants, but also in plastics, medicine, food, cosmetics, toys and many other products and are as such widely used on a daily basis by most people.

Petroleum substances are highly complex with regard to chemical composition and are, without exception, so-called UVCB substances (Substances of **U**nknown or **V**ariable composition, **C**omplex reaction products or **B**iologicals) due to their variable composition. Petroleum substances contain hundreds (for lighter products, such as gasoline) up to hundreds of millions (for heavier products, such as lubricating oils) of molecules of which the relative concentrations may vary to some extent over time.
Virtually all existing methodologies for human and environmental risk assessment are based on exposure to single substances or – at best – exposure to a combination of a very limited number of substances. Therefore risk assessment methodologies need to be (further) developed for complex substances, such as UVCBs, including petroleum products.

Shell considers scientific research to develop suitable methodologies to assess the health risks of petroleum substances of paramount importance and desires to cooperate with academic institutions to support this type of fundamental scientific research.

By supporting this special chair Shell aims:

- to obtain better insight of potential health effects of petroleum substances and more generally to better understand the possible effects and interactions due to combination exposure to complex substances and, in particular, to do this through application and further development of alternatives to animal testing,
- to better characterize human exposure to environmental contaminants, including petroleum substances and their breakdown- and combustion-products, using human biomonitoring techniques,
- to develop novel non-animal based methodologies to characterise and evaluate health risks due to exposure to UVCBs such as petroleum products, and

Three types of information are essential to assess the health risks of exposure to chemical substances. Firstly, the intrinsic toxicity needs to be determined ('hazard identification'). Secondly, the relationship between exposure concentration and the adverse effects needs to be defined ('hazard characterisation'). Finally it is essential to assess exposure for each relevant population (e.g. workers, consumers, elderly, children, species in the ecosystem) and each relevant route of exposure (e.g. via inhalation, through dermal contact, via food or drinking water)('exposure assessment'). Based on these data a potential health risk can be assessed ('risk assessment'). For UVCBs, and petroleum substances in particular, these three aspects are highly complex. In addition, there is an increasing concern that the general approach as currently applied may fail. This is triggered by the increasing attention for combined exposures. In most instances people are not only potentially exposed via more than one route of exposure but also to various man-made chemicals at the same time (Meek, Boobis et al. 2011, ECETOC 2012). Furthermore, it is increasingly obvious that the largest uncertainty in the assessment of human health risks due to chemical exposure in food and via the environment (outside and indoor air pollution, contamination of soil and surface water) resides in the estimation of the actual exposure levels (EC 2013).

Both the intrinsic toxicity and the relationship between exposure and effect are generally determined through animal experiments and sometimes on the basis of epidemiological data. The exposure assessment is usually not straightforward and this is particularly true for the general population. In the occupational situation there has always been a lot of attention for exposure via inhalation and virtually all occupational exposure limits are expressed as airborne concentrations. The focus for the general population, in contrast, is usually on oral exposures via food and drinking water. As a consequence existing guidelines for estimating exposure of the general populations are usually based on maximum concentrations in food and drinking water.

Knowledge on and application of the appropriate health risk assessment methodologies for contaminants in our food and the environment is a central theme in both the education and the research of the Chair of Toxicology of Wageningen University. For students in various BSc and MSc programmes the appropriate assessment of health risks of exposure to chemical substances is of great importance

since a good risk assessment is essential for appropriate risk management. Currently the emphasis is on novel non-animal based testing methods for hazard identification and hazard assessment, with less emphasis on novel methods for exposure assessment, which is the third important aspect of risk assessment. Exposure science is undergoing a fundamental change with the development of new approaches and tools that go beyond the estimation of exposure based on occurrence of contaminants in food and consumption patterns. In particular the possibilities for assessing exposure by application of human biomonitoring (the assessment of total exposure by determination of substances or their reaction products in blood or urine) are not yet fully explored. Based on human biomonitoring data and so-called physiologically-based kinetic (PBK) computer models actual exposure levels can be predicted (Lyons, Yang et al. 2008, Campbell, Clewell et al. 2012, Jongeneelen, Ten Berge et al. 2013). The proposed special chair aims to strengthen this aspect both in education and research. This is of utmost importance as it is more and more obvious that the largest uncertainties in human health risk assessment reside in the uncertainties in the actual exposure levels.

Shell wants to contribute to the scientific development of this field of research and at least one PhD will be sponsored by Shell, the petrochemical or oil industry on a relevant project.
The research will primarily focus on (1) the hazard assessment, more specific reproduction and developmental toxicity, of complex substances, such as petroleum UVCBs by application of *in vitro* alternative non-animal based testing techniques and (2) the exposure assessment and biological monitoring of (complex) substances in our environment and resulting human exposure using human biomonitoring in combination with PBK modeling.
This fits well with Shell's own research aiming to set up and further develop alternatives for animal testing for hazard assessment and human biomonitoring. For instance, Shell is closely involved in the development and application of non-animal tests to predict human reproductive and developmental toxicity (www.crackit.org.uk). It has been shown that single *in vitro* tests for developmental toxicity have very little predictive value and that rather a combination of test systems should be applied to allow meaningful predictions for developmental toxicity (Piersma, Bosgra et al. 2013, Kroese, Bosgra et al. 2015). In this approach the translation of the concentration applied in those *in vitro* systems to the human situation remains an important challenge to which the present project will contribute as well. At the Division of Toxicology there is ample experience with such translation of in vitro concentration-response data to in vivo dose-response data using PBK modelling (Louisse, de Jong et al. 2010, Strikwold, Spenkelink et al. 2013, Li, Flick et al. 2016). This provides a unique opportunity for collaboration within the group. Furthermore Shell has always been very active in the field of human biomonitoring. For instance, biomonitoring of exposure to benzene is being applied for more than fifty years at the international level using methodologies developed internally by Shell (Van Haaften and Sie 1965, van Sittert, Boogaard et al. 1993, Boogaard and van Sittert 1995, Boogaard and van Sittert 1996, Arnold, Angerer et al. 2013). Other examples of methods developed by Shell are the biomonitoring of exposure to ethylene oxide, propylene oxide and 1,3-butadiene using haemoglobin adducts which are internationally accepted and applied (Boogaard, Rocchi et al. 1999, Boogaard 2002, Albertini, Sram et al. 2003).
Biomonitoring data are stored in the OneHealthIT database of Shell Health and form, in combination with the other (bio)medical data stored in this system, a unique database for toxicological research and the validation of models (de Jong 1991, Tsai, Wendt et al. 2001, Tsai, Fox et al. 2004, Tsai, Ahmed et al. 2007, van Amelsvoort, Slangen et al. 2009). Data available in the OneHealthIT database would, for instance, allow the validation and integration of the various models for biomonitoring that have been developed under the CEFIC-Long-range Research Initiative (LRI) programme[1] (which were initiated and

[1] LRI is a worldwide research programme, established by the associations of the chemical industries in Europe (CEFIC), the USA (ACC) and Japan (JCIA). The LRI sponsors independent research on specific themes of which human biomonitoring is one of the more important. Most of the programmes are conducted in collaborations of universities, research institutes and in some cases governmental or industrial institutes. Recipients of CEFIC-LRI grants in the field of human biomonitoring include: Cranfield University, England; Hamner Institute of Health Sciences, NC, USA; Dow Chemicals, USA; Health Protection Agency, England; Industox, Netherlands; National Research Centre for the Working Environment, Denmark; Nofer Institute of Occupational Medicine, Poland; TNO Quality of Life, Netherlands; University of Hasselt, Belgium; University of Copenhagen, Denmark; University of Parma, Italy; Santoxar, Netherlands; Syngenta Central Toxicology Laboratory, England; UK Health & Safety Laboratory, England; VITO, Belgium.

monitored by the candidate). In this way the knowledge and experience acquired within the industry can be applied in the field of toxicological risk assessment of environmental contaminants (such as polycyclic aromatic hydrocarbons and electrophilic chemicals) and lead to a more efficient and reliable health risk assessment of exposure to man-made chemicals in the general population. In addition, it allows the adaptation and refinement of existing models by making direct links between the concentrations used in the *in vitro* test systems and the internal concentrations as measured by human biomonitoring. In this way not only a much more reliable health risk assessment can be made, but at the same time the use of mammalian species for testing can be greatly reduced or completely avoided. Finally the data base provides unique human kinetic data for the validation of human PBK models on contaminants. Such data are often difficult to obtain given that human experiments with deliberate exposure to contaminants are considered unethical and cannot be performed.
It is Shell policy to publish results of research in the open, peer-reviewed literature (see Appendix 1). For all research sponsored under the CEFIC-LRI programme and also for the research performed by the proposed special chair publication of the results is an explicit condition (see Appendix 2).

Societal importance of the proposed special chair.

There is an increasing concern in the general population, but also amongst industrial workers and authoritative bodies, with regard to the potential health risks due to exposure to man-made chemicals. In addition, there is a strong trend within regulatory authorities to apply the precautionary principle in situations where man-made chemicals are involved. On the one hand this leads to reconfirmation of concerns and on the other hand to usually expensive, but in some instances unnecessary, restrictive measures. The precautionary principle is, by definition, applied when there is a lack of sound scientific data. Hence the generation of such data may contribute to more effective policies.
Furthermore, the current European chemicals legislation, including REACH (= Registration, Evaluation and Authorisation of Chemicals), demands an assessment of the potential health risk of a very large number of chemicals, namely all chemicals with production volumes greater than 1 ton/year, with increasing demands for data at increasing volumes (up till > 1000 tons/year, which triggers a complete dataset). For classified substances REACH requires, in addition to the identification of the potential hazards, an assessment of the exposure via all possible routes of exposure in a variety of populations (workers, consumers, general public). Traditional methodologies for both the identification of hazards (in particular for reproductive hazards) and the assessment of exposure are too inefficient to be applied to large numbers of different chemicals. Moreover, they are not suitable to be applied to complex substances, such as petroleum UVCBs, and also when exposure may occur via more than one route (e.g. by inhalation and orally through food or drinking water, or indirectly via air pollution).
By developing more efficient methods to characterise the total exposure to populations it may be determined in which cases restrictive measures or more research is needed and in which cases the actual health risk is negligible. Human biomonitoring, where applicable in combination with generic physiologically-based kinetic (PBK) models, is a highly promising approach to achieve this, and the method chosen in the projects of the newly proposed special chair.

Independency

It is important to recognise that the proposed special chair and the intended research will be financed by industry and may lead to critical questions with regard to the reliability and independency of the research results. We are fully aware of this and will do the utmost to safeguard and stress the independence of the work. The Code of Conduct for Research (gedragscode wetenschapsbeoefening) will be fully adhered to, and, in addition it is of paramount importance to be absolutely transparent on the financing and to emphasise that all research projects can and will be conducted and reported in a scientifically objective and independent way. In all cases it is contractually agreed that the financing organisations have no influence on the content of the various research projects and their output. The candidate followed specific training on communication since it is obvious that the industrial financing may be perceived as a conflict of interest and transparent and adequate actions and communication is

essential. The nature of the work, the type of projects, and the output generated should always show and illustrate that the work performed is science-based and in the interest of the science of risk assessment and public health policies as a whole.

Benefits for Wageningen University and Research centre (WUR)

Quantitative health risk assessment and support of public health policies are both important issues that receive a lot of attention. In addition, in both of these fields significant changes in scientific methodologies are expected, based on state-of-the-art scientific technology, including developments in the area of alternative mammalian species-free testing strategies, as well as in the area of –omics technology and *in silico* approaches. These developments are also of importance for the academic educational programmes.
Contaminant issues in both the food supply chain and the environment in general, as well as the potential adverse health effects of exposure to man-made chemicals via the environment and consumer products (REACH) are in the focus of attention of authorities, media and consumers. These themes are also of paramount importance to the Department of Agrotechnology and Food Sciences of WUR. These themes are also close to existing research areas that are currently studied within the Division of Toxicology such as the development of biomarkers and toxicological risk analysis, ecotoxicology and food toxicology and the development of alternatives for animal testing. Furthermore to ensure consumer protection, policy support, and the availability of appropriate knowledge in industry, not only fundamental research is needed but also graduates with a profound understanding of the area of risk assessment are essential.

Within the Division of Toxicology of Wageningen University ample knowledge in relation to the first two pillars of (hazard identification and hazard characterisation) is available, but not specifically with regard to complex substances, such as for example petroleum UVCBs. The proposed special chair aims to strengthen the third pillar of risk assessment, i.e. the exposure assessment, in both education and research. The proposed special chair also aims to fulfill the need for hazard identification and characterisation of complex mixtures, and the further development of alternative testing strategies in particular in the area of reproductive and developmental toxicity, and to conduct research and provide education in the area of human biomonitoring, exposure assessment and health risk assessment of complex substances at an academic level.

2. Task and mission of Wageningen University in relation to the proposed special chair

The mission of Wageningen UR is: “To explore the potential of nature to improve the quality of life”. With an ever increasing world population the pressure on land-use will increase and the availability of fossil fuels will decrease. As a consequence, there is a growing need for more sustainable food production and alternative sources of energy with emphasis on safe and healthy food and environmental conditions. An adequate and reliable assessment of the potential risks of the substances used in these processes, such as plant protection agents, fertilisers, food additives, industrial chemicals, lubricants in food-processing machines, and contaminants from food packaging materials is of vital importance to ensure and maintain a healthy food chain and living environment.

To assess the human as well as the environmental health risk of substances and to control these risks, knowledge on three aspects is essential: knowledge on i) the intrinsic toxicity (‘hazard identification’) of a substance, ii) the relationship between the exposure to the substance and the adverse effect (‘hazard characterisation’) and iii) the extent of exposure (the concentration to which a group of individuals is exposed) for every relevant route of exposure (via inhalation, the skin, food or drinking water). Only when reliable data on these three aspects are available, a potential health risk can be assessed. The newly proposed special chair will contribute to all three aspects providing unique expertise and databases in the field of biomonitoring and use of these data in exposure assessment and the in the

development and validation of novel non-animal based testing strategies to define and characterise the hazard of combined exposure to complex mixtures.

Specific collaborations within Wageningen UR

Further collaborations are foreseen with RIKILT (amongst others with regard to toxicogenomic technologies), with Biometris (amongst others with regard to the development of quantitative mathematical methods for physiologically-based kinetic models), and the Laboratory of Biochemistry (amongst others with regard to proteomics technologies).

Other collaborations.

Models for exposure to potentially reproductive and developmentally toxic substances in food and the environment are currently primarily developed at RIVM and at Shell. Within the framework of the proposed chair the collaboration with RIVM, in particular with the group of Prof.Dr. Aldert H. Piersma will be strengthened.

3. Importance for education

The contribution of the proposed chair to education comprises:

- New, to be developed, lectures on exposure and human biomonitoring and lectures on occupational toxicology within the context of the course on General Toxicology (TOX 20303) for students Nutrition and Health and Health, Molecular Sciences, Biology and Food technology.
- New, to be developed, lectures 'Human biomonitoring', 'Fate in the environment and toxicokinetics' and 'Exposure to and effects of air pollution' within the context of the course on Environmental Toxicology (TOX 30806).
- Supervision of MSc students (chair Toxicology) in the area of exposure assessment, human biomonitoring and human as well as environmental health risk assessment.
- Providing trainee opportunities[2] and coaching of MSc students at Shell Health in Den Haag, in particular for end-to-end health risk assessments.
- Contributions to the Post-Doctoral Education Toxicology (PET) for the modules: "Occupational Toxicology" and "Risk assessment".
- Contributions to the PATON courses "Toxicology" and "Chemical Mutagenesis and Carcino-genesis".

The special chair is involved in the supervision and execution of three PhD projects:

a. **Exposure to polycyclic aromatic hydrocarbons and prenatal developmental toxicity of petroleum substances (CONCAWE project); PhD-student:** 5.1.2.e [redacted]

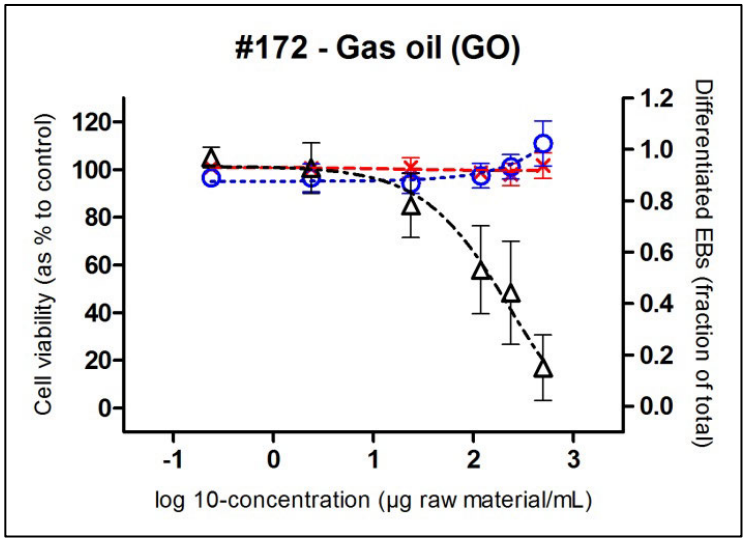
   REACh is the first chemicals legislation in the world to demand as a standard requirement testing for prenatal developmental toxicity. Although other legislations do not require this type of testing yet, it is expected that it is just a matter of time until similar requirements will be included. As a consequence of this legislation, all petroleum substances have to be tested for

[2] A first trainee-ship was effectuated and led to publication in the peer-reviewed literature: Tsitou P, Heneweer M, Boogaard PJ. Toxicogenomics *in vitro* as an alternative tool for safety evaluation of petroleum substances and PAHs with regard to prenatal developmental toxicity. *Toxicol in vitro* 2015;29:299-307

prenatal developmental toxicity which theoretically would require massive numbers of experimental animals (~1500 rats per test). CONCAWE is the European petroleum refining industries' organisation for environmental science. Up till now, CONCAWE's approach has been to group various, similar petroleum substances into categories and to apply read-across with the scarce available data. It is expected that this approach will be questioned and that there will be an increasing demand on actual test data on individual petroleum substances. Since prenatal developmental toxicity studies require not only a large number of animals but also a lot of time, alternative test methods are highly desirable. It is generally accepted that prenatal developmental toxicity as is found with certain petroleum substances is associated with the presence of polycyclic aromatic hydrocarbons (PAH) in these products. *In vitro* model systems for detecting developmental toxicity will be used to characterise the potential developmental toxicity of petroleum substrances and results obtained will be compared to available *in vivo* data to validate the approach and elucidate to what extent the developmental toxicity of the mixtures can actually be ascribed to their PAC constituents.

Recent investigations suggest that, similar to other toxicological endpoints, also the complex ontogeny of prenatal development defects lead to response-specific gene expression patterns. The proposed research aims to determine the response-specific gene expression (toxico-genomics) over time for a series of PACs with and without adverse effects on the prenatal development. Subsequently, these response-specific gene expressions are also determined for a series of petroleum substances with and without adverse effects on the prenatal development to determine the specific perturbation of relevant pathways. The results obtained in this project will elucidate to what extent effects on the prenatal development can be coupled to PCA profiles. Subsequently, these profiles can be used in combination with human biomonitoring and biokinetic models (*vide infra*) in order to assess potential health risks for the unborn child caused by certain products in the food chain and via specific consumer products.

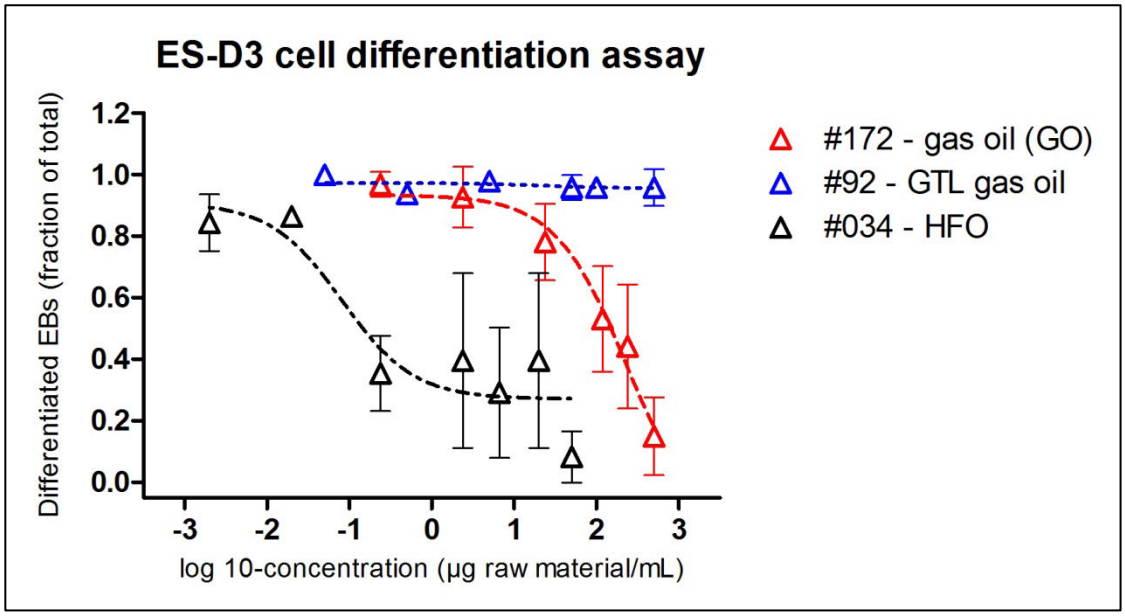
This project already started in October 2015 and the figures below presents some of the initial results obtained.



← *In vitro* developmental toxicity potency of gas oil:
Gas oil induces a reduction in differentiation in the embryonic stem cell test (EST), an *in vitro* assay for developmental toxicity, without causing cytotoxicity

X 1-day exposure ES-D3 cell viability assay
o 5-days exposure ES-D3 cell viability assay
Δ ES-D3 cell differentiation assay

➧ At non-cytotoxic concentrations, petroleum substances are able to inhibit the differentiation of ES-D3 cells in a concentration-dependent manner, related to their PCA content (HFO contains relatively high concentration of PCA whereas gas oil contains low levels of PCA). In contrast, GTL gas oil, which is totally devoid of aromatic constituents, did not decrease viability and also did not inhibit differentiation of the ES-D3 cells



b. <u>Integration of modelling approaches to predict human internal exposure levels of petroleum product constituents and link these to the concentrations of these constituents as they are applied in *in vitro* test systems to assess reproductive hazard and risks</u> (Shell project); PhD student: vacancy; start in 2017)

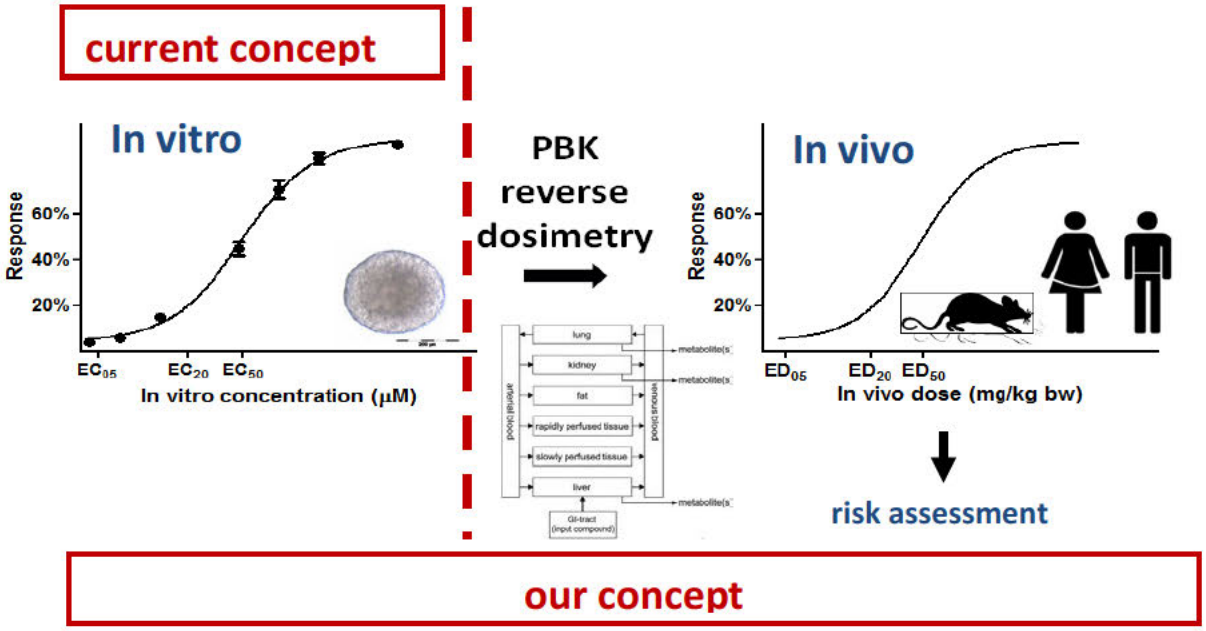
Total human exposure to chemicals is usually estimated by applying a number of assumptions with regard to the uptake from food, drinking water, by inhalation and via the skin. Human biomonitoring allows assessment of internal exposure and it not only integrates all these potential routes of exposure but automatically accounts for bioavailability and metabolism. However, an integrated approach to make reliable estimates of internal exposure and linking these to the *in vitro* concentrations that are being applied in experimental animal-free test systems is still lacking.

This PhD project aims at addressing this problem using petroleum substance constituents as testing material and a variety of *in vitro* reproductive toxicity assays as test system. The project has two stages.
Firstly, it comprises the development of integrated methodology, based on physiologically-based kinetic (PBK) modelling to describe fate, transport, and biokinetics during the life cycle of specific constituents of petroleum products for various populations (old/young, normal/obese). Several projects in the above-mentioned framework of the CEFIC-LRI programme have studied the relation between exposure and internal dose of chemicals in humans to better understand risk assessments for low-level exposures such as occur as a result of the presence of low levels of chemicals in the food-chain and the environment. These projects were undertaken by many different institutes in Europe and the USA and addressed a variety of specific issues related to human biomonitoring (Hansen, Raaschou-Nielsen et al. 2006, Hansen, Mathiesen et al. 2008, Den Hond, Govarts et al. 2009, Govarts and al. 2010, Spaan, Fransman et al. 2010, Bevan, Jones et al. 2013, Aylward, Hays et al. 2014, Koch, Aylward et al. 2014, Smolders, Koch et al. 2014). As a consequence, the results are scattered over the scientific literature and lack integration. This project aims at integration of the various approaches and subsequent application to specific

constituents of petroleum substances. The modelling results can be validated with reliable human biomonitoring studies and thereto data will be used that are available in data bases such as the Shell Health OneHealthIT data-base (de Jong 1991, Boogaard and van Sittert 1994, Boogaard and van Sittert 1995, Tsai, Ahmed et al. 2005, Tsai, Ahmed et al. 2007, van Amelsvoort, Slangen et al. 2009) and the various data-bases which have been developed in the framework of the CEFIC-LRI programme (Hansen, Raaschou-Nielsen et al. 2006, Hansen, Mathiesen et al. 2008, Bevan, Jones et al. 2013).

Secondly, the PhD project aims at further development of the PBK models to link the concentrations that are applied in hazard identification (especially in *in vitro* systems) and hazard characterisation to the internal concentrations as measured in human populations and their corresponding external dose levels. The concentration-response curves for effects on cells in culture defined at the current state-of-the-art can at best be used for identification of possible hazards but are of no use when in risk assessment points of departure to define safe levels of human exposure need to be defined. As a result, these current approaches are unfit for risk assessment unless a method is available to translate the *in vitro* data to *in vivo* dose-response curves that can replace the data from animal bioassays. PBK modeling can translate *in vitro* concentration-response curves to *in vivo* dose-response curves. Figure 1 illustrates how the use of PBK modeling-based reverse dosimetry can modify the current *in vitro* based testing into a novel concept that enables definition of *in vivo* dose-response curves required for risk assessment. The concept can also provide dose-response curves for toxicity in man. This approach leads to more reliable human health risk assessments whilst at the same time the use of experimental animals can be reduced or even made redundant.

The project aims at developing this approach for UVCB substances such as petroleum substances which comprise extremely large numbers of individual constituents. As it is impossible to develop PBK models for the various constituents individually, the project will in the first instance aim at developing generic PBK models that use primarily physico-chemical data as input (Boogaard, Hays et al. 2011, Boogaard, Aylward et al. 2012, Jongeneelen, Ten Berge et al. 2013). These models should allow distinguishing between substances or constituents that are extremely unlikely and those that are likely to pose a human health risk. For the latter category the model can subsequently be refined with newly generated data to assess whether the predicted risk is indeed expected to occur in reality.



c. Reverse-dosimetry based exposure and risk assessment of genotoxic carcinogenic food processing contaminants in the current food chain [redacted] **PhD-student:** [redacted]

The modern food chain contains a number of contaminants that are of concern because they are genotoxic carcinogens. These contaminants may arise from environmental contamination and from food processing and include compounds like acrylamide, acrolein, glycidyl esters, heterocyclic amines (HCAs), polycyclic aromatic compounds (PCAs), and furans. These contaminants are all of public health concern and have undergone or are undergoing safety assessments by risk assessment bodies, such as the European Food Safety Authority (EFSA) or Joint Expert Committee on Food Additives (JECFA). Safety assessments prepared by EFSA and JECFA often indicate the need for more accurate exposure estimates, which is in line with the emerging view that the largest uncertainty in the assessment of human health risk due contaminants resides in the estimation of the actual exposure levels (EC 2013). Exposure science is undergoing a fundamental change with the development of new approaches and tools that go beyond the assessment of exposure based on the mere occurrence of contaminants in food and consumption patterns. An important option consists of monitoring biomarkers of exposure, based on detailed knowledge of the toxicokinetics of the contaminant, to enable use of specific metabolites in body fluids or tissues as quantitative exposure indicators, as opposed to less reliable methods such as food frequency questionnaires. This approach requires translation of the biomarker concentrations to external dose levels needed for risk assessment by physiologically-based kinetic (PBK) modeling-based reverse dosimetry.

This project aims to develop methods to use data on biomarkers of exposure for genotoxic carcinogenic contaminants present in the modern food chain to estimate external dose levels suitable for risk assessment using PBK modeling-based reverse dosimetry. This requires the selection of representative biomarkers for selected contaminants, the availability of representative analytical data on these biomarkers, development of a PBK model for these biomarkers, and a reliable risk assessment methodology.

Mercapturic acids have been shown to be good biomarkers of exposure to electrophilic compounds and compounds with electrophilic metabolites (Boogaard and van Sittert 1996, de Rooij, Boogaard et al. 1997, Brouwer, Verplanke et al. 2000, Boogaard, van Sittert et al. 2001, Boogaard 2009). Since many genotoxic carcinogens are electrophilic in nature, mercapturates will be investigated as potential biomarkers of exposure to genotoxic carcinogenic food process contaminants. Important food processing contaminants are acrolein and acrylamide and both are metabolised to mercapturic acid following glutathione conjugation through normal metabolic pathways and excreted into the urine. Acrolein is metabolized to 3-hydroxy-propylmercapturic acid (3-HPMA, *N*-acetyl-*S*-3-hydroxypropylcysteine) (ATSDR 2007, Stevens and Maier 2008) and, following oxidation to acrylic acid, also to 2-carboxyethylmercapturic acid (CEMA, *N*-acetyl-*S*-2-carboxyethylcysteine) (ATSDR 2007, Stevens and Maier 2008). Acrylamide is metabolized to acrylamide mercapturic acid (AAMA, N-acetyl-S-(2-carbamoylethyl)-L-cysteine) and excreted into the urine (Schettgen, Musiol et al. 2008).
Several of these mercapturates have been applied in biomonitoring studies to assess exposure to acrolein in healthy, non-smoking volunteers (Carmella, Chen et al. 2007, Schettgen, Musiol et al. 2008, Alwis, deCastro et al. 2015, Hecht, Koh et al. 2015, Park, Carmella et al. 2015) (Carmella, Chen et al. 2007, Schettgen, Musiol et al. 2008, Alwis, deCastro et al. 2015, Hecht, Koh et al. 2015, Park, Carmella et al. 2015). When using mercapturates as urinary biomarkers of exposure it is of importance to take potential confounders into account. For instance, 3-HPMA may also be formed from other compounds such as allylamine, allyl halides, and allyl alcohol and ester (ATSDR 2007) and urinary excretion of allyl mercapturic acid, which may serve as biomarker of exposure to allyl halides, may also be formed from the consumption of garlic (de Rooij, Boogaard et al. 1996, de Rooij, Boogaard et al. 1997).

Hydroxylated metabolites PCAs, such as 1-hydroxypyrene, 3-hydroxybenz[a]pyrene, and several hydroxyphenanthrenes, have been shown to be reliable biomarkers to assess occupational and environmental exposure to PCAs and may also be useful to assess exposure to PCAs that are present in as process contaminants in food (Boogaard and van Sittert 1994, Jongeneelen 1994, Jacob and Seidel 2002, Hansen, Mathiesen et al. 2008, Boogaard 2009, Boogaard 2011, Oliveira, Slezakova et al. 2016).

Biomarker data will be collected for the selected model process contaminants data from the literature, from existing databases, such as OneHealthIT, and, where needed, from newly collected samples. In the latter case, analytical methodologies will be developed based on the existing knowledge with regard to the bioanalysis of mercapturates and hydroxylated PCAs within Shell. Where possible, biomarkers will be selected that are not specific for single compounds, but which result from exposure to multiple compounds whilst taking into account potential confounding factors. PBK models for the process contaminants of interest will be developed as far as they are not already available at WU-TOX or from the CEFIC-LRI programme (Bevan, Angerer et al. 2012, Aylward, Kirman et al. 2013, Jongeneelen, Ten Berge et al. 2013). If not available, models can be defined using *in vitro* assays with relevant tissue fractions to derive the required kinetic parameter values, while parameters for physico-chemical and physiological parameters can be obtained from literature and/or by QSAR approaches (Louisse, de Jong et al. 2010, Strikwold, Spenkelink et al. 2013, Louisse, Bosgra et al. 2015, Punt, Paini et al. 2016). The PBK Models will be validated against the available *in vivo* data and, once validated, will be used to convert available data on biomarkers for the different process related contaminants to *in vivo* exposure levels of the human population. Monte Carlo models will be used to extend the data available to a larger population. The exposure assessments thus obtained will be compared to exposure scenarios available from current risk assessment performed by authoritative bodies such as EFSA and JECFA. In addition the results obtained will be used to update the current risk assessment for the compounds. Given that the selected process contaminants are genotoxic carcinogens, risk assessment will be done using the MOE approach (Hays, Aylward et al. 2008, Aylward, Becker et al. 2011, Hays and Aylward 2012). This will provide novel insight in the state-of-the-art of human health risks associated with exposure to these food processing derived contaminants.

4. Research interest

The field of the proposed chair contributes to fulfillment of the need to come to more reliable and more efficient human and environmental health risk assessments for complex substances (UVCBs) without the use of animal bioassays. An important aim of the proposed chair is the integration of available data and models, in particular regarding exposure, and the selective generation of new, additional, data in experimental animal-free test systems to come to a rapid and reliable health risk assessment.
To achieve this, test systems will be set-up and validated to test complex substances (UVCBs), including highly lipophilic petroleum substances, without using experimental animals. Furthermore the internal Shell database (OneHealthIT) will be used to obtain exposure data (air measurements and human biomonitoring data) of substances such as occur in petrochemical industries.
The proposed chair envisions to contribute to a further integration between environmental, and food toxicology and between experimental and fundamental toxicology. In addition, the chair aims to integrate various aspects of human biomonitoring and to develop new methods that allow a more reliable and efficient application of human biomonitoring data in human health risk assessment, especially by developing PBK models that allow translation of biomonitoring data to corresponding external dose levels. An important starting point will be the integration of concepts, methods and (biokinetic) models, that have recently been developed by a large variety of institutes, amongst others in the framework of the CEFIC-LRI programme, to get a better and more efficient evaluation of the health risks associated with the exposure to man-made chemicals via the food-chain, the environment and the occupational situation (Smolders, Bartonova et al. 2010, Blaauboer, Boekelheide et al. 2012, Yoon,

Efremenko et al. 2014). Furthermore, using data from the sources mentioned above, hypotheses on low-dose extrapolation for certain chemicals may be verified or falsified and models for risk assessment constructed and validated.

Acquisition of external funding for research

External funding will be sought through the EU Horizon 2020 (H2020) programme and its spin-offs, especially in the framework of the HBM4EU programme that is currently under development (http://www.eea.europa.eu/themes/human/human-biomonitoring). The Dutch partner is RIVM and contacts on human biomonitoring and PBK modeling have already been established with Dr. Mirjam Luijten. In addition, external funding may be obtained through NWO-STW, especially in the area of alternatives to animal testing and the methodologies to explain and integrate results of alternative testing into the health risk assessment paradigm.
For transnational research collaboration with China funding can be obtained through the Cooperation China (NSFC). Costs of travel, subsistence and seminars are funded to cover either a short stay in China of a Dutch scientist or for a Chinese in the Netherlands. Joint Chinese-Dutch seminars can be funded as well. The funding is based on a joint agreement between NWO and the National Natural Science Foundation of China (NSFC) in Beijing.
External funding for the described research may also be obtained from the various branch organisations within the (petro)chemical industry with whom already tight links exist in this research area. In the chemical industry, especially in the framework of the Long-range Research Initiative, research to improve exposure assessments and in particular human biomonitoring, is an important theme. In the oil industry refinement of health risk assessment methodologies by improved exposure assessment is an important topic. In particular via the Health Management Group of CONCAWE (CONservation of Clean Air and Water in Europe, the oil companies' European organisation for environment, health and safety)[3] additional opportunities for funding of the research can be realised. In addition, there are good links to COPHES (Consortium to Perform Human Biomonitoring on a European Scale), a programme under the 7th FP of the EU in which a variety of programmes are being planned in the same field ("supporting 'applied & collaborative research by higher education institutions, research centres and enterprises', in the fields of 'health, food, agriculture and biotechnology' and 'environment'").

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[3] The first project for CONCAWE has already been obtained and has started late 2015 (see above)

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Appendix 1

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Appendix 2

Publication on the basis of CEFIC-LRI sponsored research in the Human Biomonitoring programme, which was initiated (RfP) and monitored by candidate

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Nevenwerkzaamheden

Opdrachtgever / client	Duur van	Duur tot	Nevenwerkzaamheid	Beschrijving	Betaalde werkzaamheden	Inkomsten voor
Shell International bv	01-07-1990	30-07-2021	Global Discipline Lead & Manager Toxicology	The functional lead for all toxicology activities for the Shell Group, part of the Risk Sciences Team of Shell Health	J	Betrokkene zelf
Toxikonsult	01-03-2000	Geen einddatum	Eigenaar	Organisatie voor toxicologisch advies	J	Betrokkene zelf
Toxys	01-09-2021	Geen einddatum	Advies	Lid Scientific Advisory Board	J	Betrokkene zelf
TaTa Steel	26-08-2022	Geen einddatum	HSE Expert committee	Expert committee advises TaTa Steel on environmental health issues	J	Betrokkene zelf
ChlorSolv	18-08-2023	Geen einddatum		Toxicologische advisering inzake REACH en klassificatie & labelling van gechloreerde koolwaterstof oplosmiddelen	J	Betrokkene zelf
Ministerie VWS	01-03-2023	Geen einddatum	Gezondheidsraad	Commissie Biologische Grenswaarden	J	Betrokkene zelf