miljø og sundhed

Sundhedsstyrelsens Rådgivende Videnskabelige Udvalg for Miljø og Sundhed Formidlingsblad 17. årgang, nr. 3, december 2011

Læs om

moderne indeklimaforskning

hormonforstyrrende stoffer

PFOA & PFOS

dioxin-like potential of environmental compounds

Se også

kalender 2012

Indhold

Miljø og sundhed

Bladet henvender sig primært til forskere, beslutningstagere og administratorer, der beskæftiger sig med miljø og sundhed.

Udgives af:

Sundhedsstyrelsens Rådgivende Videnskabelige Udvalg for Miljø og Sundhed

Redaktion:

Jens Peter Bonde (ansv)
Steffen Loft
Tina Kold Jensen
Hilde Balling

17. årgang, nr.3, december 2011.

Oplag 1.200, tilsendes gratis ved henvendelse til:

Hilde Balling, Sundhedsstyrelsen
hib@sst.dk

Tryk: Rosendahls Schultz Grafisk
ISSN 1395-5241
ISSN elektronisk 1601-4146
http://miljoogsundhed.sst.dk/blad/ms1103.pdf

Miljø og Sundhed

En læser har skrevet til undertegnede og efterlyst bladets definition på miljø, idet en del mennesker efter spørgerens mening vil opfatte miljø som synonymt med det ydre miljø.

Det tilstræbes fra redaktionens side, at indholdet i nærværende blad holdes inden for rammerne af nedenstående afgræsning af området "miljø og sundhed".

"De miljøfaktorer, som kan påvirke menneskers helbred, omfatter fysiske, kemiske, biologiske og psykosociale faktorer. Påvirkningerne fra disse miljøfaktorer sker hovedsageligt gennem vand, luft, jord og levnedsmidler, på arbejdspladser og i boliger og institutioner - påvirkninger, som i et samspil med arveanlæg, levekår og livsstil har betydning for risikoen for at udvikle sygdom".

Skjoldbruskkirtlen kan påvirkes af kemiske stoffer medførende ændringer i blodet af skjoldbruskkirtelhormonerne. M. Petersen har undersøgt nogle af disse stoffer i rotteforsøg.

Fluorstofferne PFOS og PFOA er påvist i vand, luft, slam, jord og sedimenter samt i blodet hos dyr og mennesker overalt i verden. K. Eriksen har undersøgt disse stoffer i relation til visse kræftformer samt mulige eksponeringskilder.

M. Long og E. Bonefeld-Jørgensen har skrevet et omfattende review om miljøkemikaliers dioxinlignende potentiale og belyser emnet gennem beskrivelser af egne undersøgelser af pesticider, phthalater og phytoøstrogener, dels som enkeltstoffer, dels som blandinger af flere stoffer.

F. Gyntelbergs og I. Andersens artikel nr. 2 om dansk indeklimaforskning beskriver undersøgelser af effekter af udsættelse for VOCs, støv og skimmelsvampe i indemiljøet.

Indholdet i alle fire artikler falder klart inden for ovenstående afgrænsning af "miljø og sundhed", og redaktionen kan roligt love, at det også vil være trenden fremover.

Rigtig god jul!

Hilde Balling

Moderne indeklimaforskning i Danmark fra begyndelsen af 1990erne til dato: En øjenvidnerapport.

Af Finn Gyntelberg og Ib Andersen

I forrige nr. af dette tidsskrift beskrev vi den moderne danske indeklimaforskning fra dens start i 1962 til begyndelsen af 1990erne. Det var en periode, hvor den danske forskning var banebrydende og førende på dette nye område, og hvor antallet af forskere i andre lande stadig var begrænset. Siden er antallet af internationale forskningsaktører på området vokset betydeligt. Det skyldes især behovet i alle lande for stadig større besparelser i bygningsmassens energiforbrug og ønsket om reduktion af de sundheds- og komfortmæssige ulemper, der er affødt af denne udvikling. Dansk indeklimaforskning har derfor ikke i samme grad som tidligere været dominerende i denne periode, men den har stadig leveret meget væsentlige bidrag af ny viden.

Det historiske perspektiv i denne artikel er knap en snes år, hvilket givetvis er for kort til sikkert at vurdere den langsigtede holdbarhed og effekt af denne forskning. Alligevel vil vi prøve herpå med en indgangsvinkel, der primært er medicinsk-fysiologisk og sundhedsmæssig.

Indsatsområder for den danske forskning

I begyndelsen af 1990erne var den danske indeklimaforskning blevet veletableret. Faktisk så veletableret, at vi var det land i verden, der da havde flest aktive klimakamre i forhold til befolkningens størrelse. Der var mere end ét klimakammer pr. million indbyggere. Desuden var der dannet en række erfarne forskningsgrupper inden for både det medicinsk-fysiologiske og det tekniske område.

Vi anser de vigtigste udviklinger inden for området i denne periode at være:

- paradigmeskiftet fra T-VOC (total volatile organic compounds) som relevant målemetode for irritanter i indeluften til en toksikologisk baseret vurdering af reaktive VOCs og disses nedbrydningsprodukter
- etablering af guidelines for indeluftkvalitet
- undersøgelser af effekter af støv i indeluft
- undersøgelser af effekter af skimmelsvampe i bygningsmassen

Paradigmeskift

I begyndelsen af perioden var interessen som de foregående år koncentreret om effekten af kemiske påvirkninger. Men medens tidligere formaldehyd og dettes effekter var i fokus, var det nu primært VOCs dvs. volatile organic compounds (eller på dansk organiske opløsningsmidler) og disses effekter. Indeklimagruppen ved Hygiejnisk Institut, Århus Universitet - det nuværende IMA - Institut for Miljø- og Arbejdsmedicin havde i 1980erne, i erkendelse af vanskelighederne ved at analysere alle de mange forskellige organiske opløsningsmidler i nybyggede og nyrenoverede bygninger, foreslået T-VOC konceptet, dvs. at se på effekten af totalmængden af alle VOCs. I forbindelse hermed blev der indført en standardblanding af de 22 VOCs, der hyppigst var blevet påvist i feltstudier. I en række klimakammerstudier med denne T-VOC blanding påviste Mølhave og medarbejdere, at blandingen gav forringet luftkvalitet og at tærsklen for irritation lå på 2–5 mg/m^3. Blandingen udløste irritation i både øjne og øvre luftveje (Mølhave 2001).

På AMI - Arbejdsmiljøinstituttet - det nuværende Nationale Forskningscenter for Arbejdsmiljø - NFA - førte et snævert samarbejde mellem indeklimakemikeren P. Wolkoff og toksikologen G. D. Nielsen til en mere individuel vurdering af de enkelte VOCs.

Deres synspunkt var, at sundhedseffekterne af VOCs ikke skulle relateres til WHO klassifikationen af de enkelte stoffer efter kogepunkt, men mere til en toksikologisk vurdering af sundhedseffekter af den enkelte VOC og af nedbrydningsprodukter heraf. De fandt, at de normalt forekommende indeluftkoncentrationer af kemisk non - reaktive VOCs ikke ville kunne forklare de irritative indeklimaklager i de undersøgte indemiljøer. I modsætning hertil kan reaktive VOCs være f.eks. 1000 gange mere irriterende end et lignende, men ikke - reaktivt kemisk stof. De to forskere begyndte derfor at skelne imellem *non - reaktive* VOCs med høj irritationstærskel og *reaktive* VOCs, som oxideres af ozon og derved producerer en cocktail af multifunktionelle stoffer, herunder bl.a. formaldehyd. Rigtigheden heraf blev påvist både i forsøg med mus og i humane øjenstudier.

Denne udvikling illustrerer et klassisk videnskabeligt dilemma: Måler vi de rigtige komponenter eller måler vi fortrinsvis de komponenter, der er rimelig lette at måle - i dette tilfælde T-VOCs?

Etablering af guidelines for indeluftkvalitet

En meget relevant videreudvikling i perioden var arbejdet hen imod en etablering af grænseværdier for indeluft i ikke – industrielle bygninger. På engelsk: ”Indoor Air Guidelines” eller IAGs. Disse grænseværdier måtte være anderledes – og lavere – end de gennem mange år etablerede arbejdshygiejniske grænseværdier for industrielle arbejdspladser. Sidstnævnte forudsætter sunde arbejdstagere og en påvirkningsstid på otte timer om dagen igennem 40 år. Indeluftgrænseværdier for boliger må inkludere hensynet til særligt følsomme som børn, gamle og syge personer og må forudsætte ophold indendørs 24 timer i døgnet gennem et helt liv. De allerede etablerede grænseværdier for forureningskomponenter udendørs var ikke omfattende nok i betragtning af de mange forskellige komponenter, der afgives til indeluften fra byggematerialer, personer og aktiviteter.

AMIs første forslag til særlige indeklimagrænseværdier blev fremsat i et særligt nr. af Indoor Air (Levin 1998). I 2010 blev dette arbejde suppleret med et forslag til en grænseværdi for luften indendørs, som ville sikre mod formaldehyds kræftfremkaldende effekt (Nielsen og Wolkoff 2010).

Det er særdeles tilfredsstillende, at Verdensundhedsorganisationen WHO i perioden har været og stadig er en drivende kraft bag etableringen og publiceringen af ”Guidelines for Indoor Air Quality”.

Et vigtigt instrument for saneringen af sundhedsskadelige, funktions– og komfortnedsættende stoffer i byggematerialer er den i perioden gennemførte EU kemikalielovgivning REACH. Dennes indførelse blev i mange år forsinket ikke, bare af industriens lobbyvirksomhed, men også af toksikologer, der ønskede alle klassiske undersøgelsesmetoder bragt i anvendelse for hvert kemisk stof. Igen et klassisk videnskabeligt/regulativt dilemma: ”Det bedste er ofte det godes værste fjende”. På AMI var man i 1992 af den opfattelse, at da man i EU anvendte ca. 100.000 kemiske stoffer, hvoraf 1.700 i meget store mængder, ville det af hensyn til befolkningernes sundhed være hensigtsmæssigt hurtigt at få etableret sundhedsmæssige guidelines for et betydeligt antal af disse. Da mange af sådanne guidelines måtte fastsættes ud fra mere begrænsede toksikologiske data end klassisk uddannede toksikologer normalt anvendte, måtte disse guidelines derfor betragtes som tentative og anvendes med forsigtighed, ligesom der samtidig måtte etableres en praksis med hyppige revisioner. Herved kunne det sikres, at disse værdier altid var baseret på den nyeste toksikologiske viden. Synspunktet vandt ikke tilslutning blandt klassiske toksikologer, der for hvert kemisk stof ønskede fuldstændige datasæt. Et resultat heraf er, at det i dag stadig kun er muligt at etablere guidelines for ret få stoffer.

Undersøgelse af effekter af støv i indeluft

I 2008 publicerede Mølhave og medarbejdere resultaterne af fem provokationsstudier, hvor

de inflammatoriske og allergiske effekter af luftbåret kontorstøv blev undersøgt i klimakammerstudier på mennesker. Det laveste niveau for effekt var ca. 75 µg svævestøv/m^3 luft. Støv fra forskellige bygninger havde forskellig effekt, men det generelle billede var, at støvet nedsatte øjets tårefilmsstabilitet og øgede antallet af eosinofile celler i næseskyllevand (nasal lavage). Deltagernes komfort blev reduceret ved disse støvudsættelser, og der var øget irritation i øjne, næse og svælg.

I 2005 publicerede Mølhave og medarbejdere resultaterne af et klimakammerstudie af samspillet mellem ozon (0,3 ppm) og luftbåret støv (75 µg/m^3) fra kontorlokaler.

Studiet omfattede en mindre gruppe atopiske, men ellers raske personer og viste en signifikant potentiering, når de to påvirkninger optrådte samtidig frem for hver for sig. Forskerne fandt signifikant nedsættelse af lungefunktionen (peak expiratory flow) og øget ubehag.

For at opnå en enkel og billig metode til at vurdere det inflammatoriske potentiale i indeluftstøv udviklede Allermann (2001) på AMI en metode, hvor lungeepitel i en *in vitro* model blev udsat for støv. Effekten af denne samlede påvirkning af kemiske og biologiske forureninger blev vurderet ved at måle frisætning af cytokinen Interleukin 8. I et større samarbejdsprojekt med bl.a. Arbejds- og Miljømedicinsk Klinik, Bispebjerg Hospital, blev der undersøgt støv fra 10 skoler med få og 10 skoler med mange indeklimasymptomer. Det viste sig (Allerman et al 2003), at støvets inflammatoriske potentiale gjorde det muligt at skelne mellem skoler med få og med mange gener. Et tilsvarende studie af kontorer (Pejtersen et al. 2006) viste, at den samme korrelation eksisterede for kontorstøv i enkelt- og fåmandskontorer, medens indeklimagener i storrumskontorer måtte have andre årsager.

Spørgsmålet om indeluftens forurening med kemiske stoffer kan være af betydning for de stadigt hyppigere forekommende luftvejsallergier blev behandlet af Nielsen og medarbejdere i 2007. De undersøgte, om flere kemiske stofgrupper, bl.a. ftalater og kvarternære ammoniumforbindelser, kunne have en adjuvanseffekt, dvs. om stofferne var i stand til at forstærke effekten af kendte allergener - f.eks. husstøvmideafføring. De fandt adskillige højpotente adjuvanter, men i betragtning af de lave koncentrationer i indeluften syntes disse fund kun at være af praktisk betydning for industrielle arbejdspladser (Nielsen et al. 2007).

Disse studier indikerer, at støvudsættelse kan forklare mange gener i form af øjen- og luftvejsirritation. Reduktion af støvgenerering er derfor vigtig, men kan ikke fuldt ud opnås med ventilation. Gedigen rengøring er stadig af afgørende betydning. I 1994 publicerede Schneider et al. guidelines for rengøringskvalitet.

Skimmelsvampe i bygninger

I slutningen af 1990erne og begyndelsen af dette århundrede var der en ret betydelig interesse for, hvad skimmelsvampeforurening i indemiljøet betød for menneskers komfort og helbred. Private og offentlige sponsorer gjorde det muligt at gennemføre et stort forskningsprogram til videre afklaring af spørgsmålet. Programmet blev ledet af en gruppe tilknyttet Statens Byggeforskningsinstitut (SBI) i samarbejde med flere forskningsinstitutter og formand for ledergruppen blev F. Gyntelberg fra Arbejds- og Miljømedicinsk Klinik, Bispebjerg Hospital. Programmet fik det internationale navn "The Danish Moulds in Building Program". Resultaterne af dette program er publiceret i mere end 50 videnskabelige artikler og i en omfattende rapport, som blev udgivet af Forskningsministeriet (2001). De helbredsmæssige effekter blev undersøgt dels ved en omfattende epidemiologisk undersøgelse på fugtskadede skoler med tørre skoler som kontrol og i et dobbeltblindt eksponeringsstudie med placebokontrol. Det eksperimentelle studie afslørede ikke markante effekter af skimmelsvampeeksponering sammenlignet med kontrolforsøg, men studiet blev kun gennemført på få personer, hvorfor det ikke er helt konklusivt. Det store epidemiologiske studie

viste, at udsættelse for skimmelsvampe havde sammenhæng med almen- og slimhindesymptomer hos først og fremmest personer, der ikke producerede kønshormoner, dvs. børn før pubertet og postmenopausale kvinder. Fundet vedr. de ældre kvinder var dog lidt usikkert. Et interessant observationsstudie af Ebbehøj på en svømmehals medarbejdere før og efter renovering af fugtskader fandt en reduktion i indeklimaklageforekomsten fra 66 % til 4 %, hvor der inden renoveringen blev målt en høj forekomst af skimmelsvamp i hallen.

Brauer og Mikkelsen har gennemført nogle elegante metodologiske indeklimastudier med særlig fokus på bias ved spørgeskemaundersøgelser. De observerede, at personers svar på spørgeskemaer var afhængigt af i hvilken sammenhæng de bliver spurgt. Hvis de fik at vide, at undersøgelsen handlede om indeklimagener i hjemmet blev der registreret flere klager vedrørende hjemmets indeklima og omvendt, hvis fokus var på arbejdspladsens indeklima.

Den teknisk-videnskabelige indeklimaforskning

De to væsentligste aktører på dette område i perioden var Danmarks Tekniske Universitet (DTU) og Ålborg Universitet med Arkitekt-/ingeniørgruppen og Statens Byggeforskningsinstitut.

O. Fanger havde på DTU etableret en stærk forskergruppe af både danske og udenlandske forskere med meget brede relationer til indeklimaforskere over hele kloden. Hovedområdet for forskningen var menneskers opfattelse af indeluftkvalitet og komfort. Det blev vist, at forsøgspersoner under kontrollerede forhold arbejdede langsommere i let forurenet luft end i ren luft og at de havde mere hovedpine i den forurenede luft. I skoler fandtes, at en øget ventilation og lavere temperatur øgede elevernes præstationer ved regning og stavning. Fangers gruppe indgik også i adskillige danske multicenterstudier.

I gruppen arbejdede også J. Sundell og C. G. Bornehag i en årrække. De tog initiativet til at samle en række forskere fra adskillige lande med henblik på at gennemgå litteraturen og fremlægge den viden, der her var samlet om luftfugtighed, ventilation, kæledyr mv. og om de sundhedsmæssige effekter af disse påvirkninger.

Ved Ålborg Universitet har P. V. Nielsen og hans gruppe udviklet meget brugbare modeller til vurdering af ventilationsforhold.

På SBI blev der i perioden konstrueret en række klimakamre til studie af sundheds- og komforteffekter af byggematerialers afgivelse af indeluftforureninger. Instituttet deltog også i opbygning af mærkningsordningen for byggematerialers afgivelse af forureningskomponenter.

Pga. sin store viden om skimmelsvampe var instituttet en vigtig partner i det store danske multicenterprojekt om skimmelsvampe i bygninger, hvor især Gravesens betydelige erfaring på forskningsområdet var uundværlig. Senere fulgte instituttet op på denne problemstilling med renoveringsprojekter af skimmelsvampehærgede bygninger.

Bygningers energiforbrug har også været i centrum i en række studier, hvor der både blev leveret forskningsresultater og en målbevidst omsættelse af disse til praktiske anvisninger for byggebranchen.

Afsluttende bemærkninger

Dansk indeklimaforskning har stadig et højt aktivitetsniveau. Ved det sidste Indoor Air møde i Austin Texas juni 2011, med deltagelse af forskere fra store dele af det globale samfund, fremlagde danske forskere fra især DTU, SBI og NFA (det tidligere AMI) adskillige interessante og relevante forskningsresultater. Det var resultater, der vidner om, at dansk indeklimaforskning også i de næste ti til tyve år har gode muligheder for at være med i den internationale frontforskning om indeklima.

Hormonforstyrrende stoffers indflydelse på skjoldbruskkirtelhormonerne, samt på hjernens udvikling hos rotter - et ph.d. projekt.

Af Marta Axelstad Petersen, DTU Fødevareinstituttet

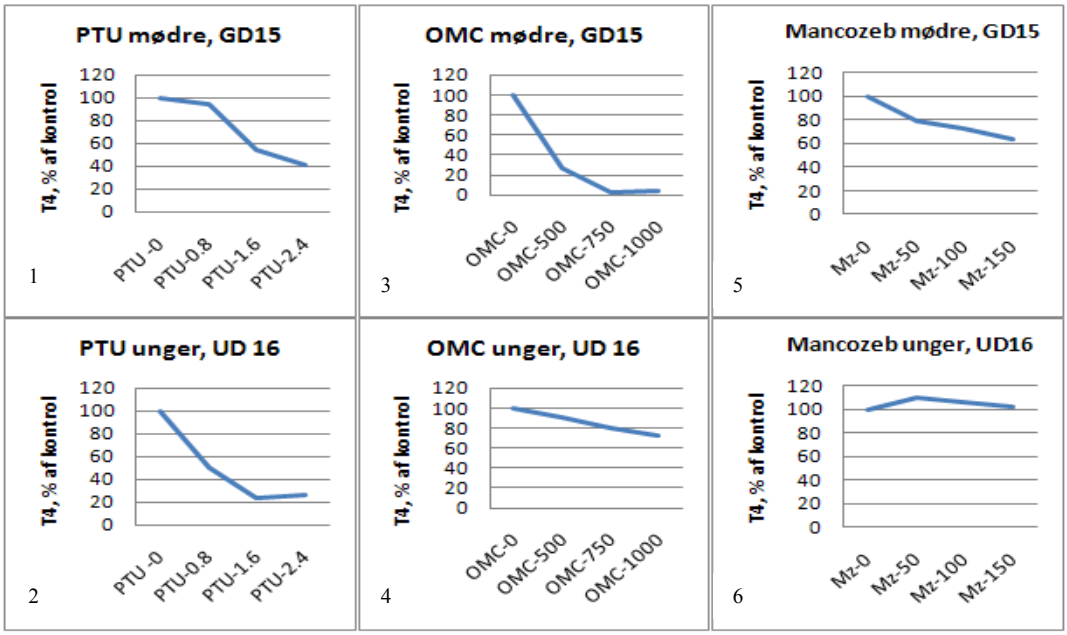
Baggrund og formål

Skjoldbruskkirtelen, også kaldet glandula thyreoidea, producerer skjoldbruskkirtelhormonerne triiodothyronin (T_3) og thyroxin (T_4). Udover deres rolle i kroppens stofskifteprocesser spiller disse hormoner en afgørende rolle for nervecelledifferentieringen under hjernens udvikling. Hos mennesker kan selv moderate og forbigående fald i moderens T_4-niveauer under graviditeten have negativ indflydelse på barnets neurologiske udvikling og føre til forsinket mental og motorisk udvikling (1-5). For at opretholde korrekte hormonniveauer er skjoldbruskkirtelen afhængig af et tilstrækkeligt jodindtag, men den kan også påvirkes af en række stoffer i vores miljø. Disse kaldes skjoldbruskkirtelforstyrrende stoffer og er kemikalier, som via forskellige mekanismer kan ændre indholdet af T_3 og T_4 i blodet. De omfatter bl.a. en lang række industrikemikalier og pesticider, samt stoffer der anvendes i produkter til personlig pleje (6-8).

En måde at belyse årsagssammenhængen mellem udsættelse for hormonforstyrrende stoffer, effekten på skjoldbruskkirtelhormonerne samt negative påvirkninger af hjernens udvikling kan være at undersøge det i en dyremodel. Det overordnede formål med ph.d.-projektet var derfor at undersøge, hvordan den neurologiske udvikling hos rotter ville blive påvirket af skjoldbruskkirtelforstyrrelser i fostertilværelsen samt at finde ud af, om det er muligt at forudsige adfærdsændringer hos afkommet ved hjælp af T_4-målinger i de eksponerede rottemødres blod. Denne viden ville kunne bruges af de regulerende myndigheder til at identificere risikoen for skadelige virkninger på hjernens udvikling efter udsættelse for skjoldbruskkirtelforstyrrende stoffer ved blot at måle T_4 niveauer i en blodprøve fra de eksponerede rottemødre.

Metode

Projektet omfattede tre store dyreforsøg i hvilke effekterne på rotters hjerneudvikling blev undersøgt efter eksponering for stoffer, som påvirker skjoldbruskkirtlen. I det første forsøg blev det kendte skjoldbruskkirteltoksiske stof propylthiouracil (PTU) undersøgt. Denne undersøgelse af et modelstof blev udført for at lære mere om forholdet mellem T_4-nedsættelser i fostertilstanden og efterfølgende adfærdsændringer hos det voksne rotteafkom. Herefter fulgte undersøgelser af to miljømæssigt relevante kemikalier. Det første stof var UV-filteret octyl methoxycinnamat (OMC), mens det andet undersøgte stof var svampemidlet mancozeb. Begge stoffer er meget udbredte, og begge giver skjoldbruskkirtelforstyrrelser, men der er ikke tidligere publiceret nogen adfærdsundersøgelser med stofferne. Det eksperimentelle design for de tre forsøg var som følger: drægtige rotter blev doseret med teststoffet fra dag 7 i drægtigheden, indtil slutningen af laktationsperioden, dvs. indtil ungerne var 16 dage gamle. Hvert stof blev undersøgt i tre doser, med en gruppestørrelse på ca. 18 drægtige hunrotter per hold. En uge efter dosering var påbegyndt blev blodprøver fra mødrene analyseret for T_4-niveauer. På ungedag (UD) 16 blev noget af afkommet aflivet, der blev taget blodprøver, og flere organer blev udtaget. Fra hvert kuld blev et par af ungerne også fravænnet til senere adfærdsundersøgelser. Disse undersøgelser inkluderede bl.a. vurdering af afkommets indlæringsevne og motoriske aktivitet. Dyrenes



Figur 1-6. T_4 nedsættelser, vist som % af kontrol i de tre forsøg. T_4 er målt hos mødre doseret med hhv. PTU, OMC og Mancozeb på dag 15 i drægtighedsperioden (GD15) (figur 1, 3,5), og hos 16 dage gamle unger (UD 16) (figur 2, 4, 6).

hørelse blev også vurderet, og det samme gjorde en række effektmål omkring dyrenes reproduktionssystem.

Resultater og diskussion

Resultaterne fra den første undersøgelse viste, at eksponeringen for PTU gav de forventede effekter på skjoldbruskkirtelsystemet hos både mødre og afkom, idet både mødrenes og afkommets T_4-niveauer faldt betydeligt som resultat af doseringen (figur 1 og 2). Skjoldbruskkirtlernes vægt og histologi var også kraftigt påvirket. Som forventet, på baggrund af en lang række tidligere adfærdsstudier af PTU (9-10), sås også effekter på afkommets hjerneudvikling. Både indlæringsevne og hørelse var nedsat, og aktivitetsniveauet var forøget hos afkommet i den gruppe, der havde fået højest dosis PTU (tabel 1). Alle disse ændringer var forventede, og de var ydermere signifikant korreleret med nedsatte T_4-niveauer hos mødrene. Dette tydede på, at graden af T_4-nedsættelse under udviklingen kunne være en indikator for graden af adfærdsmæssige forstyrrelser og høreskader hos rotter.

I OMC studiet medførte alle de undersøgte doser massive T_4-nedsættelser hos mødrene (figur 3), mens effekterne på ungernes skjoldbruskkirtelsystem var forholdsvis begrænsede (figur 4). Der sås derimod en del andre effekter i OMC afkommet, idet hannerne viste reducerede organvægte af reproduktionsorganerne og et reduceret sædcelleantal. Disse effekter var muligvis forårsaget af OMCs østrogene egenskaber. Afkommets adfærd var også ændret, dog anderledes end forventet.

I hunafkommet var den motoriske aktivitet nedsat i den højeste dosisgruppe, mens OMC doserede hanner udviste forbedret rumlig indlæringsevne (tabel 1) i forhold til kontrolrotterne. Disse adfærdsændringer var ikke korreleret til mødrenes T_4-niveauer i graviditeten, og var sandsynligvis ikke forårsaget af tidlig T_4-mangel, da de adskilte sig væsentligt fra de effekter, som blev set i PTU undersøgelsen, samt fra effekter set i andre af den type undersøgelser.

Tabel 1. Oversigt over resultaterne fra adfærds- og høretest udført i de tre forsøg. ↑ betyder forbedret, ↓ betyder nedsat, - betyder upåvirket og tomt felt betyder ikke målt.

	aktivitet		**indlæring**		**hørelse**
	♀	♂	♀	♂	♀ & ♂
PTU	↑	↑		↓	↓
OMC	↓	-	-	↑	-
Mnz	-	-	-	-	-

I det sidste studie førte dosering af drægtige rotter med svampemidlet Mancozeb til et moderat, men dog signifikant fald i mødrenes T_4-niveauer under drægtigheden (figur 5), mens ungernes skjoldbruskkirtelsystem på dag 16 var helt upåvirket (figur 6). I denne undersøgelse blev der på trods af de nedsatte T_4 niveauer i drægtigheden ikke set nogen adfærdseffekter (tabel 1).

Konklusion og perspektiver

Resultaterne fra de tre undersøgelser viste, at PTU med ret stor sandsynlighed blev overført fra mødrene til afkommet via moderkagen og modermælken, idet stoffet påvirkede ungernes skjoldbruskkirtelsystem og hjerneudvikling i forventet retning. Derimod kan både toksikokinetiske og toksikodynamiske faktorer muligvis forklare de overraskende fund i de to andre forsøg. Det er sandsynligt, at overførslen af OMC og mancozeb over moderkagen og mælken ikke var tilstrækkelig stor til at påvirke ungernes skjoldbruskkirtelsystem og dermed deres hjerneudvikling. Ydermere kan forskelle i stoffernes virkningsmekanisme og kinetik have gjort, at en given eksponering af ungerne ikke medførte lige så store T_4 sænkninger, som det var tilfældet hos mødrene.

I de to undersøgelser med hhv. OMC og mancozeb blev det ydermere vist, at i modsætning til hvordan det forholder sig hos mennesker, så er det hos rotter ikke muligt at korrelere mødrenes T_4-nedsættelser i drægtighedsperioden med negative effekter på hjerneudviklingen hos afkommet. Det blev derfor konkluderet, at målinger af T_4-værdier hos drægtige rottemødre efter udsættelse for skjoldbruskkirtelforstyrrende stoffer ikke kan anvendes til at forudsige effekter på hjernens udvikling hos rotteungerne. En mulig forklaring på de observerede forskelle mellem rotter og mennesker kan være, at mens mange af hjernens modningsprocesser sker før fødslen hos mennesker, så foregår en del af disse efter fødslen hos rotter (11). T_4-nedsættelser i fostertilstanden kan derfor være mere kritiske for hjerneudviklingen hos mennesker end hos rotter. Da vi i øjeblikket stadig ved meget lidt om, hvilke tidspunkter der hos rotter er mest afgørende for hjernens udvikling i forhold til hormonforstyrrelser, samt om de komplekse feedback-mekanismer og kompenserende processer i skjoldbruskkirtelhormonsystemet, kan vi ikke p.t. bruge mødrenes T_4-målinger som parameter til at forudsige adfærdsforandringer hos rotteafkommet. Det er dog stadig meget vigtigt, at menneskers eksponering for stoffer, som i dyreforsøg viser sig at give skjoldbruskkirtelforstyrrelser og nedsatte T_4-niveauer, reguleres nøje, da T_4 nedsættelser i graviditeten hos mennesker kan have alvorlige følger for børnenes hjerneudvikling.

Ph.d. forsvaret blev afholdt den 12. maj 2011 på DTU Fødevareinstituttet. Bedømmelsesudvalget bestod af: John Christian Larsen (DTU Fødevareinstituttet Formand), Grete Østergaard (KU, Panum) og Helmuth Lillienthal (Ruhr University of Bochum). Projektets vejleder var: Ulla Hass (DTU Fødevareinstituttet). Studierne, som ligger til grund for afhandlingen, blev støttet af Miljøstyrelsen. Afhandlingen bygger på disse tre artikler og kan fås i PDF format ved at kontakte forfatteren: maap@food.dtu.dk

I) Axelstad M, Hansen, PR, Boberg J, Bonnichsen M, Nellemann C, Lund SP, Hougaard KS, Hass U. *Developmental neurotoxicity of Propylthiouracil (PTU) in rats: relationship between transient hypothyroxinemia during development and long-lasting behavioural and functional changes.* Toxicol Appl Pharmacol 2008;232:1-13.

II) Axelstad M, Boberg J, Hougaard KS, Christiansen S, Jacobsen PR, Mandrup KR, Nellemann C, Lund SP, Hass U. *Effects of pre- and postnatal exposure to the UV-filter Octyl Methoxycinnamate (OMC) on the reproductive, auditory and neurological development of rat offspring.* Toxicol Appl Pharmacol 2011;250:278-90.

III) Axelstad M, Boberg J, Nellemann C, Kiersgaard M, Jacobsen PR, Christiansen S, Hougaard KS, Hass U. *Exposure to the widely used fungicide Mancozeb causes thyroid hormone disruption in rat dams but no developmental neurotoxicity in the offspring.* Toxicol Sci 2011;120:439-46.

Referencer

1. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. *Maternal thyroid deficiency during pregnancy and subsequent neuro-psychological development of the child*. New Engl J Med 1999;341:549-55.

2. Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, Visser W, Steegers EA, Verhulst FC, de Rijke YB, Tiemeier H. *Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study*. J Clin Endocrinol Metabol 2010;95:4227-34.

3. Kooistra L, Crawford S, van Baar AL, Brouwers EP, Pop VJ. *Neonatal effects of maternal hypothyroxinemia during early pregnancy*. Pediatrics 2006;117:161-7.

4. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J, Chen Y, Wang W, Chawinga M, Zhang L, Yang L, Zhao Y, Hua T. *Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months*. Clin Endocrinol (Oxf.) 2010;72:825-9.

5. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL. *Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy*. Clin Endocrinol (Oxf). 1999;50:149-55.

6. Boas M, Main KM, Feldt-Rasmussen U. *Environmental chemicals and thyroid function: an update*. Curr Opin Endocrinol Diabetes Obes 2009;16:385-91.

7. Brucker-Davis F. *Effects of environmental synthetic chemicals on thyroid function.* Thyroid 1998;8:827-56.

8. Crofton KM. *Thyroid disrupting chemicals: mechanisms and mixtures*. Int J Androl 2008; 31:209-23.

9. Akaike M, Kato N, Ohno H, Kobayashi T. *Hyperactivity and spatial maze learning impairment of adult rats with temporary neonatal hypothyroidism*. Neurotoxicol Teratol 1991;13:317-22.

10. Kobayashi K, Tsuji R, Yoshioka T, Kushida M, Yabushita S, Sasaki M, Mino T, Seki T. *Effects of hypothyroidism induced by perinatal exposure to PTU on rat behaviour and synaptic gene expression*. Toxicology 2005;212:135-47.

11. Howdeshell K. *A model of the development of the brain as a construct of the thyroid system*. Environ Health Perspec 2002;110:337–48.

PFOA & PFOS: Eksponering og kræftrisiko - resumé af et ph.d. projekt.

Af Kirsten Thorup Eriksen, Institut for Epidemiologisk Kræftforskning, Kræftens Bekæmpelse

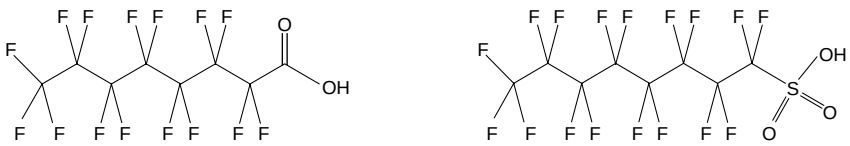
Perfluoroktansyre (PFOA) og perfluoroktansulfonat (PFOS) tilhører en gruppe af kemiske forbindelser kaldet fluorstoffer, som anvendes i en række forbrugerprodukter. Deres tilstedeværelse i miljøet, forekomst i blod og organer hos mennesker verden over samt toksicitet i dyremodeller har rejst bekymring om eventuelle sundhedsskadelige effekter hos mennesker. PFOA og PFOS er blevet associeret med tumorudvikling i dyreforsøg, men viden om stoffernes kræftfremkaldende potentiale hos mennesker er mangelfuld.

Baggrund: Fluorstoffer

Fluorstoffer er syntetisk fremstillede forbindelser bestående af en fluoreret kulstofkæde typisk 4-14 kulstof-atomer i længde og en ladet gruppe, primært carboxylsyre eller sulfonat. PFOA og PFOS er de to mest velbeskrevne og udbredte fluorstoffer. De består begge af et skelet på 8 kulstofatomer (figur 1A-B).

Kulstof- og fluorbindinger (C-F bindinger) er blandt de stærkeste bindinger i organisk kemi og fuldt fluorerede kulstofkæder er stabile selv ved høje temperaturer og nedbrydes ikke af stærke syrer, baser eller oxidationsmidler. Fluordelen giver ekstremt lav overfladespænding og bidrager til fluorstoffers unikke vandskyende og lipofobe natur. På grund af deres overfladeaktive egenskaber anvendes fluorstoffer i en bred vifte af industri- og forbrugerprodukter. De anvendes blandt andet i produktionen af "non-stick" belægninger på stegepander, vandtætte og åndbare tekstiler, brandslukningsskum og beskyttende belægninger til tæpper, møbler, papir og fødevareemballage (figur 2). Velkendte handelsnavne er Teflon®, Gore-Tex® Stainmaster™ og Scotchgard™.

De stabile fluorstoffer er blevet påvist i en lang række miljømatricer verden over, herunder vand, luft, slam, jord og sedimenter, og stofferne er detekteret verden over i blodprøver og organer hos dyr og mennesker (1,2). I modsætning til andre persistente stoffer, såsom dioxiner og polychlorerede biphenyler, ophobes fluorstoffer ikke i fedtvævet, men ophobes derimod i blodet (bundet til serumproteiner), lever og nyre. Halveringstiden i blodet er anslået til cirka 4 år for PFOA og 5 år for PFOS hos mennesker (3).



A. B.

Figur 1. Kemisk struktur af A: PFOA and B: PFOS.

Figur 2. Fluorstoffer anvendes i en række industri- og forbrugerprodukter, herunder non-stick køkkengrej, vandtætte og åndbare tekstiler, tæppebeskyttelse, beskyttende belægninger til papir og fødevareindpakning samt brandslukningsskum.

På grund af fluorstoffers persistens i miljøet, forekomst i menneskers blod og organer og toksicitet i dyremodeller er der rejst bekymring om potentielle skadelige helbredseffekter hos mennesker. Det kræftfremkaldende potentiale af PFOA og PFOS er blevet undersøgt i forskellige *in vitro* forsøg, dyreforsøg og enkelte studier fra arbejdsmiljøet, dog uden at kunne drage endelige konklusioner. Viden om fluorstoffers kræftfremkaldende potentiale hos befolkningen er således mangelfuld.

Formål med ph.d. projektet

Jeg har i mit ph.d. projekt *("PFOA & PFOS: Exposure and human cancer risk")* ønsket at undersøge fluorstoffer i relation til kræftrisiko hos mennesker samt hvilke faktorer, der determinerer menneskets fluorstofniveau i blodet. Projektet havde tre hovedformål:

- At klarlægge eksponeringskilder og determinanter for PFOA og PFOS plasmaniveauer hos mennesker.
- At undersøge fluorstoffers kræftfremkaldende potentiale i mennesker ved:
  - At undersøge om fluorstoffer øger niveauet af reaktive iltradikaler (ROS) og oksidativt beskadiget DNA i humane leverceller.
  - At undersøge sammenhængen mellem PFOA og PFOS plasmaniveauer og risiko for udvikling af prostatakræft, blærekræft, pankreaskræft og leverkræft i mennesker.

Eksponeringskilder og determinanter for PFOA og PFOS plasmaniveauer

Den eksisterende viden om forekomsten af PFOA og PFOS i miljøet tillader ikke endelige konklusioner om specifikke eksponeringskilder. Det er derfor ikke fuldt anskueliggjort, hvordan disse fluorstoffer kommer ind i blodbanen. Mulige eksponeringskilder og eksponeringsruter inkluderer fødevarer (4), drikkevand (5), migration fra fødevareemballage, personlige plejeprodukter og køkkenudstyr (6,7), støv i hjemmet samt indendørs- og udendørsluft (8).

For bedre at klarlægge fluorstofeksponering hos mennesker, undersøgte vi sammenhængen mellem kostvaner og livsstilsfaktorer i forhold til PFOA og PFOS plasmaniveauer hos 652 danske mænd fra Kost, Kræft og Helbred kohorten (KKH kohorten) (9). KKH kohorten er en kohorte på 57.053 danskere i alderen 50-64 år, der blev inviteret til deltagelse i 1993-97. Oplysninger om livsstil, kostvaner samt biologisk materiale blev indsamlet ved indrullering. I vores tværsnitsstudie af 652 mænd fra KKH kohorten, undersøgte vi sammenhængen mellem dagligt indtag af hovedkostgrupperne (rødt kød, fisk, fjerkræ, æg, korn, frugt, grøntsager, mejeriprodukter, kartofler, drikkevand og snacks), alkohol, primære madlavningsmetode, bopælsområde, alder, rygning og BMI og PFOA og PFOS niveauer målt i plasma. Blandt de undersøgte kostgrupper var det kun indtagelse af æg, der var signifikant positivt associeret med PFOS plasmaniveauer. Vi fandt også sammenhænge mellem indtagelse af kartofler og PFOA og

PFOS plasmaniveauer, men resultaterne var ikke signifikante. Samlet set tyder studiet på, at kosten ikke er den primære eksponeringskilde i Danmark. Anvendelserne af fluorstoffer er dog mangfoldige, og vi kunne i studiet ikke tage højde for andre potentielle kilder såsom afsmitning fra fødevareemballage, forurenet støv og luft.

Studiet viste også, at mennesker bosiddende i Aarhusområdet havde 30 % højere plasmaniveauer af både PFOA og PFOS end mennesker, der boede i København. Disse resultater tyder på, at der er geografisk variation i eksponeringskilderne i Danmark. Enkelte undersøgelser har vurderet forekomsten af fluorstoffer i Danmark (10) og i de nordiske lande, herunder Danmark (11). Ingen af disse undersøgelser vurderede plasmaniveauer som markør for eksponering og resultaterne kan derfor ikke sammenlignes direkte med vores, men samlet set tyder det på, at Danmark har en udbredt fluorstofforurening med mulig geografisk variation i menneskets eksponering.

Fluorstoffer og kræftrisiko

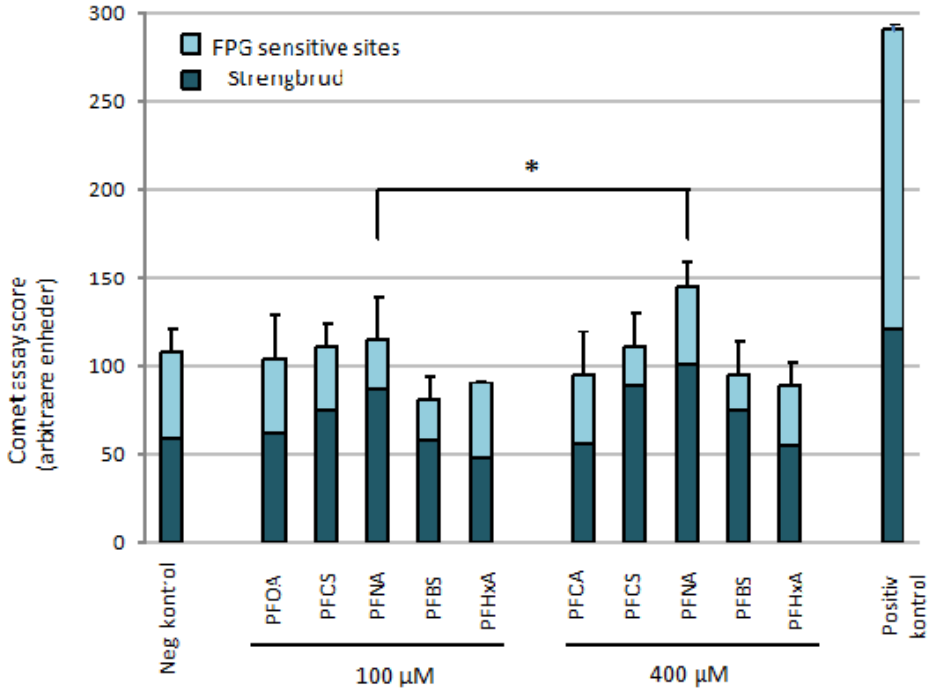
Virkningsmekanisme

En række undersøgelser har vist, at PFOA og PFOS ikke er aktive i forskellige mutagenicitetstest (12-15), hvorimod kronisk eksponering for relativt høje doser er forbundet med tumorudvikling i lever, pankreas og testis i gnavere (12,13). U.S. Environmental Protection Agency har således klassificeret PFOA som værende kræftfremkaldende i dyr og som "muligvis" kræftfremkaldende i mennesker (16). Mekanismer forbundet med fluorstoffers tumorudvikling i dyr er ikke fuldt klarlagt, men fluorstoffer er såkaldte "peroxisom proliferatorer (PPs)" og menes at forårsage leverkræft hos gnavere via aktivering af den såkaldte "peroxisom proliferator-aktiveret receptor-α (PPARα))". PPARα virker som transkriptionsfaktor og spiller en afgørende rolle i reguleringen af bl.a. celledifferentiering. Forskellige studier indikerer, at der er artsforskelle i responsen på PPs, blandt andet udtrykker humane leverceller omkring ti gange mindre PPARα end celler fra gnavere (17). Aktiveringen af PPARα hos gnavere menes at øge ROS dannelsen og niveauet af oksidative DNA skader (18), som er indikatorer på et karcinogent potentiale, men denne virkningsmekanisme er tvivlsom hos mennesker. Vi ønskede at undersøge fluorstoffers evne til at danne ROS og oksidativt beskadiget DNA i humane leverceller og vi anvendte en levercellelinje (HepG2), eftersom leveren er målorgan for fluorstoffer. Valget af celler med menneskelig oprindelse var vigtig, netop fordi ekstrapolering af resultater i celler fra gnavere er diskuterbar på grund af artsforskelle, særligt i relation til PPARα aktivering. Vi undersøgte PFOA, PFOS samt tre mindre undersøgte fluorstoffer (PFBS, PFNA og PFHxA).

Vi fandt en mindre stigning i intracellulær ROS dannelse hos celler udsat for PFOA og PFOS sammenlignet med ikke-eksponerede celler, men hverken PFBS, PFHxA eller PFNA øgede niveauet af ROS. Vi fandt ingen stigning i DNA skader (målt som strengbrud og såkaldte FPG sensitive sites) efter eksponering med fluorstoffer undersøgt ved Comet assay (figur 3), kun PFNA gav en beskeden stigning i strengbrud. Samlet set viste vores studie, at det blandt fem fluorstoffer kun var få, der havde en mindre effekt i form af ROS dannelse eller oksidative DNA skader i en cellelinje repræsenterende den menneskelige lever.

Kræftrisiko i den danske befolkning

Kun få epidemiologiske undersøgelser af kræftrisiko og -dødelighed hos mennesker i relation til PFOA og PFOS er blevet gennemført, og kun i arbejdsmiljøer (19-22). På grund af den manglende viden om det kræftfremkaldende potentiale i mennesker ønskede vi at undersøge sammenhængen mellem PFOA og PFOS eksponering og kræftrisiko. Vi undersøgte sammenhængen mellem PFOA og PFOS plasmaniveauer og kræftrisiko i den danske prospektive KKH kohorte. De undersøgte kræftformer var prostatakræft, blærekræft, pankreaskræft og leverkræft, valgt på grund af indikationer på kræftrisiko i



Figur 3. DNA skader målt som strengbrud og FPG sensitive sites i HepG2 celler eksponeret for fem forskellige fluorstoffer ved 100 µM og 400 µM i 24 timer (analyseret ved Comet assay). Hver søjle repræsenterer middelværdien fra tre forskellige forsøg. *Statistisk signifikante effekter på streng brud sammenlignet med ikke-eksponerede celler (neg. kontrol).

arbejdsmiljøer og dyreforsøg. Vi identificerede 713 deltagere med prostatakræft, 332 med blærekræft, 128 med pankreaskræft, og 67 med leverkræft i KKH kohorten ved hjælp af Cancerregisteret og Patologidatabanken og en sammenligningsgruppe på 772 personer blev udvalgt. Vores statistiske analyser viste ingen signifikante forskelle i kræftrisiko for de undersøgte kræftformer i forhold til PFOA og PFOS plasmaniveauer (tabel 1). En 30 % - 40 % stigning i risikoen for prostatakræft blev observeret for alle tre øverste kvartiler af PFOS plasmaniveauer sammenlignet med den laveste kvartil, men resultaterne var ikke signifikante. Samlet set viste vores undersøgelse, at plasmaniveauer af PFOA og PFOS ikke er associeret med risiko for prostatakræft, blærekræft, pankreaskræft eller leverkræft i en dansk kohorte repræsenterende den danske midaldrende befolkning.

Tolkning af resultater og perspektiver

Resultaterne af vores studier indikerer:

- En geografisk variation i eksponeringen af fluorstoffer i Danmark.
- At kosten ikke er primær kilde til fluorstof eksponering i Danmark.
- At ROS og oksidative DNA skader ikke er relevant for potentielt skadelige effekter af fluorstofeksponering hos mennesker.
- At PFOA og PFOS eksponering ikke er forbundet med øget risiko for prostatakræft, pankreaskræft, blærekræft og leverkræft i den danske befolkning.

Vores epidemiologiske undersøgelse indikerede ikke, at eksponeringsniveauet af fluorstoffer i den generelle population bør betragtes som kræftfremkaldende, hvilket er i tråd med vores cellestudie, der generelt set ikke viste

Tabel 1. Justerede risikoestimater (IRR) for prostatakræft, blærekræft, pankreaskræft og leverkræft for de tre øverste kvartiler af PFOA og PFOS plasmaniveauer sammenlignet med laveste kvartil.

		PFOA			PFOS		
Organ	Kvartil	Kræfttilfælde/ sammenligning-gruppe	IRR	95 % KI	Kræfttilfælde/ sammenligning-gruppe	IRR	95 % KI
Prostata	K1	179/175	1,00	·	179/208	1,00	·
	K2	178/165	1,09	0,78-1,53	178/161	1,35	0,97-1,87
	K3	178/182	0.94	0,67-1,32	180/160	1,31	0,94-1,82
	K4	178/158	1,18	0,84-1,65	176/151	1,38	0,99-1,93
	Trend*	713/680	1,03	0,99-1,07	713/680	1,05	0,97-1,14
Blære	K1	84/151	1,00	·	83/145	1,00	·
	K2	82/215	0,71	0,46-1,07	84/198	0,76	0,50-1,16
	K3	83/184	0,92	0,61-1,39	83/195	0,93	0,61-1,41
	K4	83/222	0,81	0,53-1,24	82/234	0,70	0,46-1,07
	Trend*	332/772	1,00	0,95-1,05	332/772	0,93	0,83-1,03
Pankreas	K1	32/179	1,00	·	32/161	1,00	·
	K2	32/216	0,88	0,49-1,57	32/183	1,02	0,57-1,84
	K3	32/178	1,33	0,74-2,38	32/184	1,24	0,67-2,31
	K4	32/199	1,55	0,85-2,80	32/244	0,91	0,51-1,65
	Trend*	128/772	1,03	0,98-1,10	128/772	0,99	0,86-1,14
Lever	K1	17/108	1,00	·	17/108	1,00	·
	K2	17/141	1,00	0,44-2,23	17/193	0,62	0,29-1,33
	K3	17/281	0,49	0,22-1,09	17/217	0,72	0,33-1,56
	K4	16/242	0,60	0,26-1,37	16/254	0,59	0,27-1,27
	Trend*	67/772	0,95	0,86-1,06	67/772	0,97	0,79-1,19

* I trendanalyserne blev PFOA and PFOS plasmaniveauerne indsat som kontinuerte variable; IRR blev estimeret per 1 ng/ml øgning i PFOA plasmaniveauer og per 10 ng/ml øgning i PFOS plasmaniveauer.

øgede niveauer af oksidative DNA skader efter eksponering for fluorstoffer. Fluorstofniveauerne målt i dette projekt var væsentligt lavere end dem, der rapporteres i erhvervsrelaterede studier (23,24) hvilket kan forklare, hvorfor vi ikke gentager tidligere indikationer på kræftrisiko blandt erhvervseksponerede arbejdere. Eksponeringen spænder relativt bredt i vores studie, hvilket ellers giver et fint grundlag for at opdage en kræftfremkaldende virkning, hvis en sådan findes ved disse relativt lave eksponeringsniveauer.

Som nævnt er PFOA og PFOS blevet forbundet med tumorudvikling ved længere tids eksponering for relativt høje doser i dyrestudier (12,13). Denne uoverensstemmelse med vores resultater kan skyldes udsættelse for lavere doser i befolkningen samt at fluorstoffers kræftfremkaldende potentiale er artsspecifik og at den mekanisme, der er involveret i levertumorudvikling hos gnavere (PPARα aktivering) ikke er relevant hos mennesker. For at ekstrapolere fra dyr til menneske er det netop en nødvendighed, at de fysiologiske forhold

såsom cellestruktur og biokemi er sammenlignelig mellem dyr og menneske.

Fluorstoffer har de senere år fået stor opmærksomhed på grund af deres allestedsnærværende forekomst i miljøet og i mennesker. Selv om vores projekt ikke antyder, at PFOA og PFOS eksponeringer i den almindelige befolkning er kræftfremkaldende, er yderligere forskning nødvendig for at undersøge dette i andre kohorter samt for andre kræftformer. Det kræftfremkaldende potentiale bør også vurderes i andre humane cellelinjer, repræsenterende forskellige vævstyper. Selv om PFOA og PFOS stadig er de mest undersøgte fluorstoffer, er det ligeledes vigtigt i fremtidige undersøgelser at inddrage nyudviklede fluorstoffer, da disse kan have forskellige biologiske effekter.

Ph.d. projektet blev gennemført med støtte fra the International Epidemiology Institute, som har modtaget økonomisk støtte fra 3M Company. 3M Company havde ingen indflydelse på studie design eller tolkning af resultater. Ph.d. projektet blev gennemført under vejledning af Ole Raaschou-Nielsen og Mette Sørensen, Kræftens Bekæmpelse, og Steffen Loft og Peter Møller, Københavns Universitet.

Yderligere oplysninger:
Kirsten Thorup Eriksen
kirsthor@cancer.dk

Referencer

1. Giesy JP, Kannan K. *Global distribution of perfluorooctane sulfonate in wildlife.* Environ Sci Technol 2001;35:1339-42.

2. Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, Seed J. *Perfluoroalkyl acids: a review of monitoring and toxicological findings.* Toxicol Sci 2007;99:366-94.

3. Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, Zobel LR. *Half-life of serum elimination of perfluorooctanesulfonate,perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers.* Environ Health Perspect 2007;115:1298-1305.

4. Fromme H, Tittlemier SA, Volkel W, Wilhelm M, Twardella D. *Perfluorinated compounds - Exposure assessment for the general population in western countries.* Int J Hyg Environ Health 2008;212:239-70.

5. Emmett EA, Shofer FS, Zhang H, Freeman D, Desai C, Shaw LM. *Community exposure to perfluorooctanoate: relationships between serum concentrations and exposure sources.* J.Occup.Environ.Med 2006; 48, 759-70.

6. Tittlemier SA, Pepper K, Seymour C, Moisey J, Bronson R, Cao XL, Dabeka RW. *Dietary exposure of Canadians to perfluorinated carboxylates and perfluorooctane sulfonate via consumption of meat, fish, fast foods, and food items prepared in their packaging.* J Agric Food Chem 2007;55:3203-10.

7. Sinclair E, Kim SK, Akinleye HB, Kannan K. *Quantitation of gas-phase perfluoroalkyl surfactants and fluorotelomer alcohols released from nonstick cookware and microwave popcorn bags.* Environ Sci Technol 2007;41:1180-5.

8. Bjorklund JA, Thuresson K, De Wit CA. *Perfluoroalkyl compounds (PFCs) in indoor dust: concentrations, human exposure estimates, and sources.* Environ Sci Technol 2009;43:2276-81.

9. Tjonneland A, Olsen A, Boll K, Stripp C, Christensen J, Engholm G, Overvad K. *Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark.* Scand J Public Health 2007;35:432-41.

10. Bossi R, Strand J, Sortkjaer O, Larsen MM. *Perfluoroalkyl compounds in Danish wastewater treatment plants and aquatic environments.* Environ Int 2007;34:443-50.

11. Kallenborn R, Berger U, Järnberg U. *Perfluorinated alkylated substances (PFAS) in the Nordic environment.* Tema Nord, Nordic Council of Ministers, Copenhagen, Denmark, 2004.
http://www.sft.no/nyheter/dokumenter/pfas_nmr2004.pdf

12. Kennedy GL Jr, Butenhoff JL, Olsen GW, O'Connor JC, Seacat AM, Perkins RG, Biegel LB, Murphy SR, Farrar DG. *The toxicology of perfluorooctanoate.* Crit Rev Toxicol 2004; 34:351-84.

13. OECD (Organisation for Economic Co-operation and Development). ENV/JM/RD (2002)17/FINAL. *Hazard assessment of perfluooroctane sulfonate (PFOS) and its salts.* 2002.

14. Fernandez FP, Perez Martin JM, Herrero O, Peropadre A, de la PE, Hazen MJ. *In vitro assessment of the cytotoxic and mutagenic potential of perfluorooctanoic acid.* Toxicol In Vitro 2008;22:1228-33.

15. Oda Y, Nakayama S, Harada KH, Koizumi A. *Negative Results of umu Genotoxicity Test of Fluorotelomer Alcohols and Perfluorinated Alkyl Acids.* Environ Health Prev Med 2009; 12:217-19.

16. U.S. EPA (U.S. Environmental Protection Agency). *Basic Information on Perfluorooctanic acid (PFOA) and Fluorinated Telomers:* http://www.epa.gov/oppt/pfoa/

17. Palmer CN, Hsu MH, Griffin KJ, Raucy JL, Johnson EF. *Peroxisome proliferator activated receptor-alpha expression in human liver.* Mol Pharmacol 1998;53:14-22.

18. O'Brien ML, Spear BT, Glauert HP. *Role of oxidative stress in peroxisome proliferator-mediated carcinogenesis.* Crit Rev Toxicol 2005;35:61-88.

19. Gilliland FD, Mandel JS. *Mortality among employees of a perfluorooctanoic acid production plant.* J Occup Med 1993;35:950-4.

20. Lundin JI, Alexander BH, Olsen GW, Church TR. *Ammonium perfluorooctanoate production and occupational mortality.* Epidemiology 2009;20:921-8.

21. Alexander BH, Olsen GW, Burris JM, Mandel JH, Mandel JS. *Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility.* Occup Environ Med 2003;60: 722-9.

22. Alexander BH, Olsen GW. *Bladder cancer in perfluorooctanesulfonyl fluoride manufacturing workers.* Ann Epidemiol 2007;17:471-8.

23. Olsen GW, Burris JM, Burlew MM, Mandel JH. *Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations.* J Occup Environ Med 2003;45:260-70.

24. Olsen GW, Logan PW, Hansen KJ, Simpson CA, Burris JM, Burlew MM, Vorarath PP, Venkateswarlu P, Schumpert JC, Mandel JH. *An occupational exposure assessment of a perfluorooctanesulfonyl fluoride production site: biomonitoring.* AIHA J (Fairfax, Va) 2003;64;651-9.

Dioxin-like potential of environmental compounds

By Manhai Long and Eva Cecilie Bonefeld-Jørgensen, Centre for Arctic Environmental Medicine, Department of Public Health, Aarhus University

Introduction

Dioxins and dioxin-like compounds

Humans are exposed to diverse harmful environmental contaminants such as persistent organic pollutants (POPs). Among POPs, dioxins and dioxin-like compounds (DLCs) are some of the most toxic chemicals that are highly persistent in the environment. It has been documented that exposure to dioxins and DLCs may cause a series of negative effects both in animal experiments and in human epidemiological studies such as carcinogenicity (1), immunotoxicity and adverse effects on reproduction, neurobehaviour (2). The most famous events about dioxins and their toxicity are the use of Agent Orange in the Vietnam War (1961-71) and the industrial disaster in Seveso, Italy (1976), where dioxins such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was the primary toxic component and caused high exposure of the residential populations. Dioxins and DLCs are never produced for commercial purposes and are made inadvertently during many processes involving chlorine by burning chlorine-based chemical compounds with hydrocarbons. The major source of dioxin in the environment comes from waste-burning incinerators of various sorts and also from backyard burn-barrels. Paper bleaching, production of Polyvinyl Chloride (PVC) plastics and production of chlorine and organochlorine chemicals (e.g. pesticides) are also the sources of dioxins and DLCs in the environment. Human exposure to dioxins and DLCs is mainly through the consumption of contaminated food. Since these compounds are fat-soluble, they do bioaccumulate through the food chain and are found in e.g. meat, fish, milk, dairy products, fats, and oils that are the main sources of exposure for adults, and newborns get an additional exposure via breast feeding.

The classical dioxins and DLCs include 7 polychlorodibenzo-*p*-dioxins (PCDDs), 10 polychlorodibenzofurans (PCDFs), and 12 dioxin-like polychlorinated biphenols (DL-PCBs) (non-*ortho* coplanar PCBs: PCB 77, 81, 126, and 169 and mono-*ortho*-substituted PCBs: PCB 105, 114, 118, 123, 156, 157, 189) (3,4) (fig. 1). The most toxic dioxin is TCDD. The biological and toxicological effects of dioxins and DLCs are mediated via the aryl hydrocarbon receptor (AhR) (5,6).

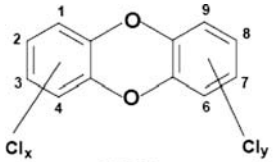
Ah-receptor and Ah-receptor ligands

The Ah-receptor (AhR) is an intracellular ligand-dependent transcriptional factor. The AhR binds dioxins and DLCs and is transactivated and by cellular processes mediate the toxicity of these compounds. Most tissues in mammals express the AhR constitutively (7,8).

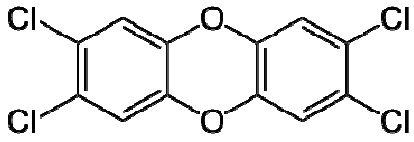
Mechanistically, the function of AhR is similar to that of the steroid hormone receptors (9). Upon binding to the ligand (for example TCDD), the cytosolic ligand-AhR complex translocates into the nucleus and dimerizes with the AhR translocator (Arnt). The ligand-AhR-Arnt complex then binds to specific DNA sequences, the dioxin-responsive elements (DREs), and thus stimulates the transcription of adjacent genes including e.g. CYP1A1 and CYP1B1 (9,10) (fig. 2).

Classical AhR ligands are planar and can occupy a hydrophobic pocket within AhR, such as PCDDs, PCDFs and DL-PCBs mentioned as well as polycyclic aromatic hydrocarbons e.g. benzo[a]pyrene (5). TCDD is the most potent known AhR ligand. However, more recent studies reveal that compounds of diverse structure and lipophility can bind AhR and induce gene expression, such compounds can be synthetic (e.g. methylenedioxybenzenes) or naturally occurring (e.g. indoles)

Polychlorinated Dibenzodioxins (PCDDs)

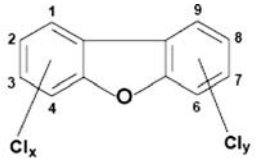


PCDDs-general structure

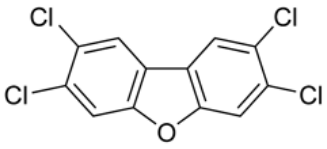


2,3,7,8-tetrachlorodibenzodioxin (TCDD)

Polychlorinated Dibenzofurans (PCDFs)

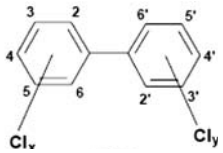


PCDFs-general structure

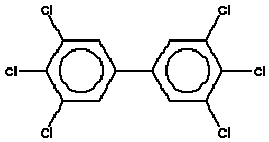


2,3,7,8-tetrachlorodibenzofuran

Polychlorinated Biphenyls (PCBs)



PCBs-general structure



3,3',4,4',5,5'-pentaCB (PCB126)

Fig. 1. The structure of classical dioxins and dioxin-like compounds.

(11,12). Therefore humans are exposed to a mixture of man-made and natural AhR-modulation compounds. It is necessary to identify and characterize possible AhR ligands in the environment and biota and monitor the actual concerted action of these compounds on the AhR function in humans as well as elucidate their effects *in vitro* and *ex vivo*.

Measurement of the dioxin-like potential of compounds (Detection of AhR ligands)

Due to different origin, solubility, volatility and metabolic stability, dioxin and dioxin-like compounds (DLCs) occur as complex mixtures with concentrations of the individual compounds differing substantially. This complexity, along with differences in toxicity, increases the difficulty of risk evaluation. To estimate the total toxicity of dioxins and related compounds, the concept of the Toxic Equivalency Factor (TEF) has been developed. TEF is a number representing the toxic potency of a particular compound to induce AhR mediated effects related to the reference substance, TCDD. The TEFs of TCCD is set to 1.0. Table 1 shows the WHO-TEF values of dioxins and DLCs (13). The concept of TEQ (TCDD toxic equivalent) has thus been introduced to simplify risk assessment and regulatory control (3). The classical TEQs are calculated by multiplying the concentration of individual PCDDs/PCDFs/PCBs by their respective TEFs.

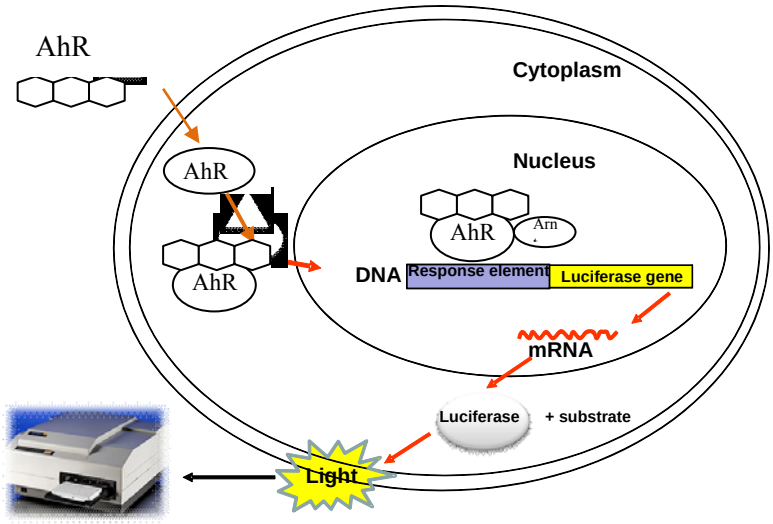


Fig. 2. The model of AhR- mediated signal transduction pathway and the principle of the AhR-transactivation bioassay.
When the AhR ligand interacts with the Ah receptor, the ligand-receptor complex will be activated and translocate to the nucleus and dimerizes with the AhR translocator (Arnt). Subsequently, the ligand-receptor complex will bind to dioxin response elements of the DNA, thus activating luciferase gene expression. The resulting mRNA translates into luciferase enzyme that catalyses a bioluminescent reaction, using luciferin as a substrate. The amount of light is proportional to the dioxin-like activity of the compounds. The luciferase data is given as relative light units (RLU), and subsequently, this is corrected to the protein concentration of the exposed cells.

Previous studies emphasize that assessment of the toxicological potential of a chemical mixture is much more complex than can be deduced by a given TEF dependent calculated TEQ value (14,15). There are several drawbacks using the TEF concept for risk assessment of mixtures of POPs such as the very expensive, high volume requirement and time consuming gas chromatography mass spectrometry (GC-MS) determinations, small concentrations of individual congeners, presence of compounds not routinely measured or unknown substances with AhR affinity, the lack of TEF values for several POPs, and possible antagonistic or synergistic interactions between POPs (16-18). Thus there is a need for an integrated risk assessment of dioxins and DLCs.

A variety of different *in vitro* assays for studies of AhR-mediated toxicities were suggested (19). Since AhR acts as a transcription factor, reporter gene assays for assessment of its activity have become widespread during the last decade. The AhR-mediated transactivation bioassay is a mechanistically based technique that can detect all the compounds that can activate the AhR and AhR-dependent gene expression (i.e. AhR agonists). To facilitate the identification of AhR agonists, recombinant cell lines have been established by transient or stable transfection of a wide of type cell lines with the firefly luciferase reporter gene under transcriptional control of the specific dioxin responsible DNA sequences, the DREs. These constructed cell lines still contain the complete machinery which is involved in the mode of action of DLCs. They are capable of quantifying compounds that have the potency to transactivate the AhR, resulting in the production of the luminescent enzyme luciferase. The cellular response can be measured by adding suitable reagents (e.g., the substrate luciferin and ATP), and quantifying the produced luminescence emission by an automated luminometer (fig. 2). The measured luminescence is

Table 1. The classic AhR ligands and WHO-TEF values for humans*

Compounds	WHO 2005 TEF
Chlorinated dibenzo-p-dioxins	
2,3,7,8-TCDD	1
1,2,3,7,8-PeCDD	1
1,2,3,4,7,8-HxCDD	0.1
1,2,3,6,7,8-HxCDD	0.1
1,2,3,7,8,9-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OCDD	0.0003
Chlorinated dibenzofurans	
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.03
2,3,4,7,8-PeCDF	0.3
1,2,3,4,7,8-HxCDF	0.1
1,2,3,6,7,8-HxCDF	0.1
1,2,3, 7,8,9-HxCDF	0.1
2,3,4,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,6,7,8,9-HpCDF	0.01
OCDF	0.0003
Non-ortho-substituted PCBs	
3,3',4,4'-tetraCB (PCB77)	0.0001
3, 4,4',5-tetraCB (PCB81)	0.0003
3,3',4,4',5-pentaCB (PCB126)	0.1
3,3',4,4',5,5'-hexaCB (PCB169)	0.03
Mono-ortho-substituted PCBs	
2,3,3',4,4'-pentaCB (PCB105)	0.00003
2,3',4,4',5-pentaCB (PCB114)	0.00003
2,3', 4,4',5-pentaCB (PCB118)	0.00003
2',3, 4,4',5-pentaCB (PCB123)	0.00003
2,3,3', 4,4',5-hexaCB (PCB156)	0.00003
2,3, 3',4,4',5'-hexaCB (PCB157)	0.00003
2, 3',4,4',5,5'-hexaCB (PCB167)	0.00003
2,3, 3,4,4',5,5'-heptaCB (PCB189)	0.00003

* Adapted from (13)

then converted into a relative potency (REP) value for pure compounds or AhR-TEQ value for the actual mixtures found in environmental or biological sample. The rapidity and lower cost of the AhR- mediated transactivation bio-assay is attractive for analyses of high number of samples required for epidemiological studies, and as a tool to monitor and ensure reduction of contamination by DLCs in the food chain. The key application role of the AhR-mediated transactivation bioassay is in screening and relative quantification of DLCs in samples such as blood, sediments, food matrices and milk (20). The AhR-mediated transactivation bioassay have been utilized in an array of projects to study the AhR receptor-mediated activities of individual chemicals and mixtures (16-18,21-24) as well as for epidemiological purposes (25-28).

In this review, a series of studies carried out in our research group regarding the dioxin-like potential of single compounds such as pesticides, plasticizers and phytoestrogens and their mixtures, and the dioxin-like activity of complex compound mixtures in environmental and human samples are summarized.

Materials and Methods

AhR-mediated transactivation assay
The cell culture based AhR-mediated transactivation bioassay is a mechanistically based technique that can detect all the compounds that can activate or inhibit the AhR and thus AhR-dependent gene expression. The potential of the single compounds or the complex mixtures found in environmental and human samples to affect AhR function was assessed in human TV101L, rat H4IIE or mouse Hepa1.12cR hepatoma cell lines, respectively, as given in the specific studies (17,26). The samples (single compounds, compound mixtures or human biological/environmental samples) were analyzed by cell exposure alone reflecting the agonistic potential. In addition, the samples were analyzed by co-exposure with the high potent receptor ligand TCDD reflecting the potential of the samples to compete and antagonize the TCDD induced AhR transactivity as well as the ability to further increase the TCDD induced AhR transactivity.

Principle and practice in mixture analyses
Humans are exposed to a complex mixture of chemicals. Therefore, assessment of the combined effect of mixtures is very important. The method based on the principle of concentration addition (CA) has been shown to be a valid tool for assessing mixture effects of similarly and dissimilarly acting environmental contaminants *in vitro* (29,30). The CA model assumes that one chemical can be replaced totally or partly by another compound in the mixture, without changing the overall combined effect, and that they act through a similar mechanism (31). By applying the principle of CA (32), the concentration of the compounds found in a mixture, at an observed mixture effect, can be predicted using the concentration-response data for the single compound alone (22). Knowledge of the ratio of the compounds in the mixture is a prerequisite for using this method (30).

Environmental and biological samples: Extraction and fractionation methods
The environmental and biological samples can contain some factors, which may interfere with the determination of the AhR-mediated effect of samples. Hence the treatment to concentrate the tested compounds and get rid of the interfering factors is important and necessary.

Wastewater samples
Wastewater samples, collected from the influent and the effluent of two Danish sewage treatment plants (STPs), were extracted using solid phase extraction (SPE) as described (33). The extracts were analyzed for the content of a range of industrial chemicals with endocrine disrupting (ED) properties and tested for effects on the AhR transactivation, which was expressed as biological equivalents (AhR-TEQ) (33), calculated using the fixed-effect-level quantification method (34,35). The fixed-effect-level toxicity equivalents are a suitable parameter for assessing the induction potency in complex environmental samples (34).

Water stream samples
For water stream samples, a total of 9 study sites located in 6 different water systems in Jutland, Fyn and Zealand in Denmark were selected. Passive samplers have been developed to collect polar and semi-polar substances of water sample. The POCIS (Polar Organic Chemical Integrative Sampling, fig. 3) was used in studies of pesticides, estrogens and drugs (36-39). Thus passive sampling approach was used to collect the substances in the streams and POCIS were put in the selected sites. POCIS samplers were exposed at different locations in streams, which included sites both with and without sewage effluent admission. Afterwards the extracts from the POCIS sampler's membrane were used for determination of the concentration of endocrine disrupting compounds and for measurement of the AhR transactivity in the mammal Hepa 1.12cR

Fig. 3. Polar Organic Chemical Integrative Sampling (POCIS).

cell cultures as described (33). The effects on the AhR transactivation were expressed as AhR-TEQ (33), calculated using the fixed-effect-level quantification method (34,35).

Human serum and plasma samples
Serum or plasma samples were collected from Greenlandic Inuit and Europeans from Denmark, Sweden, Poland and Ukraine. To obtain the fraction containing lipophilic POPs and get rid of interfering compounds for the AhR transactivity measurements, the serum or plasma samples were extracted with ethanol: hexane and cleaned up on Florisil columns at a certified laboratory, Le Centre de Toxicologie, Sainte Foy, Quebec, Canada (40).The extracts were stored at -80° C and on the day of analysis the extracts were thawed, processed and analyzed as described in AhR transactivation assay (26).

Results and Discussion

Dioxin-like potential of pure compounds and their mixture

Pesticides
Pesticides comprise a large number of different substances with dissimilar structures and diverse toxicity. The AhR potential of the persistent organochlorine insecticide Dieldrin and 22 pesticides currently or previously used in Denmark was assessed by using AhR-mediated transactivation bioassay in the human TV101L hepatoma cells and the rat H4IIE hepatoma cells. It was shown that the fungicides Prochloraz and Iprodione as well as the insecticide Chlopyrifos elicited a dose-dependent activation of the AhR transactivation both in the human TV101L cells and the rat H4IIE cells (fig. 4A and 4B), suggesting that these pesticides can mediate their effects via AhR. Some pesticides exerted cell-specific response evidenced by the potential of the insecticide Methiocarb and the fungicide Tolchlofos-methyl to exert a significant activation of AhR only in the human TV101L liver cells in a dose-dependent manner, whereas the fungicide Chlorothalonil and herbicide Tribenuron-methyl weakly activated AhR only in the rat H4IIE liver cells at certain concentrations. The plant growth regulator Chlormequat chloride and the fungicide Prochloraz dose-dependently antagonized the TCDD induced AhR activity in the human liver cells whilst no significantly antagonistic effect of all test pesticides was observed in the rat liver cells (17).

The AhR potential of other 13 pesticides were recently evaluated using mouse hepatoma cells and it was found that 5 herbicides, 2 fungicides, 2 insecticides and 1 organophosphorus pesticide elicited AhR activating effect (manuscript in prep.). The AhR activating potential of selected single pesticides detected in the Danish water stream was also determined in our laboratory. The preliminary results showed that Atrazin, Carbofuran, Dimethoate, Linuron, Propoconazole and Diuron alone induced weakly agonistic AhR transactivity. A dose-dependent tendency was observed for the pesticide Linuron, and Diuron. Atrazin, Tebuconazole, Bromoxynil and Ioxynil showed an antagonizing effect of the 60 pM TCDD induced AhR transactivity, in contrast Carbo furan and Simazine further increased TCDD induced AhR transactivity (unpublished data).

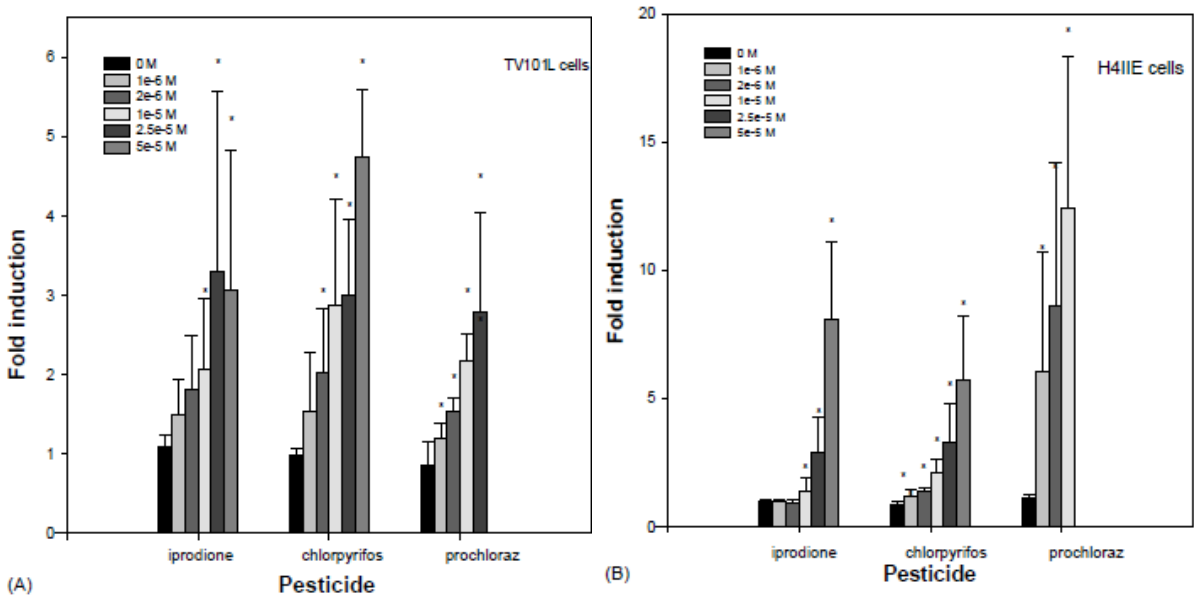


Fig. 4. Dose-response of luciferase activity induced by pesticides in human TV101L cells (A) and rat H4IIE cells (B) (17).
Fold induction is the luciferase activity of pesticide divided by the luciferase activity of solvent control. Values represent the mean ± SD of three independent assays.
*: significantly different from solvent control.

Phthalates and Phenols

As a part of the EU-sponsored research project ENDOMET, the potential of several widely used plasticizers in the industry being released to the environment was assessed i*n vitro f*or their potential to affect the AhR function. The plasticizers investigated were bisphenol A (BPA), BPA dimethacrylate (BPA-DM), alkylphenols (4-n-octylphenol (nOP), 4-n-nonylphenol (nNP), 4-tert-octylphenol (tOP)), bis-ethylhexyladipate (DEHA), phthalates (dibutyl phthalate (DBP), bis-ethylhexyl phthalate (DEHP), di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP), dioctyl phthalate (DNOP), benzylbutyl (BBP)) and 2-phenylphenol (2-PP), 4-chloro-3-methyl phenol (CMP), resorcinol and 2,4-dichlorophenol (2,4-DCP). The combined effect of an equipotent mixture of BPA, nNP, BBP, CMP, resorcinol and tOP was also assessed.

The plasticizers nNP, DBP, DEHP and DIDP elicited weak agonistic AhR activity (fig. 5). When co-treatment with TCDD, nNP, Resorcinol and BBP further increased TCDD induced AhR transactivity dose-dependently, whereas BPA, nNP and CMP inhibited the TCDD-induced AhR activity at the highest tested concentration (table 2) (22,24). As shown in table 3, the mixture, composed of six compounds of which only nNP had a weak agonistic AhR potential, weakly induced the AhR activity compared to the individual compounds. This suggests that these non-AhR active compounds can act together with a weak AhR agonist to increase the AhR transactivity. In the presence of TCDD, the mixture dose-dependently inhibited the TCDD-induced AhR transactivity (22).

Phytoestrogen

Phytoestrogens (PEs) are a diverse group of naturally occurring non steroidal plant compounds that have the ability to cause estrogenic and/or antiestrogenic effects due to their similar structure to natural estrogen, 17 β-estradiol. There are three main classes of PEs: isoflavonoids, coumestans and lignans (41). The effect

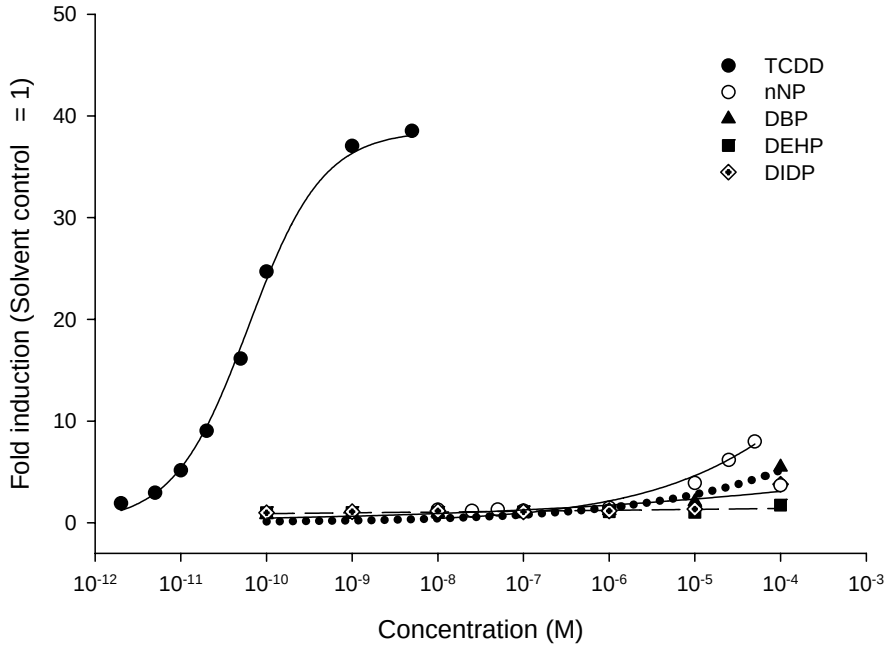


Fig. 5. AhR-mediated transactivity of TCDD and plasticizer nNP, DBP, DEHP, DIDP (22).
Fold induction is the luciferase activity of plasticizers divided by the luciferase activity of solvent control. Values are given as mean ± SD of triplicate determinations.

Table 2. Plasticizers induced competitive AhR transactivity following co-treatment with 60 pM TCDD*

	LOEC (M)	MOEC (M)	% of SC at MOEC[1]
TCDD	2×10^{-12}	1×10^{-9}	100
BPA	1×10^{-4}	1×10^{-4}	44
nNP	2.5×10^{-5}	5×10^{-5} /1×10^{-4}	146 /61
CMP	1×10^{-4}	1×10^{-4}	18
DCP	1×10^{-9}	1×10^{-9}	138
Resorcinol	1×10^{-8}	1×10^{-7}	175
DBP	-	-	-
BBP	1×10^{-8}	1×10^{-5}	165
DEHP	-	-	-
DIDP	-	-	-

* Adapted from (22,24)
LOEC: the lowest tested concentration at which a significant effect ($p < 0.05$) was detected. MOEC: the lowest tested non-cytotoxic concentration causing the maximum effect. SC: solvent control (0.1% DMSO)
[1]Percent of response obtained from compound compared to the controls at MOEC.

Table 3. The AhR transactivity induced by the single plasticizers and their mixture**

	Agonistic response (compound alone)			Competitive response (compound in the presence of EC_{50} TCDD)		
	NOEC	LOEC	EC_{50}	NOEC	LOEC	EC_{50}
Solvent control	1.0 ± 0.03	1.0 ± 0.03	1.0 ± 0.05	-	-	-
60 pM TCDD	15.2 ± 3.26*	15.2 ± 3.26*	15.2 ± 3.26*	1.0 ± 0.07[a]	1.0 ± 0.07[a]	1.0 ± 0.15[a]
Single compounds						
BPA	*1.15 ± 0.30*	*1.40 ± 0.24*	*1.49 ± 0.38*	*1.11 ± 0.14*	*1.01 ± 0.18*▲	*0.74 ± 0.45*
nNP	*1.08 ± 0.19*	*1.22 ± 0.16**	*1.85 ± 0.13**	*1.04 ± 0.16*	*1.05 ± 0.18*▲	*1.12 ± 0.04*▲
BBP	*0.99 ± 0.12*▲	*1.18 ± 0.12*	*1.28 ± 0.18*	*1.24 ± 0.31*	*1.50 ± 0.36*[b]▲	*0.26 ± 0.14*[b]
CMP	*1.01 ± 0.20*	*0.92 ± 0.18*▲	*0.81± 0.08*	*0.99 ± 0.22*	*0.73 ± 0.08*	*0.21 ± 0.06*[b]
Resorcinol	*0.86 ± 0.06*▲	*0.85 ± 0.16*▲	*0.86 ± 0.09*	*1.29 ± 0.29*	*1.21 ± 0.40*▲	*0.25 ± 0.12*[b]
tOP	*1.05 ± 0.08*▲	*1.09 ± 0.28*	*1.09 ± 0.14*	*1.15 ± 0.28*	*1.01 ± 0.29*	*0.21 ± 0.11*[b]
Mixture	**1.23 ± 0.07***	**1.63 ± 0.29***	**0.99 ± 0.26**	**0.96 ± 0.13**	**0.75 ± 0.09**[b]	**0.48 ± 0.11**[b]

**: Adapted from (22)
[a]: In the competitive assay the data of the EC_{50} TCCD cotreateatment was set to 1
NOEC: no-observed-effect concentration.
EC_{50}: half maximum effect concentration
LOEC: the lowest tested concentration at which a significant effect ($p < 0.05$) was detected.
MOEC: the lowest tested non-cytotoxic concentration causing the maximum effect.
The positive TCDD control used was EC50 = 60 pM TCDD *Significantly different from the solvent control.($p < 0.05$) in the agonistic response.
[b]: Significant different from the TCDD EC_{50} control in the competitive response ($p < 0.05$).
▲Significantly different from mixture ($p < 0.05$).
Mixture: equipotent mixture of BPA, nNP, BBP, CMP, resorcinol and tOP.
The data were expressed as Relative Luciferase Unit (RLU) per µg cell protein (22).

of mixtures of 12 food relevant PEs on the AhR transactivation were assessed. The results showed that isoflavonoid metabolites, genistein, daidzein and equol as well as their equimolar mixture, mixture of two isoflavonoid mother compounds, mixture of four lignan mother compounds and coumestrol weakly activated the AhR transactivation. The mixture of two lignan metabolites showed a weak agonistic effect on AhR, but inhibited the TCDD-induced AhR transactivity. Isoflavonoid metabolites exhibited a synergistic combined effect on AhR transactivity (manuscript submitted).

Organotin
Organotin chemicals are those compounds containing at least one bond between tin and carbon. They were found in the Danish water stream. Thus the AhR potential of organotin was assessed. The preliminary result showed that no obvious induced AhR transactivity was observed for the organotins. However, organotin elicited an antagonizing effect on the TCDD induced AhR transactivity (unpublished data).

Dioxin-like potential of environmental matrix

Wastewater
Wastewater contains multiple chemical substances, some of which have the potential to disrupt endocrine processes in living organisms (42-45). In industrialized countries most of the sewage produced is treated in a sewage

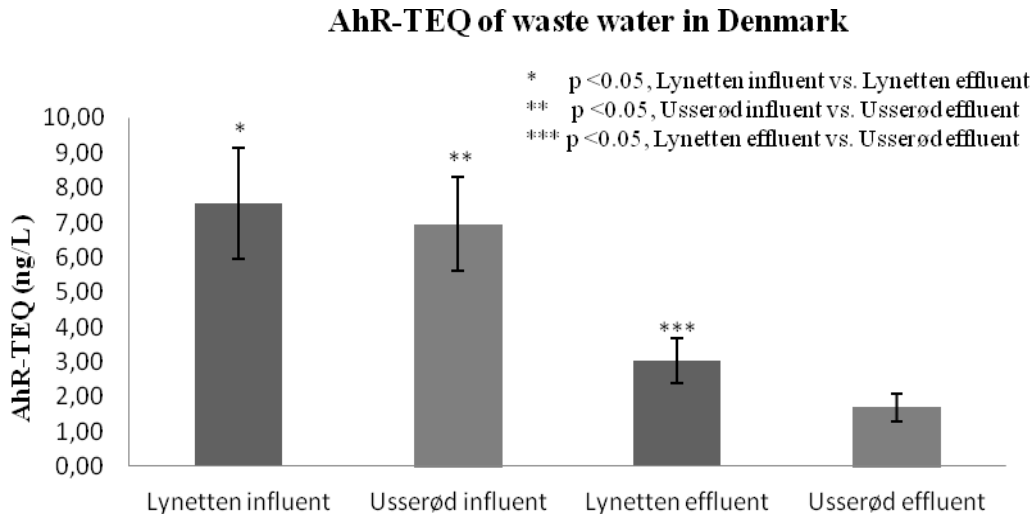


Fig. 6. AhR-TEQ of waste water of two Danish sewage treatment plants*
*Adapted from (33)
Values represent as mean ± SD of at least two independent assays. For the calculation of bio-TEQ, the fixed-effect-level quantification method was used.

treatment plant (STP) before it is discharged to receiving environmental water streams. Never theless some natural hormones and a number of man-made chemicals with the potential to disrupt endocrine activity can be found in environmental surface water because many substances are resistant to biodegradation in STPs or because they are discharged directly without any treatment (46). Thus the dioxin-like potential of wastewater from two Danish sewage treatment plants (STP), Lynetten of Copenhagen and Usserød of north of Copenhagen, was assessed using AhR-mediated transactivation bioassay.

The calculated AhR-TEQ values of Lynetten and Usserød influent were similar and no statistical significant difference between the two STPs was found for influent samples, whereas for the effluent, the AhR-TEQ of Lynetten effluent was significantly higher than that of Usserød effluent (33). For both STPs, the AhR-TEQ value of influent was significantly higher than the effluent AhR-TEQ (fig. 6). Compared to influent samples, the AhR-TEQ in the effluent samples was reduced to 39 % and 24 %, for Lynetten and Usserød, respectively (33). The findings suggested that dioxins or dioxin-like compounds exist in both tested Danish STP wastewaters. Influents contained more AhR-activating compounds than effluent, indicating that the process of both STPs can reduce but not eliminate the AhR-activating compounds.

Danish water stream

It has been demonstrated in our earlier study that the dioxin-like activities of wastewater from Danish STPs were decreased after the cleaning process, however not eliminated (33). Some natural hormones and a number of man-made chemicals with potential to disrupt endocrine activity can thus be found in surface water (46). To assess whether there are AhR-activating compounds in the Danish water streams, the stream water samples were collected by passive samplers (POCIS) at different locations in Danish streams, which included sites both with and without sewage effluent admission. It was shown that the extracts of POCIS membranes from all stations significantly induced AhR transactivity. In general, AhR-TEQ of downstream the sewage treatment plant (STP) was significantly higher

Fig. 7. Greenland map.
Blue circles indicate the Greenlandic communities where the serum dioxin-like activities were measured.

than that of upstream at the same STP station (manuscript in prep.). Thus the data suggest that dioxin-like compounds are found in Danish water streams. Furthermore, more dioxin-like compounds (DLCs) are found downstream than upstream STPs indicating a release from waste water plants to the environmental water streams. In general, the data showed that dioxin-like compounds are found in Danish water streams. DLCs are released from STP plants and higher concentrations were again found downstream compared to the upstream levels, indicating a release of dioxins and DLCs from waste water plants to environmental water streams.

Dioxin-like compounds burden in human body

Greenlandic Inuit

Laboratory studies on the effects of single chemicals or chemical mixtures *in vitro* in cell cultures and laboratory animals cannot fully elucidate the human health risks. Integration of epidemiological and biomarker studies on humans from exposed populations is needed in order to obtain information about the real health risks resulting from exposures to the accumulated complex mixtures of contaminants. The burden of POPs in the Arctic people has been monitored since 1991, and a programme for measuring the potential biological effects of these contaminants has been established (AMAP Human Health Effects Monitoring Programme) (47). As parts of the AMAP human health programme the levels of 14 different PCBs, 10 pesticides, selenium, lead and mercury were determined in Inuit within different Greenlandic districts. Furthermore, to determine the potential health risk the AhR mediated dioxin-like activity was measured *ex vivo* as a biomarker of effect of the actual complex mixtures of POPs found in serum of Inuit of different districts (fig. 7). More than 71 % of the serum POP extracts activated the AhR transactivity and the serum POP related dioxin-like activities are given by TCDD toxicological equivalence (AhR-TEQ). Similar AhR-TEQ levels were found in male and female Greenlandic Inuit (27).

The median AhR-TEQ level of male Inuit were 153 - 197 pg /g lipid (26,27), with the highest and the lowest level found in East Greenland (Tasiilaq) and North Greenland (Qaannaq), respectively (Tasiilaq ≥ Sisimiut ≥ Nuuk > Qaanaaq) (figure 8). In an earlier pilot study we also showed that the AhR-TEQ differed significantly among the districts, with the male Inuit in East Greenland (Scoresbysund) having the highest level and Inuit in mid-West Greenland Ilulissat having the lowest AhR-TEQ level (Scoresbysund ≥ Nuuk > Nanortalik > Upernavik > Ilulissat) (25). For Greenlandic female Inuit the median AhR-TEQ level was 167 pg/g lipid (27). The serum dioxin-like activity of Qaannaq women was lower than that of other districts with the order of Nuuk ≥ Tasiilaq ≥ Sisimiut > Qaannaq (fig. 8) (27).

Preliminary data for Scoresbysund, Qeqertarsuaq and Narsaq also show a high frequency of serum extracts eliciting agonistic AhR activity with the median AhR-TEQ level of 182-185 pg/g lipid (Unpublished data).

Comparison of serum dioxin-like activities between Greenlandic Inuit and Europeans

The project INUENDO, supported by the European Union, aimed to examine whether there is a correlation between human fertility and exposure to POPs, using the POP exposure proxy biomarkers PCB-153 and *p,p*'-DDE. The project involved study groups of fertile men from Europe (Kharkive, Ukraine; Warsaw, Poland; fishermen of the Swedish East Coast) and various Greenlandic districts (48).

A significant higher serum concentration of the two POP exposure markers was found for Inuit in comparison to the Europeans (49). Upon measurement of the lipophilic serum extract on the AhR transactivity we found that more than 95 % of serum samples from European men showed significantly agonistic AhR activity. As shown in table 4, the median AhR-TEQ levels were 312, 428 and 337 pg/g lipid for Warsaw, Sweden and Kharkiv, respectively (26). For Greenlandic male Inuit, the median AhR-TEQ levels of Qaannaq, Sisimut, Nuuk and Tasiilaq were 110, 189, 166 and 240-294 pg/g lipid, being significantly lower than European men mentioned above (26,27).

The influence of serum extract on the TCDD induced AhR activity differed between Greenlandic male Inuit and European men. As shown in table 4, upon co-exposure with TCDD-EC_{50} (termed as AhRcomp) the Greenlandic samples, except Nuuk men, mainly exhibited a potentiating effect on AhR by a further increasing TCDD induced AhR-transactivity whereas European men generally antagonized the TCDD induced AhR transactivity (26,27). This difference suggests that more compounds with AhR affinity is found in Europeans and

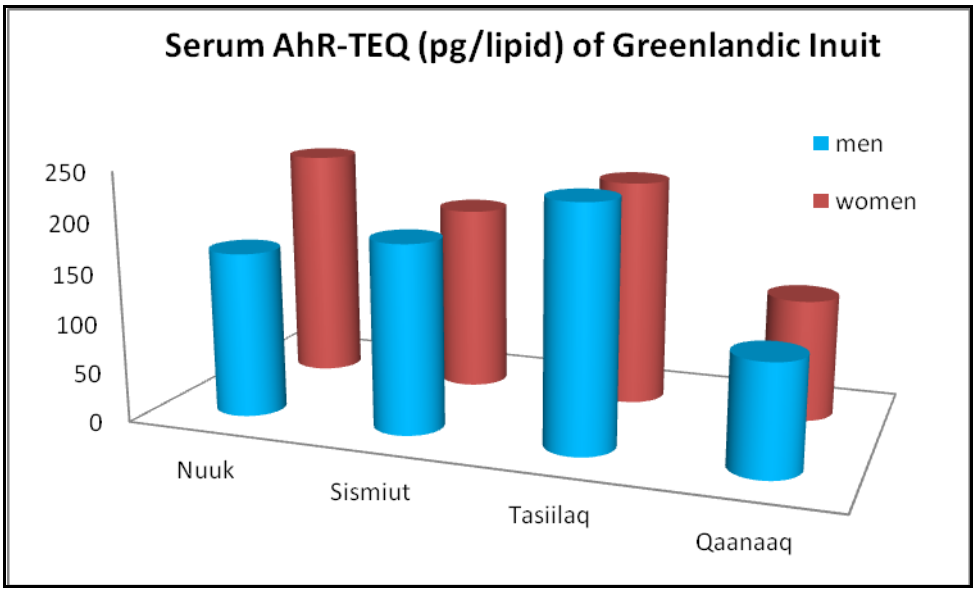


Fig. 8. Serum AhR-TEQ of Greenlandic Inuit*
* Adapted from (27)
AhR-TEQ: TCDD equivalent. Blue columns are men data and red columns are women data.

Table 4. The serum levels of dioxin-like activity of Greenlandic male Inuit and European men*

		Greenlandic					European		
		Nuuk[1]	Sisimiut[1]	Qaannaq[1]	Tasiilaq[2]	Tasiilaq[3]	Warsaw[3]	Sweden[3]	Kharkiv[3]
AhR-TEQ (pg/g lipid)	n	21	42	38	38	25	99	76	80
	median	166	189	110	240	294	312	428	337
	% agonist	79	88	100	97	100	100	95	100
AhRcomp (RLU/µg protein)	n	38	51	43	38	25	99	78	86
	median	0.78	1.21	1.35	1.04	1.32	0.96	0.93	0.82
	% add/syn	0	44	54	29	36	3	6.4	18
	% antagonist	32	4	2.3	32	0	8	12	34

* Adapted from (26,27)
[1]: Data from AMAP (2002-2005). [2]: Data from AMAP (2000-2002). [3]: Data from INUENDO (2002-2004).
AhR-TEQ: TCDD equivalent.
% agonist: percent of samples eliciting a significant increase in AhR transactivity compared to the solvent control.
AhRcomp: competitive AhR transactivity of serum extract + 60 pM TCDD, the AhR-CALUX response of 60 pM TCDD was set to 1.
% add/syn: percent of samples responding with a further increase of the 60pM TCDD induced AhR-mediated transactivity.
% antagonist: percent of samples responding with a decrease of the 60pM TCDD induced AhR-mediated transactivity.

that the profile of POPs in the body is different between Greenlandic Inuit and Europeans.

In a pilot study, we also compared the plasma POPs related dioxin-like activity between Greenlandic Inuit and young Danish women. Sixty-four percent of the serum samples from young Danish women elicited significant induced AhR transactivity and the median AhR-TEQ was 152 pg/g lipid (25), being slightly lower than that of Greenlandic Inuit (median: 207 pg/g lipid). Taking into consideration the very low plasma PCB concentrations in young Danish women compared to Greenlandic Inuit (172 µg/kg lipid vs. 2051 µg/kg lipid), we suggested that exposure to dioxins and DLCs might contribute more to the net AhR transactivity than the bioaccumulated PCBs for the Danish women. We further suggested that the composition and levels of plasma POPs, geographical location and diet have a high impact on plasma AhR transactivity.

Correlations of serum dioxin-like activity and POP biomarkers and /or lifestyle factors in Greenlandic Inuit men and European men

Because the measured serum/plasma dioxin-like activity (AhR-TEQ) was obtained from the POP fraction and POPs have been shown to be related to age, diet and lifestyle (50,51), the study was also intended to evaluate whether the serum dioxin-like activity was associated with serum POP concentrations (14 PCBs and 10 organochlorine pesticides) and/or lifestyle factors. Associations between the AhR transactivities and lifestyle factors such as age, intake of marine food and smoker years were observed, indicating that comparison of different study populations requires the inclusion of age, diet and lifestyle factors (25,27).

We also evaluated the association of serum dioxin-like activity and POP biomarkers and lifestyle factors stratified on the Inuit and the pooled European populations (Warsaw + Sweden + Kharkiv). A positive correlation between AhR-TEQ and PCB153 ($p = 0.001$) and age ($p = 0.057$) was observed for the pooled European men supporting a report showing positive correlation between serum DL-activity and age (52) while inverse correlation between age and AhR-TEQ ($p = 0.01$) was observed for the Inuit (table 5) being in accordance to the frequency of marine food intake and POPs bioaccumulation. These observations might partly explain that the differences in food intake contributing to the higher DL-activity found in Europeans compared to Inuit and suggest that the sources of body burden of dioxin-like compounds are different between Inuit and Europeans. Since Greenlandic Inuit are far from the dioxins' sources and have higher proportion of non-dioxin-like POPs that can inhibit the AhR (27,53,54) while the Europeans in general have lower non-dioxin-like POP but are closer to the sources of dioxin exposures, it might explain the higher serum dioxin-like activity observed for Europeans compared to the Greenlandic Inuit.

Using another clean-up method for serum samples it was recently reported that high levels of PCBs in Slovakian male serum samples were associated with a increased AhR mediated activity (55).

The relationship between the serum dioxin-like activity and sperm DNA fragmentation and apoptosis

The INUENDO project also assessed the sperm DNA damage and sperm apoptosis as well as semen quality (48). Unexpectedly, a significant lower level of DNA damage was found in sperm DNA from Inuit compared with European samples (56). The serum AhR-TEQ and AhRcomp negatively correlated tothe sperm DNA damage for the Greenlandic Inuit, suggesting that higher serum AhR mediated activities tend to result in lower sperm DNA damage level. It can be speculated that the observed inverse correlation between serum DL-activity and sperm DNA damage for the Inuit might have a protective effect due to the metabolism of compounds potentially stimulating sperm DNA damage, and thus partly be responsible for their lower sperm DNA damage level. In contrast, for the combined European groups positive correlations were

Table 5. The correlation of serum dioxin-like activity and the POP proxy markers, age and intake of seafood of Inuit and Europeans*

	Inuit			European[a]		
	n	r_s	p	n	r_s	p
PCB153						
AhR-TEQ	70	.14	.25	**255**	**.20**	**.001**
AhRcomp	73	-.03	.83	**254**	**-.13**	**.04**
***p,p'*-DDE**						
AhR-TEQ	70	.15	.21	255	-.09	.15
AhRcomp	73	-.09	.46	254	.01	.89
Age						
AhR-TEQ	**68**	**-.30**	**.01**	249	.12	.057
AhRcomp	73	-.20	.09	256	-.07	.26
Seafood						
AhR-TEQ	66	-.15	.22	168	.02	.77
AhRcomp	71	-.18	.14	174	-.02	.81

* Adapted from (26)
[a]: Combined data of Warsaw, Sweden and Kharkiv
r_s: Spearman correlation coefficient

observed between the sperm DNA damage and AhRcomp (57). These positive correlations of serum xenobiotic induced receptor activity and sperm DNA damage also suggest that Europeans might be more sensitive to the xenobiotics. Moreover, the intake of antioxidant selenium and n-3 fatty acids was much higher for the Inuit than the Caucasians (58,59) and it is known that selenium and n-3 fatty acids can have protective effects on human health. However, whether genetic differences and/or other ethnic cofactors are involved need further studies to elucidate this phenomenon. In addition, further studies are required to identify possible factors invol in the correlations found between POP related AhR effect and sperm DNA damage (57,60).

The relationship between the serum dioxin-like activity and breast cancer in Greenlandic Inuit

Breast cancer (BC) is the most common cancer for women in the western world. From very few cases an extraordinary increase in BC was observed in the Inuit population of Greenland and Canada although still lower than in western populations. In a recent study aiming to evaluate the association between serum levels of POPs and perfluorinated compounds (PFCs) in Greenlandic Inuit BC cases and their controls, and whether the combined POP related effect on nuclear hormone receptors affect BC risk, we observed that the BC cases had lower AhR induced serum dioxin-like activity than controls (61). We speculate that the higher serum sumPOP/sumPCB levels found in cases may have an inhibitory effect on the AhR activity and explain the observed difference between cases and controls. Non-dioxin-like PCBs are shown to have the potential to antagonize the AhR pathway (54,62). Moreover, we found in an earlier study that Inuit with high serum levels of PCB had lower AhR-TEQ compared to Europeans with lower PCB levels (26). Dioxins are reported to have antiestrogenic potentials (63-65). It can be speculated whether the lower dioxin-like AhR-TEQ level in cases could play a role in BC risk via its lower antiestrogenic potential. Alternatively, it may be explained by differences between cases and controls regarding metabo-

lic pathways involved in the biotransformation of both mono-ortho PCBs and estrogens as suggested by Demers et al. 2002 (66).

Conclusions and perspectives

The *in vitro* results showed that some pesticides, plastic components and phytoestrogens might have an effect on the AhR function, and the combined effect of compounds with no or weak AhR potency cannot be ignored, and that the combined effect of the complex mixture of compounds present in human blood must be taken into consideration for risk assessment.

The results from the wastewater study indicated that the AhR-mediated transactivity can be used for a more sensitive biomonitoring of effects of effluents from STPs as a supplement to chemical analyses, and as a tool to evaluate the effectiveness of treatment within the STP. A significant effect was detected in effluent samples and although lower than the influent it is indicating that the wastewater treatment processes is not efficient enough to prevent contamination of environmental surface waters and thus the release of dioxins and dioxin-like compounds from STPs to the environment. Whether this contamination by dioxins and dioxin-like compounds might have adverse effects on human health as well as the ecosystem needs further research.

The *ex vivo* results from our human studies suggested that the serum dioxin-like activity of the complex mixture of DL-compounds seems to reflect the POP profile in human blood. Greenlandic Inuit had lower serum AhR-TEQ level compared to European men, probably due to long distance from the DLCs sources and therefore UV degradation of the high potent dioxin and/or the high level of non-DL POPs and/or dietary habit. We have the experience that e.g. high level of non-DL PCBs can have an inhibitory effect on AhR transactivity. PCBs do generally biomagnify through the aquatic food chains. However, the biomagnifications of PCBs in the aquatic food chain is congener-specific evidenced by that the concentration of dioxin-like PCBs (e.g. PCB77, PCB 126 and PCB169) showed no obvious biomagnifications while non-dioxin-like PCBs such as PCB 138 was biomagnified (67,68). Owing to this selective biotransformation effect during the bioaccumulation in the food chain, the concentration of some dioxin-like PCBs might be reduced whereas non-dioxin-like PCBs accumulate causing the variation of the composition of PCBs in the body of Inuit. This selective bioaccumulation of POPs in the food chain may contribute to the negative correlation between serum POPs and dioxin-like activity observed in Greenlandic Inuit, and lifestyle, genetics and age must be taken into account for the assessment of dioxin-like activity in epidemiological studies.

Hence the AhR-mediated transactivation bioassay provides a cost-effective and integrated screening for determining dioxin-like activity for a wide range of compounds and complement chemical instrumental analysis and *in vivo* studies, being a screening tool for detecting the dioxin-like activity of human and other biological samples, environmental and commercial chemicals.

The results mentioned in this review were based on the *in vitro* and *ex vivo* data. The *in vivo* analyses take into account all possible biological factors that can influence stress responses at all levels of life, and incorporate many important processes (pharmacokinetics, metabolism, interactions with multiple binding and transport proteins which can affect uptake into target organs). These *in vivo* processes are limited and therefore elucidated to a less degree in *in vitro* analyses. We found that some pesticides, plastic components and phytoestrogens affect the AhR function *in vitro*. It is interesting to study the effect of these compounds and their mixture on the AhR function *in vivo* in e.g. animal studies. It is necessary to study the bioavailability and prediction of the whole-organism responses in humans. Our *ex vivo* studies of the effect on AhR function of the complex mixtures of POPs found in human serum is a model to mimic the physiological potential of POPs to affect a cellular mechanism, e.g. AhR function, and the possible health risk.

We observed a significant difference and different feature of correlations of the level of sperm DNA damage and serum dioxin-like activity between Greenlandic Inuit and European Caucasians. But little is known about the differences in total anti-oxidative capacity and gene polymorphisms between Inuit and Caucasians for the genes involved in POP metabolism. Currently, we are determining the gene polymorphisms of CYP1A1, CYP1A2 and CYP1B1 in Inuit and Caucasians. Possibly these genetic data can contribute to elucidate whether the different level of sperm DNA damage do relate to different genotypes of genes involved in metabolic activation of POPs.

Acknowledgements

The authors thank all those who have contributed to the reported data. These include researchers associated with the Centre for Arctic Environmental Medicine & Unit of Cellular and Molecular Toxicology, Department of Public Health, Aarhus University: postdoctoral researchers Tanja Kruger and Mandana Ghisari, laboratory assistant Birgitte Sloth Andersen and Dorte Olsson. Also thanked are Associate Professor Bente Deutch, Associate Professor Jens C Hansen, senior scientist Anne Marie Vinggaard, scientist Peter Laier of Danish Veterinary and Food Administration, Professor Pierre Ayotte and Professor Eric Dewailly of Institut National de Sante Publique du Quebec, Canada as well as the colleagues in the INUENODO project www.inuendo.dk. The studies were carried out with financial support from the Danish Ministry of the Environment - Danish Environmental Protection Agency (DANCEA and HORM-DMAU project), the European Union (ENDOMET project and INUENDO project), Danish Research Agency (DAN-ED project), AMAP Human Health Effects Monitoring Programme, Danish Medical Research Council, International Polar Year Committee and Commisson for Scientific Research in Greenland.

Further information:
Manhai Long ml@mil.au.dk
Eva Bonefeld-Jørgensen ebj@mil.au.dk

Referencer

1. Steenland K, Bertazzi P, Baccarelli A, Kogevinas M. *Dioxin revisited: developments since the 1997 IARC classification of dioxin as a human carcinogen.* Environ Health Perspect, 2004;112(13):1265-8.

2. Lindstrom G, Hooper K, Petreas M, Stephens R, Gilman A. *Workshop on perinatal exposure to dioxin-like compounds. I. Summary.* Environ Health Perspect 1995;103(Suppl 2:135-42.

3. Van den Berg M, Birnbaum L, Bosveld AT, Brunstrom B, Cook P, Feeley M, Giesy JP, Hanberg A, Hasegawa R, Kennedy SW, Kubiak T, Larsen JC, van Leeuwen FX, Liem AK, Nolt C, Peterson RE, Poellinger L, Safe S, Schrenk D, Tillitt D, Tysklind M, Younes M, Waern F, Zacharewski T. *Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife.* Environ Health Perspect 1998;106(12):775-92.

4. van den Berg M, Peterson RE, Schrenk D. *Human risk assessment and TEFs.* Food Addit Contam 2000;17(4):347-58.

5. Poland A, Knutson JC. *2,3,7,8-tetrachloro-dibenzo-p-dioxin and related halogenated aromatic hydrocarbons: examination of the mechanism of toxicity.* Annu Rev Pharmacol Toxicol 1982;22:517-54.

6. Schmidt JV, Bradfield CA. *Ah receptor signaling pathways.* Annu Rev Cell Dev Biol 1996;12:55-89.

7. Carver LA, Hogenesch JB, Bradfield CA. *Tissue specific expression of the rat Ah-receptor and ARNT mRNAs.* Nucleic Acids Res 1994;22(15):3038-44.

8. Dolwick KM, Schmidt JV, Carver LA, Swanson HI, Bradfield CA. *Cloning and expression of a human Ah receptor cDNA.* Mol Pharmacol 1993;44(5):911-7.

9. Hankinson O. *The aryl hydrocarbon receptor complex.* Annu Rev Pharmacol Toxicol 1995; 35:307-40.

10. Whitlock JP Jr. *Induction of cytochrome P4501A1.* Annu Rev Pharmacol Toxicol 1999; 39:103-25.

11. Denison MS, Heath-Pagliuso S. *The Ah receptor: a regulator of the biochemical and toxicological actions of structurally diverse chemicals.* Bull Environ Contam Toxicol 1998;61(5):557-68.

12. Ciolino HP, Daschner PJ, Yeh GC, *Dietary flavonols quercetin and kaempferol are ligands of the aryl hydrocarbon receptor that affect CYP1A1 transcription differentially.* Biochem J 1999;340(Pt 3):715-22.

13. Van den Berg M, Birnbaum LS, Denison M, De Vito M, Farland W, Feeley M, Fiedler H, Hakansson H, Hanberg A, Haws L, Rose M, Safe S, Schrenk D, Tohyama C, Tritscher A, Tuomisto J, Tysklind M, Walker N, Peterson RE. *The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds.* Toxicol Sci 2006;93(2):223-41.

14. Bonefeld Jorgensen EC, Ayotte P. *Toxicological properties of persistent organic pollutants and related health effects of concern for the arctic populations.* AMAP Assessment 2002: Human Health in the Arctic, 2003. Chapter 6 p. 57-74.

15. Van Overmeire I, Clark GC, Brown DJ, Chu MD, Cooke WM, Denison MS, Baeyene W, Srebrnik S, Goeyens L. *Trace contamination with dioxin-like chemicals: evaluation of bioassay-based TEQ determination for hazard assessment and regulatory responses.* Environmental Science & Policy 2001;4(6): 345-57.

16. Aarts JM, Denison MS, Cox MA, Schalk MA, Garrison PM, Tullis K, de Haan LH, Brouwer A. *Species-specific antagonism of Ah receptor action by 2,2',5,5'-tetrachloro- and 2,2',3,3'4,4'-hexachlorobiphenyl.* Eur J Pharmacol 1995;293(4):463-74.

17. Long M, Laier P, Vinggaard AM, Andersen HR, Lynggaard J, Bonefeld-Jorgensen EC. *Effects of currently used pesticides in the AhR-CALUX assay: comparison between the human TV101L and the rat H4IIE cell line.* Toxicology 2003;194(1-2):77-93.

18. Safe SH. *Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment.* Crit Rev Toxicol 1994;24(2):87-149.

19. Behnisch PA, Hosoe K, Sakai S, *Bioanalytical screening methods for dioxins and dioxin-like compounds a review of bioassay/biomarker technology.* Environ Int 2001;27(5):413-39.

20. Windal I, Van Wouwe N, Eppe G, Xhrouet C, Debacker V, Baeyens W, De Pauw E, Goeyens L. *Validation and interpretation of CALUX as a tool for the estimation of dioxin-like activity in marine biological matrixes.* Environ Sci Technol 2005;39(6):1741-8.

21. Garrison PM, Tullis K, Aarts JM, Brouwer A, Giesy JP, Denison MS. *Species-specific recombinant cell lines as bioassay systems for the detection of 2,3,7,8-tetrachlorodibenzo-p-dioxin-like chemicals.* Fundam Appl Toxicol 1996;30(2):194-203.

22. Kruger T, Long M, Bonefeld-Jorgensen EC, *Plastic components affect the activation of the aryl hydrocarbon and the androgen receptor.* Toxicology 2008;246(2-3):112-23.

23. Anderson GR, Hasan A, Yin H, Qadri I, Quattrochi LC, *Regulation of the CYP1A1 gene by 2,3,7,8-tetrachlorodibenzo-p-dioxin but not by beta-naphthoflavone or 3-methylcholanthrene is altered in hepatitis C virus replicon-expressing cells.* Mol Pharmacol 2006;-70(3):1062-70.

24. Bonefeld-Jorgensen EC, Long M, Hofmeister MV, Vinggaard AM. *Endocrine disrupting potentials of bisphenol A, bisphenol A dimethacrylate, 4-n-nonylphenol and 4-n-octylphenol in vitro-new data and a brief review.* Environ Health Perspect 2007;115 Suppl 1:69-76.

25. Bonefeld-Jorgensen EC, Long M. *Dioxin-like activity in the blood of Greenlandic Inuit and Danish women: a pilot study.* Int J Circumpolar Health 2010;69(2):181-94.

26. Long M, Andersen BS, Lindh CH, Hagmar L, Giwercman A, Manicardi GC, Bizzaro D, Spano M, Toft G, Pedersen HS, Zvyezday V, Bonde JP, Bonefeld-Jorgensen EC, *Dioxin-like activities in serum across European and Inuit populations.* Environ Health 2006;5:14.

27. Long M, Deutch B, Bonefeld-Jorgensen EC, *AhR transcriptional activity in serum of Inuits across Greenlandic districts.* Environ Health 2007:6:32.

28. Windal I, Denison MS, Birnbaum LS, Van Wouwe N, Baeyens W, Goeyens L. *Chemically activated luciferase gene expression (CALUX) cell bioassay analysis for the estimation of dioxin-like activity: critical parameters of the CALUX procedure that impact assay results.* Environ Sci Technol 2005;39(19):7357-64.

29. Birkhoj M, Nellemann C, Jarfelt K, Jacobsen H, Andersen HR, Dalgaard M, Vinggaard AM, *The combined antiandrogenic effects of five commonly used pesticides.* Toxicol Appl Pharmacol 2004;201(1):10-20.

30. Payne J, Rajapakse N, Wilkins M, Kortenkamp A. *Prediction and assessment of the effects of mixtures of four xenoestrogens.* Environ Health Perspect 2000;108(10): 983-7.

31. Kortenkamp A. *Ten years of mixing cocktails: a review of combination effects of endocrine-disrupting chemicals.* Environ Health Perspect 2007;115 Suppl 1:98-105.

32. Payne J, Scholze M, Kortenkamp A. *Mixtures of four organochlorines enhance human breast cancer cell proliferation.* Environ Health Perspect 2001;109(4):391-7.

33. Kusk KO, Kruger T, Long M, Taxvig C, Lykkesfeldt AE, Frederiksen H, Andersson AM, Andersen HR, Hansen KM, Nellemann C, Bonefeld-Jorgensen EC. *Endocrine potency of wastewater: contents of endocrine disrupting chemicals and effects measured by in vivo and in vitro assays.* Environ Toxicol Chem 2011;30(2):413-26.

34. Brack W, Segner H, Möder M, Schüürmann G. *Fixed-effect-level toxicity equivalents - A suitable parameter for assessing ethoxyresorufin-o-deethylase induction potency in complex environmental samples.* Environ Toxicol Chem 2000;19(10):2493-501.

35. Engwall M, Broman D, Ishaq R, Näf C, Zebühr Y, Brunström B. *Toxic potencies of lipophilic extracts from sediments and settling particulate matter (SPM) collected in a PCB-contaminated river system.* Environ Toxicol Chem 1999;15(2):213-22.

36. MacLeod SL, McClure EL, Wong CS, *Laboratory calibration and field deployment of the polar organic chemical integrative sampler for pharmaceuticals and personal care products in wastewater and surface water.* Environ Toxicol Chem 2007;26(12): 2517-29.

37. Matthiessen P, Arnold D, Johnson AC, Pepper TJ, Pottinger TG, Pulman KG, *Contamination of headwater streams in the United Kingdom by oestrogenic hormones from livestock farms.* Sci Total Environ 2006;367(2-3): 616-30.

38. Mazzella N, Dubernet JF, Delmas F. *Determination of kinetic and equilibrium regimes in the operation of polar organic chemical integrative samplers. Application to the passive sampling of the polar herbicides in aquatic environments.* J Chromatogr A 2007;1154(1-2):42-51.

39. Zhang Z, Hibberd A, Zhou JL. *Analysis of emerging contaminants in sewage effluent and river water: comparison between spot and passive sampling.* Anal Chim Acta 2008; 607(1):37-44.

40. Butler Walker J, Seddon L, McMullen E, Houseman J, Tofflemire K, Corriveau A, Weber JP, Mills C, Smith S, Van Oostdam J. *Organochlorine levels in maternal and umbilical cord blood plasma in Arctic Canada.* Sci Total Environ 2003;302(1-3):27-52.

41. Cornwell T, Cohick W, Raskin I. *Dietary phytoestrogens and health.* Phytochemistry 2004;65(8):995-1016.

42. Ishihara A, Rahman FB, Leelawatwattana L, Prapunpoj P, Yamauchi K. *In vitro thyroid hormone-disrupting activity in effluents and surface waters in Thailand.* Environ Toxicol Chem 2009;28(3):586-94.

43. Ma M, Li J, Wang Z. *Assessing the detoxication efficiencies of wastewater treatment processes using a battery of bioassays/biomarkers.* Arch Environ Contam Toxicol 2005;49(4): 480-7.

44. Murata T, Yamauchi K. *3,3',5-Triiodo-L-thyronine-like activity in effluents from domestic sewage treatment plants detected by in vitro and in vivo bioassays.* Toxicol Appl Pharmacol 2008;226(3):309-17.

45. Van der Linden SC, Heringa MB, Man HY, Sonneveld E, Puijker LM, Brouwer A, Van der Burg B. *Detection of multiple hormonal activities in wastewater effluents and surface water, using a panel of steroid receptor CALUX bioassays.* Environ Sci Technol 2008; 42(15):5814-20.

46. Chang HS, Choo KH, Lee B, Choi SJ. *The methods of identification, analysis, and removal of endocrine disrupting compounds (EDCs) in water.* J Hazard Mater 2009;172(1): 1-12.

47. AMAP, *AMAP Assessment Report: Arctic Pollution Issues. Arctic Monitoring and assessment Programme (AMAP).* http://www.amap.no, 1998: p. xii+859 pages.

48. Bonde JP, Toft G, Rylander L, Rignell-Hydbom A, Giwercman A, Spano M, Manicardi GC, Bizzaro D, Ludwicki JK, Zvyezday V, Bonefeld-Jorgensen EC, Pedersen HS, Jonsson BA, Thulstrup AM. *Fertility and markers of male reproductive function in Inuit and European populations spanning large contrasts in blood levels of persistent organochlorines.* Environ Health Perspect 2008;116(3):269-77.

49. Jonsson BA, Rylander L, Lindh C, Rignell-Hydbom A, Giwercman A, Toft G, Pedersen HS, Ludwicki JK, Goralczyk K, Zvyezday V, Spano M, Bizzaro D, Bonefeld-Jorgensen EC, Manicardi GC, Bonde JP, Hagmar L. *Inter-population variations in concentrations, determinants of and correlations between 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-bis (p-chlorophenyl)-ethylene (p,p'-DDE): a cross-sectional study of 3161 men and women from Inuit and European populations.* Environ Health 2005; 4:27.

50. Bonefeld-Jorgensen EC. *Biomonitoring in Greenland: human biomarkers of exposure and effects - a short review.* Rural Remote Health 2010;10(2):1362.

51. James RA, Hertz-Picciotto I, Willman E, Keller JA, Charles MJ. *Determinants of serum polychlorinated biphenyls and organochlorine pesticides measured in women from the child health and development study cohort, 1963-1967.* Environ Health Perspect 2002;110(7): 617-24.

52. Dhooge W, van Larebeke N, Koppen G, Nelen V, Schoeters G, Vlietinck R, Kaufman JM, Comhaire F. *Serum Dioxin-like Activity Is Associated with Reproductive Parameters in Young Men from the General Flemish Population.* Environ Health Perspect 2006;114(11): 1670-6.

53. Chen G, Bunce NJ. *Interaction between halogenated aromatic compounds in the Ah receptor signal transduction pathway.* Environ Toxicol 2004;19(5):480-9.

54. Suh J, Kang JS, Yang KH, Kaminski NE. *Antagonism of aryl hydrocarbon receptor-dependent induction of CYP1A1 and inhibition of IgM expression by di-ortho-substituted polychlorinated biphenyls.* Toxicol Appl Pharmacol 2003;187(1):11-21.

55. Pliskova M, Vondracek J, Canton RF, Nera J, Kocan A, Petrik J, Trnovec T, Sanderson T, van den Berg M, Machala M. *Impact of polychlorinated biphenyls contamination on estrogenic activity in human male serum.* Environ Health Perspect 2005;113(10):1277-84.

56. Stronati A, Manicardi GC, Cecati M, Bordicchia M, Ferrante L, Spano M, Toft G, Bonde JP, Jonsson BAG, Rignell-Hydbom A, Rylander L, Giwercman A, Pedersen HS, Bonefeld-Jorgensen EC, Ludwicki JK, Lesovoy V, Sakkas D, Bizzaro D. *Relationships between sperm DNA fragmentation, sperm apoptotic markers and serum levels of CB-153 and p,p'-DDE in European and Inuit populations.* Reproduction 2006;132(6):949-58.

57. Long M, Stronati A, Bizzaro D, Kruger T, Manicardi GC, Hjelmborg PS, Spano M, Giwercman A, Toft G, Bonde JP, Bonefeld-Jorgensen EC. *Relation between serum xenobiotic-induced receptor activities and sperm DNA damage and sperm apoptotic markers in European and Inuit populations.* Reproduction 2007:133(2):517-30.

58. Hansen JC, Deutch B, Pedersen HS. *Selenium status in Greenland Inuit.* Sci Total Environ, 2004;331(1-3):207-14.

59. Van Oostdam J, Tremblay N. *Biological Monitoring: Human Tissue Levels of Environmental Contaminants, Chapter 5* in *AMAP Assessment 2002: Human Health in the Arctic.* AMAP, Editor. 2003, Arctic Monitoring and Assessment Programme (AMAP), P.O.Box 8100, N-0032 Oslo, Norway. (http://www.amap.no), xiv+137pp: Oslo, Norway, p. 31-51.

60. Kruger T, Spano M, Long M, Eleuteri P, Rescia M, Hjelmborg PS, Manicardi GC, Bizzaro D, Giwercman A, Toft G, Bonde JP, Bonefeld-Jorgensen EC. *Xenobiotic activity in serum and sperm chromatin integrity in European and inuit populations.* Mol Reprod Dev 2008;75(4):669-80.

61. Bonefeld-Jorgensen EC, Long M, Bossi R, Ayotte P, Asmund G, Kruger T, Ghisari M, Mulvad G, Kern P, Nzulumiki P, Dewailly E. *Perfluorinated compounds are related to breast cancer risk in Greenlandic Inuit: A case control study.* Environ Health 2011;10(1):88.

62. Chu I, Lecavalier P, Hakansson H, Yagminas A, Valli VE, Poon P, Feeley M. *Mixture effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin and polychlorinated biphenyl congeners in rats.* Chemosphere 2001;43(4-7):807-14.

63. Fernandez P, Safe S. *Growth inhibitory and antimitogenic activity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in T47D human breast cancer cells.* Toxicol Lett 1992;61(2-3):185-97.

64. Safe S, Astroff B, Harris M, Zacharewski T, Dickerson R, Romkes M, Biegel L. *2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and related compounds as antioestrogens: characterization and mechanism of action.* Pharmacol Toxicol 1991;69(6):400-9.

65. Safe S, Harris M, Biegel L, Zacharewski T. *Mechanism of Action of TCDD as an Antiestrogen in Transformed Human Breast Cancer and Rodent Cell Lines*, in *Banbury Report 35: Biological Basis for Risk Assessment of Dioxin and Related Compounds*. B.R. 35, Editor. 1991, Cold Spring Harbor Laboratory Press.

66. Demers A, Ayotte P, Brisson J, Dodin S, Robert J, Dewailly E. *Plasma concentrations of polychlorinated biphenyls and the risk of breast cancer: a congener-specific analysis.* Am J Epidemiol 2002;155(7):629-35.

67. IPCS, *Concise International Chemical Assessment Document 55: Polychlorinated biphenyls: human health aspects, 2003.* http://www.inchem.org/documents/cicads/cicads/cicad55.htm

68. Koslowski SE, Metcalfe CD, Lazar R, Haffner GD. *The distribution of 42 PCBs, including three coplanar congeners, in the food web of the western basin of Lake Erie.* Journal of Great Lakes Research 1994;20:260-70.

Set på internet

Rapporter

Allergi

Inhalation exposure to fragrance allergens: Are consumers at risk for respiratory allergies, RIVM 2011.
http://www.rivm.nl/bibliotheek/rapporten/340301004.html

Antibiotikaresistens

Workshop presentations - "Challenges and Solutions in the Development of New Diagnostic Tests to Combat Antimicrobial Resistance", Bruxelles 28.-29. september 2011.
http://ec.europa.eu/research/health/infectious-diseases/antimicrobial-drug-resistance/events01-presentations_en.html

Arbejdsmiljø

Arbejdsmiljø og helbred i Danmark 2010, Det Nationale Forskningscenter for Arbejdsmiljø 2011.
http://www.arbejdsmiljoforskning.dk/da/arbejdsmiljoedata/arbejdsmiljo-og-helbred

Børn

International Conference on Non-Ionizing Radiation and Children's Health, 18.-20. maj 2011, Ljubljana, Slovenien. Presentations and poster abstracts.
http://www.icnirp.org/Kids/kids&NIRa.htm

Summary of Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals, World Health Organization 2011.
http://www.who.int/ceh/publications/health_risks_exposure_chemicals/en/index.html

Forskning

Danmarks Forskningspolitiske Råds Årsrapport 2010, august 2011.
Forsknings- og Innovationsstyrelsen, august 2011.
http://www.fi.dk/publikationer/2011/danmarks-forskningspolitiske-raads-aarsrapport/

Evaluering af virkemidlet "forskningsprojekter" i Det Frie Forskningsråd, Forsknings- og Innovationsstyrelsen, oktober 2011.
http://www.fi.dk/publikationer/2011/forskningsprojekter/Hovedrapport%202011.pdf

Det Strategiske Forskningsråd: Programkomiteen for Bæredygtig Energi og Miljø. Statusrapport 2011.
Forsknings- og Innovationsstyrelsen, august 2011.
http://www.fi.dk/publikationer/2011/statusrapport-2011/

Tal om forskning, 2010, Forsknings- og Innovationsstyrelsen, oktober 2011.
http://www.fi.dk/publikationer/2011/tal-om-forskning-2010/

Fødevarer

Clostridium perfringens associated with food borne disease: final report, RIVM, 2011.
http://www.rivm.nl/bibliotheek/rapporten/330371005.html

Data collection for the identification of emerging risks related to food and feed, EFSA, august 2011.
http://www.efsa.europa.eu/en/supporting/pub/185e.htm

Estimation of the relative contribution of different food and animal sources to human Salmonella infections in the European Union. External scientific report, august 2011. Se rapporten på EFSAs hjemmeside.
http://www.efsa.europa.eu/en/supporting/pub/184e.htm?WT.mc_id=EFSAHL01&emt=1

Scientific Opinion on the risks for animal and public health related to the presence of *Alternaria* toxins in feed and food. EFSA, oktober 2011.
http://www.efsa.europa.eu/en/efsajournal/pub/2407.htm

Update on furan levels in food from monitoring years 2004-2010 and exposure assessment, EFSA, september 2011.
http://www.efsa.europa.eu/en/efsajournal/pub/2347.htm

Indemiljø

Climate Change, the Indoor Environment, and Health, Institute of Medicine of The National Academies, juni 2011.
http://www.iom.edu/Reports/2011/Climate-Change-the-Indoor-Environment-and-Health.aspx

Kemiske stoffer

Assessment of environmental contaminants' neurotoxicity: in vitro and in vivo experimental studies. Ph.d. afhandling, Karolinska Institutet, 2011.
http://publications.ki.se/jspui/handle/10616/40678

Brominated Flame Retardants (BFR) in the Nordic Environment, TemaNord 201:528, Nordisk Ministerråd.
http://www.norden.org/sv/publikationer/publikationer/2011-528

Emissions of mercury, PAHs, dioxins and PCBs related to NFR 3 "Solvent and Other Product Use in Nordic Countries", Nordisk Ministerråd, 2011.
http://www.norden.org/sv/publikationer/publikationer/2011-549

Endotoxins. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemical and the Dutch Expert Committee on Occupational Safety, 2011.
http://gupea.ub.gu.se/handle/2077/26596

Human Health Risk Assessment of Combined Exposures to Chemicals, IMM rapport 3/2011. Institütet för Miljömedicin, Stockholm, 2011.
http://ki.se/ki/jsp/polopoly.jsp?d=8459&a=9149&l=sv

Kortlægning af kemiske stoffer i tekstiler. Kortlægning af kemiske stoffer i forbrugerprodukter 113, Miljøstyrelsen 2011.
http://www.mst.dk/Publikationer/Publikationer/2011/09/978-87-92779-37-3.htm

Kortlægning og sundhedsmæssig vurdering (kun allergi) af krom i lædersko, Kortlægning af kemiske stoffer i forbrugerprodukter 112, Miljøstyrelsen 2011.
http://www.mst.dk/Publikationer/Publikationer/2011/08/978-87-92779-21-2.htm

Sources of exposure to Bisphenol A. IMM rapport 2/2011, Institütet för Miljömedicin, Stockholm, 2011.
http://ki.se/ki/jsp/polopoly.jsp?d=8459&a=9149&l=sv

Toxicological and Health Aspects of Bisphenol A Report of Joint FAO/WHO Expert Meeting 2.–5. november 2010 and Report of Stakeholder Meeting on Bisphenol A 1. november 2010, Ottawa, Canada, september 2011. Se rapporten på WHOs hjemmeside.
http://www.who.int/foodsafety/chem/chemicals/bisphenol/en/index.html

Klima

A climate-neutral lifestyle: Consumers lead the way in climate protection, Umweltbundesamt, 2011.
http://www.umweltdaten.de/publikationen/fpdf-l/4173.pdf

Luftforurening

Air pollution, genetic susceptibility and inflammation Focusing on cardiovascular effects in adults and respiratory effects in children. Ph.d. afhandling, Karolinska Institutet, 2011.
http://publications.ki.se/jspui/handle/10616/40541

Air Toxics Exposure from Vehicle Emissions at a U.S. Border Crossing: Buffalo Peace Bridge Study, Research Report 158, The Health Effects Institute, august 2011.
http://pubs.healtheffects.org/view.php?id=362

Determination of the Effects of Ambient Particulate Matter (Air Pollution) on Toll-like Receptor Signaling and Function in Human Dendritic Cells, Pilot Stusy Report, The Health Effects Institute, august 2011.
http://pubs.healtheffects.org/view.php?id=363

Emissions of transboundary air pollutants in the Netherlands 1990-2009: Informative Inventory Report 2011, RIVM 2011.
http://www.rivm.nl/bibliotheek/rapporten/

Hvad er effekten af miljøzoner for luftkvaliteten? - Vurdering for København, Frederiksberg, Aarhus, Odense, og Aalborg. Slutrapport. Faglig rapport nr. 830, Danmarks Miljøundersøgelser, 2011.
http://www2.dmu.dk/Pub/FR830.pdf

Particle Project Report 1008-2010 Particulate contribution from traffic in Copenhagen. NERI Technical Report no. 837, 2011.
http://www2.dmu.dk/Pub/FR837.pdf

Personal and Ambient Exposures to Air Toxics in Camden, New Jersey, Research Report 160, The Health Effects Institute, august 2011.
http://pubs.healtheffects.org/view.php?id=364

Supplerende målinger til luftovervågning under NOVANA - benzen og PAH. Teknisk rapport nr. 3, Aarhus Universitet, Nationalt Center for Miljø og Energi, 2011.
http://www2.dmu.dk/Pub/TR3.pdf

30 years of effect research, monitoring and modelling, United Nations Economic Commission for Europe Convention on Long-range Transboundary Air Pollution (CLRTAP) Working Group on Effects, august 2011.
http://www.umweltbundesamt.de/luft-e/index.htm

Nanomaterialer

Commission Recommendation of 18 October 2011 on the definition of nanomaterial. Official Journal of The European Union, Volume 54, oktober 2011.
http://eur-lex.europa.eu/JOHtml.do?uri=OJ:L:2011:275:SOM:EN:HTML

Environment and Human Health - Information Service, Umweltbundesamt, 2011.
http://www.umweltbundesamt.de/umid-e/index.htm

Impact of engineered nanomaterials on health: considerations for benefit-risk assessment. Joint JRC-EASAC Report, september 2011.
http://ihcp.jrc.ec.europa.eu/our_activities/nanotechnology/nanoreport-10-11/JRC-EASAC-report.pdf

Report synopsis.
http://ihcp.jrc.ec.europa.eu/our_activities/nanotechnology/nanoreport-10-11/JRC-EASAC-report-synopsis.pdf

Survey on basic knowledge about exposure and potential environmental and health risks for selected nanomaterials, Miljøstyrelsen, 2011.
http://www.mst.dk/Publikationer/Publications/2011/08/978-87-92779-09-0.htm

Nyhedsbreve

Arbejdstilsynets e- nyhedsbrev, august 2011.
http://arbejdstilsynet.dk/da/nyheder/nyhedsbrev/2011/nr-7-25-august-2011.aspx

COPHES and DEMOCOPHES nyhedsbrev.
http://www.eu-hbm.info/cophes/communication/july-newsletter

Environment and Human Health - Information Service, Umweltbundesamt, 2011.
http://www.umweltbundesamt.de/umid-e/index.htm

EU-INFORMATION nr. 4, oktober 2011.
http://www.fi.dk/publikationer/2011/eu-information-nr-4-oktober-2011/eu-information-nr-4-oktober-2011

Nanosafety newsletter, Observatory for Micro and NanoTechnologies.
http://www.omnt.fr/index.php/en/actualite/newsletter

Newsletter WHO CC nr. 10, august 2011.
http://www.gesundheitsamt-bw.de/MLS/EN/WHOCC/Seiten/Newsletter-WHOCC.aspx

Risikovurdering

Integrated Probabilistic Risk Assessment for carcinogens: A first exploration, RIVM, 2011.
Toxicogenomics in risk assesment, RIVM 2011.
http://www.rivm.nl/bibliotheek/rapporten/320121002.html

Støj

Safe and Sound - Guide to Hearing Conservation in the Music and Entertainment Industry, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, 2011.
http://www.baua.de/en/Publications/Expert-Papers/Gd10.html

The role of noise events in noise research, policy and practice (peaks, events or both): Report of expert meeting 25 and 26 October 2010, Utrecht, RIVM, august 2011.
http://www.rivm.nl/bibliotheek/rapporten/815120005.html

Zoonoser

Facts sheets fra EFSA oktober 2011:

EFSA explains zoonotic diseases: Food-borne zoonoses.
http://www.efsa.europa.eu/en/corporate/pub/factsheetfoodbornezoonoses.htm

EFSA explains zoonotic diseases: Zoonotic E. Coli.
http://www.efsa.europa.eu/en/corporate/pub/factsheetecoli.htm

EFSA explains zoonotic diseases: Campylobacter.
http://www.efsa.europa.eu/en/corporate/pub/factsheetcampylobacter.htm

EFSA explains zoonotic diseases: Antimicrobial Resistance.
http://www.efsa.europa.eu/en/corporate/pub/factsheetamr.htm

EFSA explains zoonotic diseases: Salmonella.
http://www.efsa.europa.eu/en/corporate/pub/factsheetsalmonella.htm

Flått og flåttbårne sykdommer. Lyme borreliose og skogflåttencefalitt i 2010, Folkehelseinstituttet i Norge 2011.
http://www.fhi.no/eway/default.aspx?pid=233&trg=MainArea_5661&MainArea_5661=5583:0:15,1134:1:0:0:::0:0

Healthy Animals, Healthy Canada, Council of Canadian Academies, 2011.
http://www.scienceadvice.ca/en/assessments/completed/animal-health.aspx

Andre rapporter

Abstracts of the 23rd Annual Conference of the International Society of Environmental Epidemiology (ISEE). September 13-16, 2011, Barcelona, Spanien.
http://ehp03.niehs.nih.gov/article/fetchArticle.action?articleURI=info%3Adoi/10.1289/ehp.isee2011

Collection of Extended Abstracts from: International conference on Energy, Environment and Health - Optimization of future Energy Systems, CEEH Scientific Report No. 9, 2011.
http://www.ceeh.dk/CEEH_Reports/Report_9

Description of the CEEH health effect model, CEEH Scientific Report No. 7a, 2011.
http://www.ceeh.dk/CEEH_Reports/Report_7a/CEEH_Report_7a_ver1.pdf

Guidelines for drinking-water quality, fourth edition, World Health Organization, 2011.
http://www.who.int/water_sanitation_health/publications/2011/dwq_guidelines/en/index.html

The use of alternatives to testing on animals for the REACH Regulation 2011, European Chemicals Agency, 2011.
http://echa.europa.eu/publications/alternatives_test_animals_2011_en.asp

WHO International Conference on Environmental and Occupational Determinants of Cancer: Interventions for Primary Prevention, 17.-18. marts 2011. Møderapport, baggrundspapir og præsentationer.
http://www.who.int/phe/news/events/international_conference/en/index.html

Kalender 2012

Der kan linkes til møder og konferencer via adressen:
http://miljoogsundhed.sst.dk/kalender/index.html

Januar

22.-26. januar: 17 th Conference on th Application of Air Pollution Meteorology, New Orleans, Louisiana.

Februar

19.-23. februar: GRF One Health Summit 2012 One Health - One Planet - One Future Risks and Opportunities, Davos, Schweiz.

Marts

2.-3. marts: The 5th International Conference: Ecological Chemistry 2012, Chisinau, Moldovien.

18.-23. marts: 10th International Congress on Occupational Health - Occupational Health for All: From Research to Practice, Cancun, Mexico.

19.-22. marts: Analyzing Risk: Science, Assessment, and Management, Boston MA.

19.-23. marts: Eighth International Conference on Air Quality - Science and Application, Athen, Grækenland.

26.-29. marts: 6th International Conference on Environmental Mutagens in Human Populations, Doha, Qatar.

April

2.-4. april: INRS Occupational Health Research Conference 2012: Health risks associated with mixed exposures, Nancy, Frankrig.

2.-4. april: INRS Occupational Health Research Conference 2012: Risks associated to nanoparticles and nanomaterials, Nancy, Frankrig.

19.-20. april: Workplace and Indoor Aerosols Conference, Lund, Sverige.

Maj

9.-11. maj: 7th International Workshop on Non Ionizing Radiation, Edinburgh, UK.

13.-18. maj: 13th International Congress of the International Radiation Protection Association, Glasgow (Scotland), UK.

13.-18. maj : World Congress on Water, Climate & Energy 2012, Dublin, Irland.

15.-17. maj: Urban Transport 2012, A Coruña, Spanien.

16.-18. maj: 20th International Conference on Modelling, Monitoring and Management of Air Pollution, A Coruña, Spanien

20.-24. maj: 6th SETAC World Congress / SETAC Europe 22nd Annual Meeting Securing a sustainable future: Integrating science, policy and people, Berlin, Tyskland.

21.-27. maj: IFEH 12th World Congress on Environmental Health: New Technologies, Healthy Human Being and Environment, Vilnius, Litauen.

22.-24. maj: Forest Fires 2012, New Forest, UK.

30. maj - 1. juni: The Contribution of Epigenetics in Pediatric Environmental Health San Francisco, Californien.

Juni

13.-16. juni: 11th European Society of Contact Dermatology Congress, Malmö, Sverige.

17.-20. juni: Congress of the European Societies of Toxicology Stockholm, Sverige.

17.-20 juni: 2nd Urban Environmental Pollution Conference, Amsterdam, Holland.

25.-28. juni: 3rd International Conference on Transport, Atmosphere and Climate, Prien am Chiemsee, Tyskland.

Juli

2.-4. juli: Environmental Impact 2012 - First International Conference on Environmental and Economic Impact on Sustainable Development. New Forest, UK.

2.-5. juli: 7th International Conference on the Science of Exposure Assessment (X2012) Edinburgh, Scotland.

8.-12. juli: Healthy Buildings 2012, Brisbane, Australien.

10.-12. juli: Water Pollution 2012, New Forest, UK.

18.-20. juli: Risk 2012: World Congress 3, Sydney, Australien.

August

6.-10. august 2012: 8th International Conference on Urban Climate - ICUC 8, Dublin, Irland.

18.-21. august: XXI World Congress on Asthma, Quebec, Canada.

26.-30. august: Twenty-Fourth Conference of the International Society for Environmental Epidemiology, Columbia, South Carolina, USA.

27.-30. august: World Cancer Congress, Montreal, Canada.

September

4.-7. september 2012: 6th International Conference on Nanotoxicology, Beijing, Kina.

19.-21. september: 8th International Conference on Simulation in Risk Analysis and Hazard Mitigation, Kroatien.

23.-26. september: Central European Symposium on Antimicrobials and Antimicrobial resistance. CESAR 2012, Kroatien.

23.-26. september: International Conference on Environmental Odour Monitoring & Control, Palermo, Italien.

30. september - 4. oktober: NIVA Occupational Lung Diseases - Prevention and Risk Factors, Särö, Sverige.

Oktober

1.-5. oktober: Niva Introduction to occupational epidemiology. Gentofte, DK.

21.- 26. oktober: Monte Verita - EMF Health Risk Research: Lessons Learned and Recommendations for the Future - Seven Years Later.

22.-25. oktober: NIVA Indoor air quality, health, comfort and productivity, Bergen, Norge.

28.-31. oktober: SENN2012 - International Congress on Safety of Engineered Nanoparticles and Nanotechnologies, Helsinki, Finland.

November

5.-9. november: 7th Conference of the World Mycotoxin Forum and XIIIth IUPAC International Symposium on Mycotoxins and Phycotoxins, Rotterdam, Holland.

13.-15. november: Nanosafe 2012, Grenoble, Frankrig.

NB! Bidrag til kalenderen modtages gerne, hib@sst.dk

Skriv til miljø og sundhed

skriv om forskningsresultater

skriv til synspunkt

skriv et mødereferat

send nye rapporter

husk også kalenderen

Ring, skriv eller send en e-mail til:

Hilde Balling
Sundhedsstyrelsen
Islands Brygge 67
2300 København S
tlf. 72 22 74 00, lokal 77 76
fax 72 22 74 11
e-mail hib@sst.dk

http://miljoogsundhed.sst.dk

også hvis du bare har en god idé!