



## Exposure to endocrine disrupting chemicals and childrens' health 内分泌かく乱化学物質への曝露と子どもの健康

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# 概要Outline

- 内分泌かく乱化学物質の定義  
Definition endocrine disrupting chemicals
- オーデンセ・子どもコホート疫学研究  
Odense Child Cohort
- 有機フッ素化合物(PFAS)  
Perfluoroalkyl substances
- フタル酸エステル類  
Phthalates
- 良いニュース、悪いニュース  
The good news, and the bad....
- 現在進行中の研究  
Ongoing research

# ホルモン(内分泌)の特徴

## Characteristics hormones

- ホルモンは、内分泌腺で産生され、血液中を移動し、通常はホルモン受容体が関与する複雑な相互作用シグナル伝達経路を経て、離れた細胞や組織に作用を及ぼす分子(生理活性物質)である。

Hormone is a molecule produced by an endocrine gland that travels through the blood to produce effects on distant cells and tissues via integrated complex interacting signalling pathways usually involving hormone receptors

- 50種類以上のホルモンおよびホルモン関連分子(生理活性物質)が存在する(サイトカイン、神経伝達物質)

More than 50 hormones and hormone-related molecules (cytokines and neurotransmitters)

視床下部  
バソプレッシン  
オキシトシンなど

**Hypothalamus**  
Production of  
antidiuretic hormone (ADH),  
oxytocin and regulatory  
hormones

**Pineal Gland**  
Melatonin

松果体  
メラトニン

下垂体  
副腎皮質刺激ホルモン  
甲状腺刺激ホルモン  
成長ホルモン  
卵巣刺激ホルモン  
卵胞刺激ホルモン  
など

**Pituitary Gland**  
Adenohypophysis (anterior lobe):  
Adrenocorticotrophic hormone,  
Thyroid stimulating hormone,  
Growth hormone, Prolactin,  
Follicle stimulating hormone,  
Luteinizing hormone,  
Melanocyte stimulating  
hormone,  
Neurohypophysis  
(posterior lobe):  
Release of oxytocin  
and ADH

**Parathyroid Glands**  
(on posterior surface of  
thyroid gland)  
Parathyroid hormone

副甲状腺  
副甲状腺ホルモン

甲状腺  
甲状腺ホルモン  
カルシトニン

**Thyroid Gland**  
Thyroxine  
Triiodothyronine  
Calcitonin

胸腺  
チモシン

**Thymus**  
(Undergoes atrophy  
during childhood)  
Thymosins

**Heart**  
Atrial natriuretic  
peptide

心臓  
心房性ナトリウム利尿ペプチド

**Kidney**  
Erythropoietin  
Calcitriol  
Renin

肝臓  
エリスロポエチン  
カルシトリオール  
レニン

副腎  
エピネフリン  
ノルエピネフリン  
コルチゾール  
コルチコステロン  
アルドステロン  
アンドロゲン

**Adrenal Glands**  
Each suprarenal gland is  
subdivided into:  
Suprarenal medulla;  
Epinephrine  
Norepinephrine  
Suprarenal cortex:  
Cortisol, corticosterone,  
aldosterone, androgens

消化管  
グレリン、コレシストキニン  
グルカゴン様ペプチド  
ペプチドYY

**Gastrointestinal Tract**  
Ghrelin, cholecystokinin,  
glucagon-like peptide,  
peptide YY

**Adipose Tissue**  
Leptin, adiponectin,  
others

脂肪組織  
レプチン、アディポネクチン

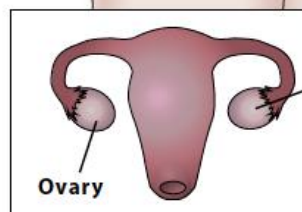
**Pancreatic Islets**  
Insulin, glucagon

膵ランゲルハンス島  
インシュリン、グルカゴン

**Testis**

**Gonads**  
Testes (male):  
Androgens (especially  
testosterone), inhibin  
Ovaries (female):  
Estrogens, progestins,  
inhibin

生殖腺  
雄：精巣 男性ホルモンなど  
雌：卵巣 女性ホルモンなど



ステロイドホルモン

Steroid hormone

Nucleus

核

1  
Receptor protein  
ホルモン受容体

3  
ホルモン受容体複合体

Hormone-receptor complex

DNA

mRNA

タンパク質の新しい合成

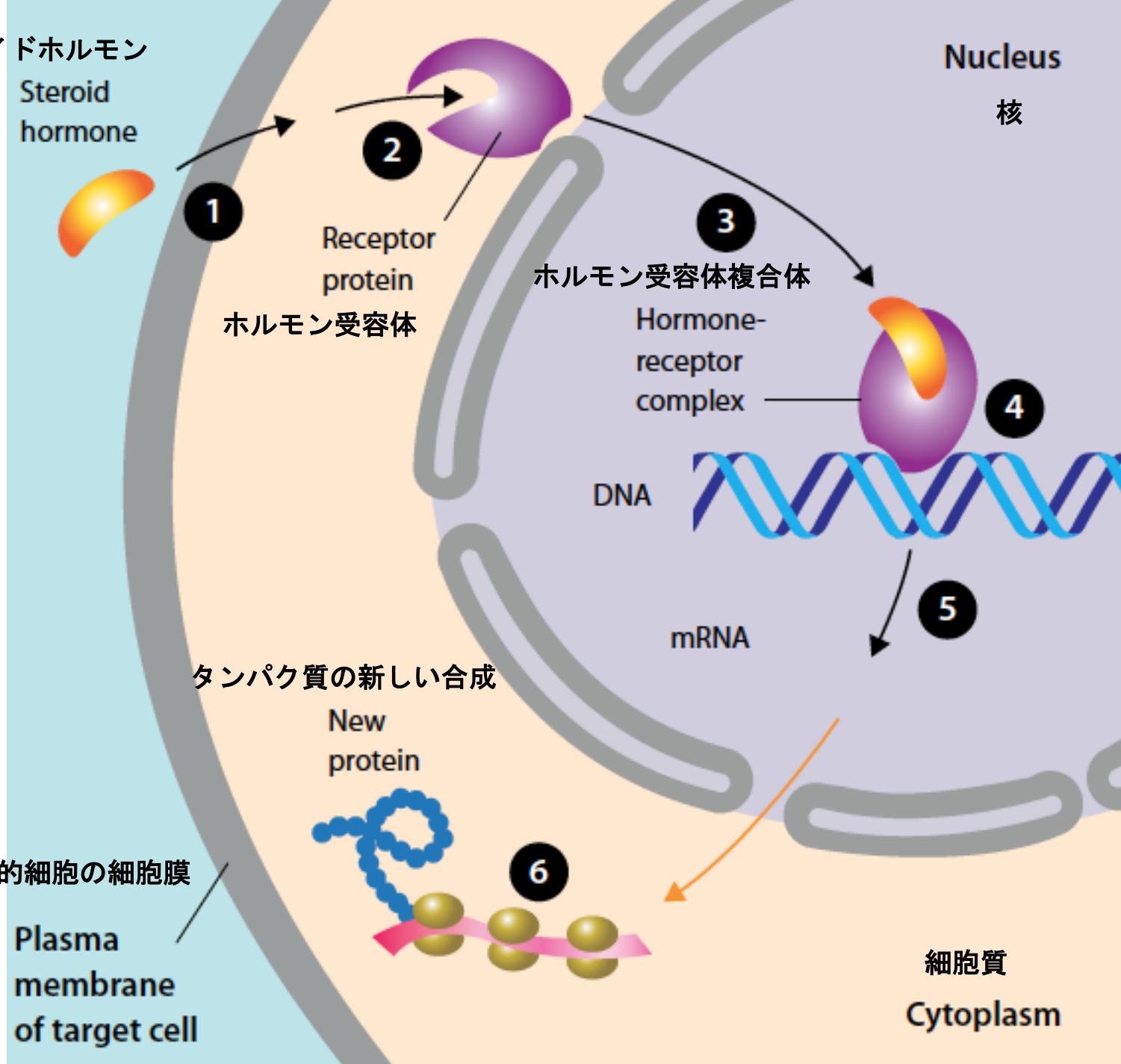
New protein

標的細胞の細胞膜

Plasma membrane of target cell

細胞質

Cytoplasm



# 内分泌かく乱化学物質

## Endocrine disrupting chemicals

内分泌系ホルモンの作用を、ニセ・ホルモンとして直接的または間接的にかく乱または阻害する化学物質

*A compound that mimics or blocks the action of endocrine hormones, either directly or indirectly*

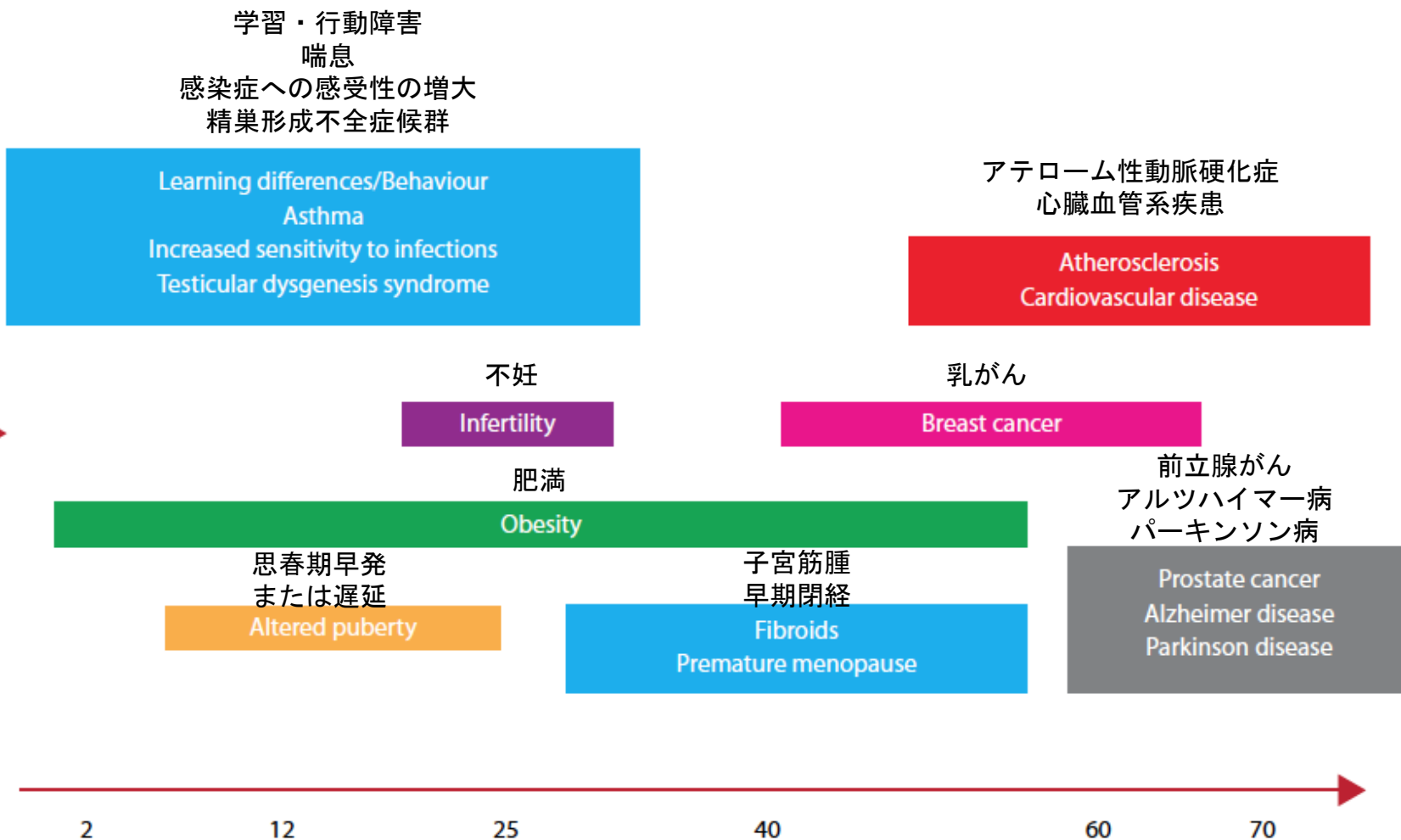
- 有機フッ素化合物 (PFAS)  
Perfluorinated substances (PFAS) compounds
- フタル酸エステル類 Phthalates
- ビスフェノールA Bisphenol A
- 農薬 Pesticides
- 日焼け止め・トリクロサン (殺菌・抗菌剤)  
Sun screens / triclosan







年齢  
Age  
(years)



# EDC(内分泌かく乱化学物質)の特徴

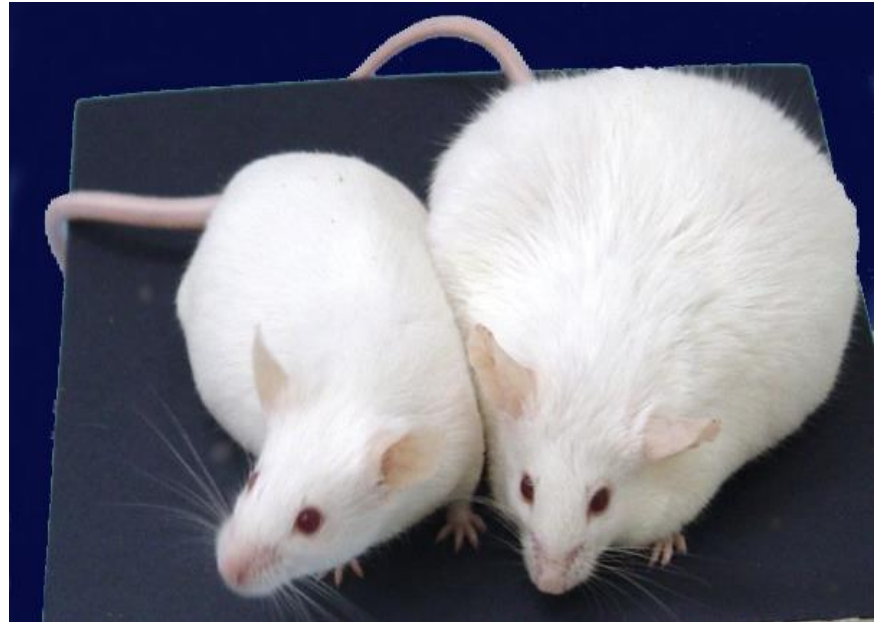
## Characteristics EDCs

1. 高用量のデータから予測できない低用量の影響  
High doses do not predict effects of low doses
2. 非特異的影響  
Unspecific effects
3. 長い潜伏期間  
Long latency
4. 影響は世代を超えて継続する  
Effects last in generations
5. カクテル効果(複合影響)  
Cocktail effects
6. 全員がばく露している  
All exposed



# 1. 低用量 Low doses

- 発達期のばく露  
Exposure during development
- 1ppb(10億分の1)のばく露  
⇒大人になってから肥満  
1 part per billion => obesity  
as adult
- 100ppb =>体重減少
- 100 ppb =>weight loss
- 胎児期のばく露は成人期の  
体重を変化させる  
Foetal exposures alter adult  
weight
- 高レベルの影響で、低レベ  
ルの影響を予測できない  
High level don't predict low  
level impacts

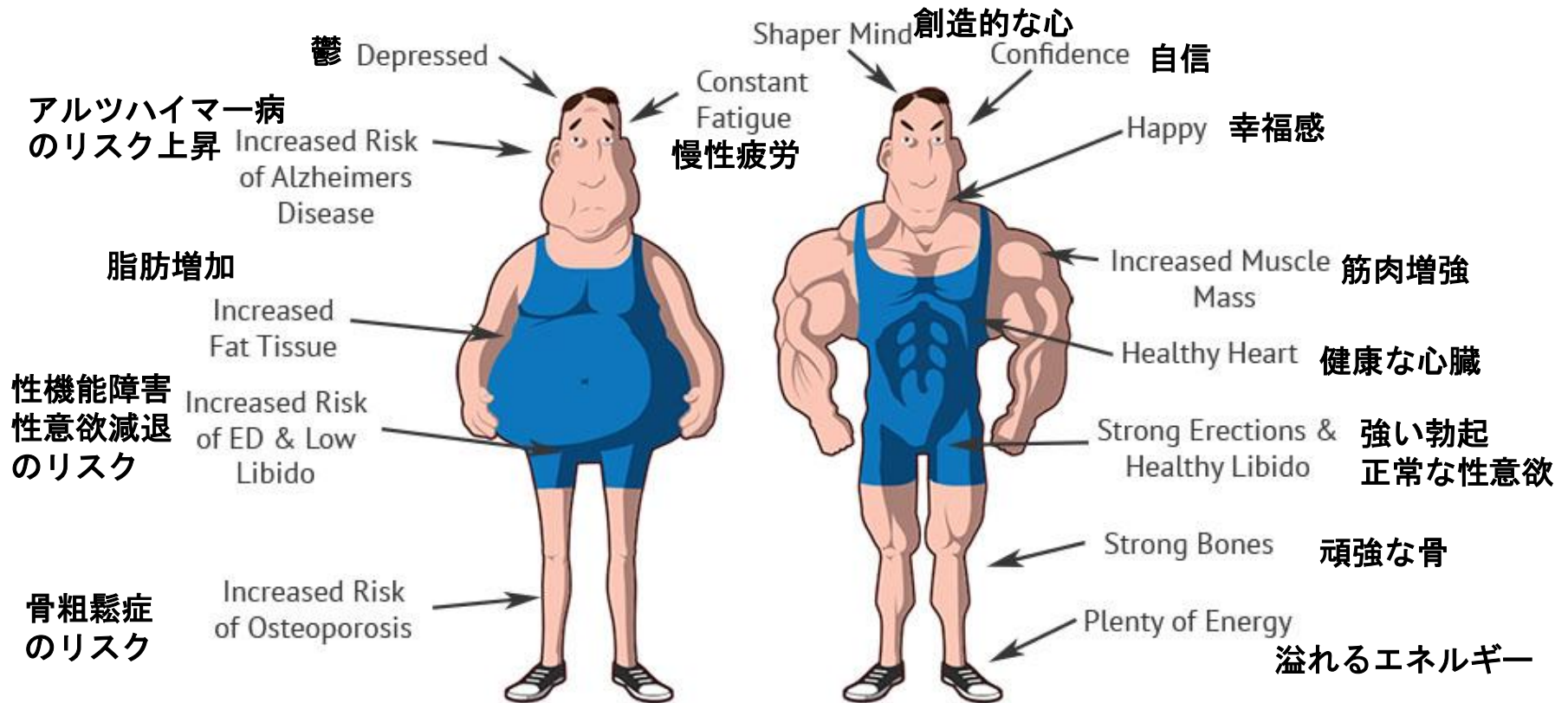


同じ系統のマウス Same strain of mice  
同じカロリー摂取量 Same caloric intake  
同じ活動量 Same activity levels

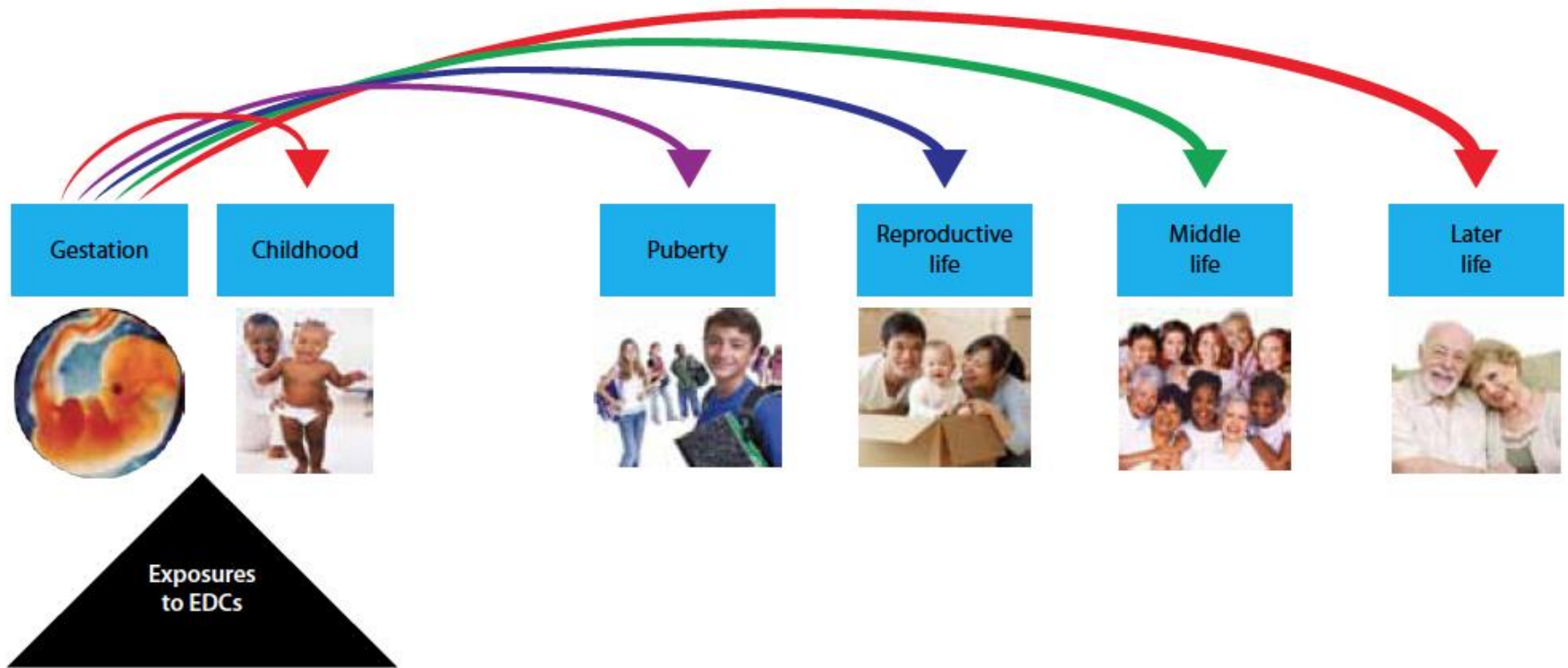
## 2. 非特異的影響 Unspecific effects

男性ホルモンは適切な濃度が有効

### Benefits of Optimal Testosterone



### 3. 長い潜伏期間 Long latency



胎児、幼児期における内分泌かく乱化学物質のばく露は、思春期、子どもを作る時期、ミドルエージ、老後にまで影響が及ぶ

## 4. 世代を超えて影響が継続

Last in generations



This ad appeared in a major medical journal in 1957.

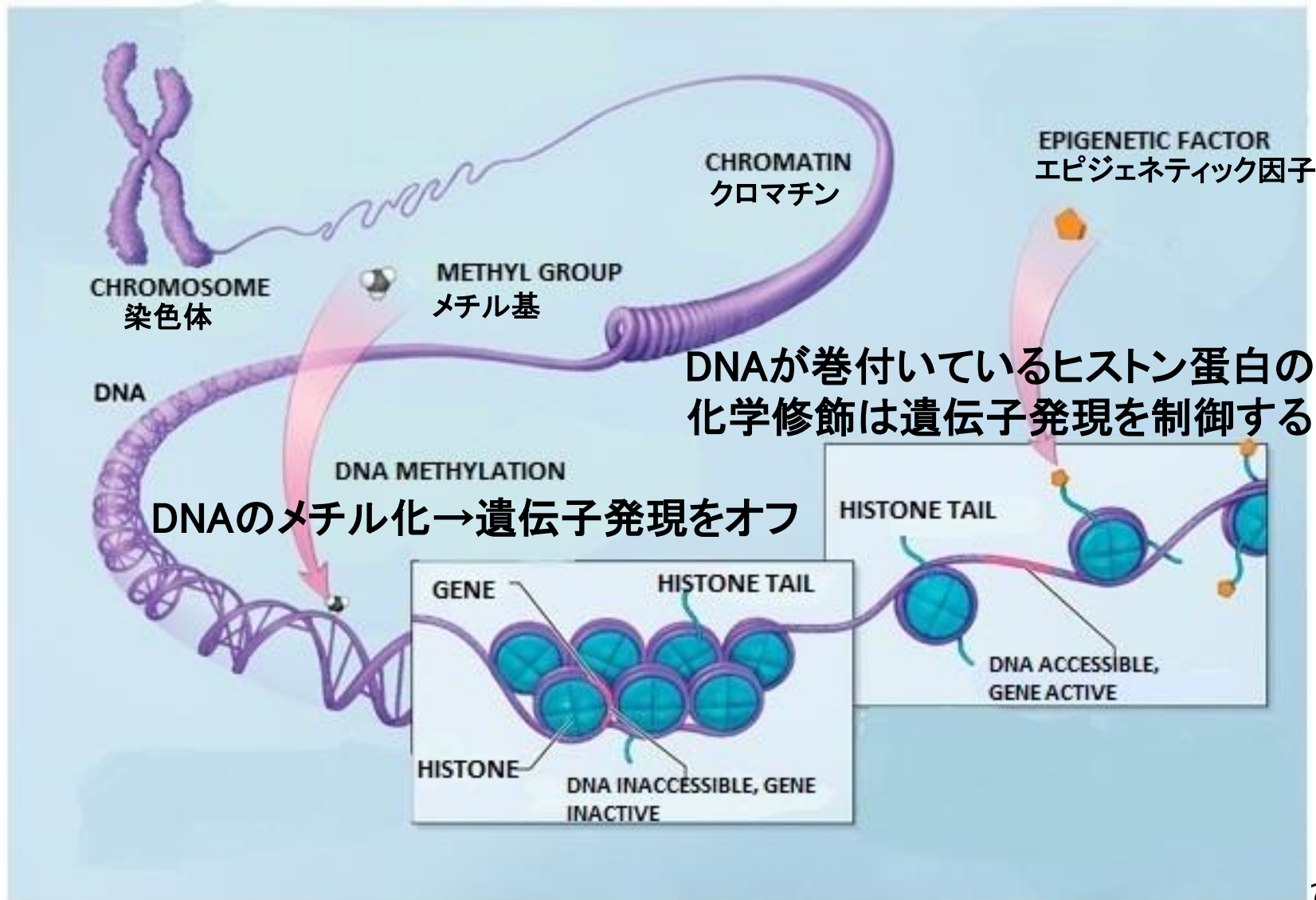
The small print at the bottom reads:

"Recommended for routine prophylaxis in ALL pregnancies... 96 per cent live delivery with desPLEX in one series of 1200 patients - bigger and stronger babies, too. No gastric or other side effects with desPLEX - in either high or low dosage."

DES(合成女性ホルモン)は安全な流産防止薬として多用されたが、次世代に子宮がんなど悪影響が起こった

# エピジェネティクス Epigenetics

DNAの塩基配列の変化によらない 遺伝子発現 を制御・伝達するシステム





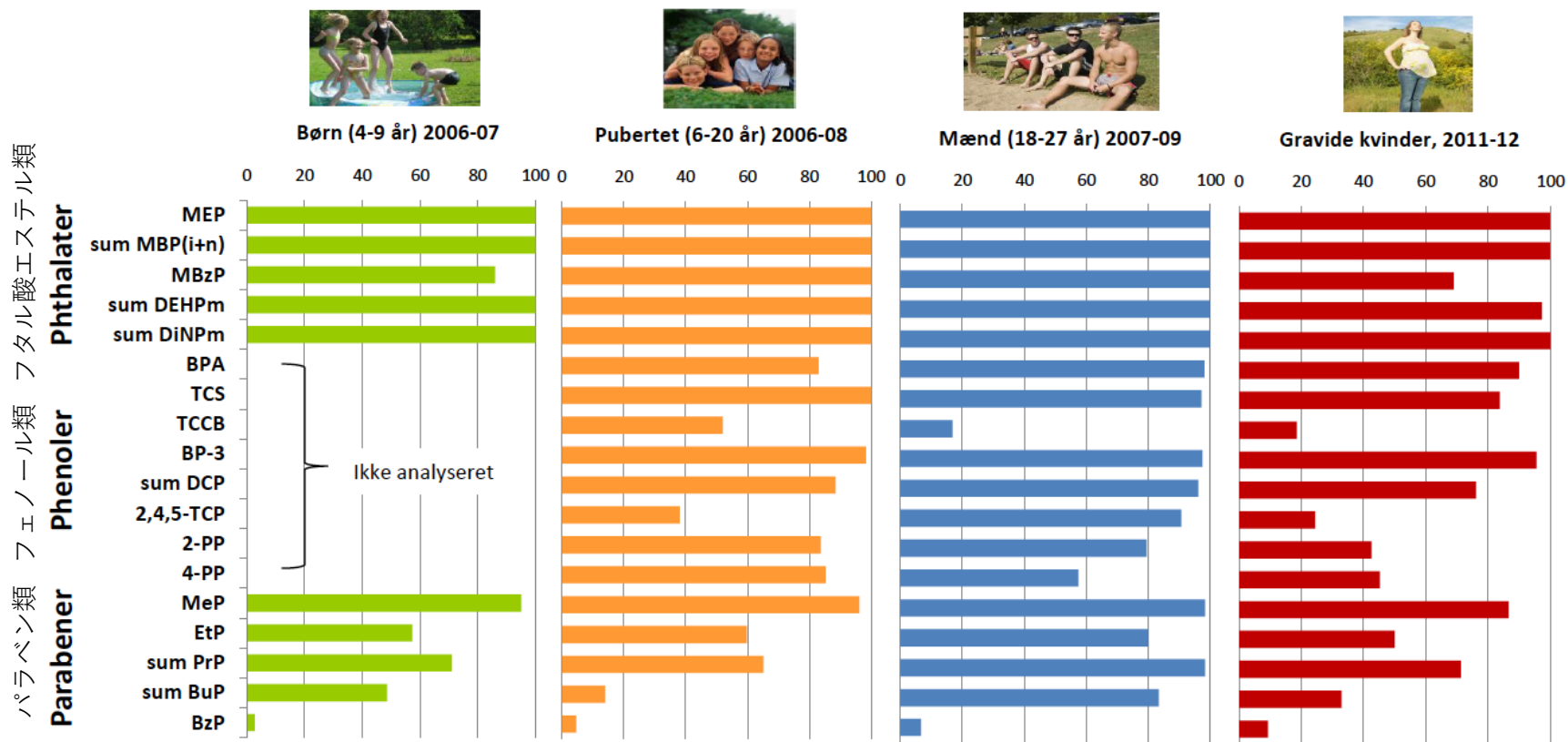
# 5. カクテル効果(複合影響)

Cocktail effects



# 6. 全員がばく露している All exposed

Procent deltagere med målbare koncentrationer af ikke-persisterende stoffer



Frederiksen et al, Reproduction, 2014



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&gt; ALT ER FRIVILLIGT!

- og du er med til at gøre en forskel.

&gt; 2492 FAMILIER DELTAGER



2551 家族が参加

2551 families participate

### Kontakt

Vi træffes på:  
Telefon: 65 41 32 44  
eller Mail: [ode.hca.obk@rsyd.dk](mailto:ode.hca.obk@rsyd.dk).

Ønsker du at modtage  
NYHEDSBREVET? Send os en mail.  
Har du fået ny mail eller andre nye  
kontaktoplysninger, så informer os  
gerne pr. mail.

### Små videoer af de forskellige undersøgelser

#### Blodprøve

I videoen her kan du se hvordan vi  
tager en blodprøve.



### Hovedomfang

I denne video kan du og dit barn se  
hvordan vi måler et hovedomfang.

### Hvad sker der i kohorten?



#### Besøg Tryllebjerget på OUH

Tryllebjerget har en



#### 7 års undersøgelsen

Her kan du læse mere om hvilke  
test vi tilbyder ved 7 års  
undersøgelsen



#### Leg på legepladsen

;)

Børn og voksne er  
meget velkommen til

### Bruger inddragelse

Har du gode ideer til nye forsknings  
emner, så er vi meget interesseret i  
at høre fra dig. Send os straks dit  
forslag på [mail](mailto:ode.hca.obk@rsyd.dk).

#### BRUGERUNDERSØGELSE 2016

[Læs opfølgning på  
brugerundersøgelsen her.](#)

#### ÅRSRAPPORT 2016

[Få adgang til Odense Børnekohortes  
årsrapport 2016 her](#)

### Odense Børnekohorte - Nyheder

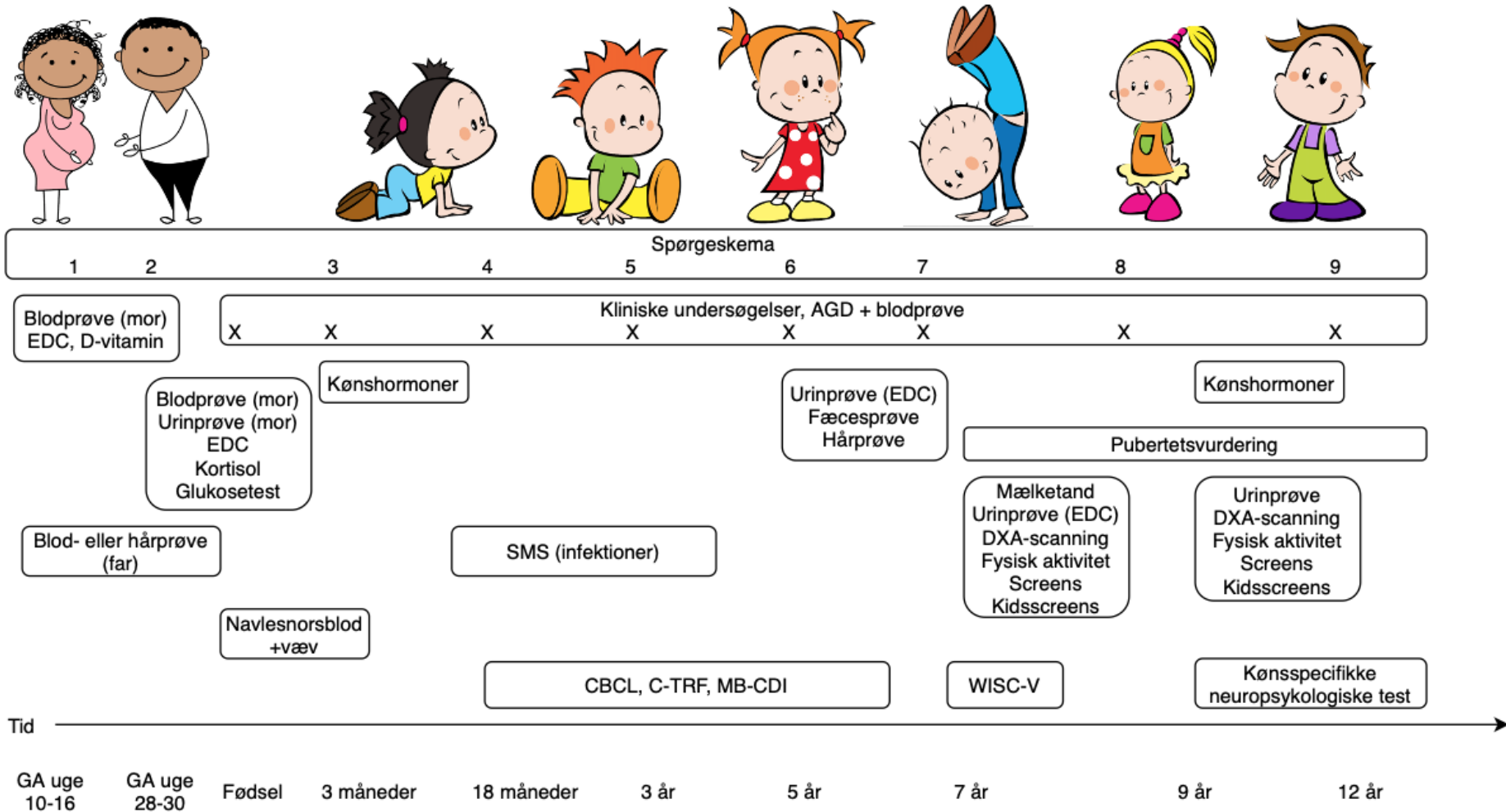
#### Informationsvideoer vedrørende kognitiv test på 7 års børn

#### Forældre information:



# オーデンセ子どもコホート疫学研究

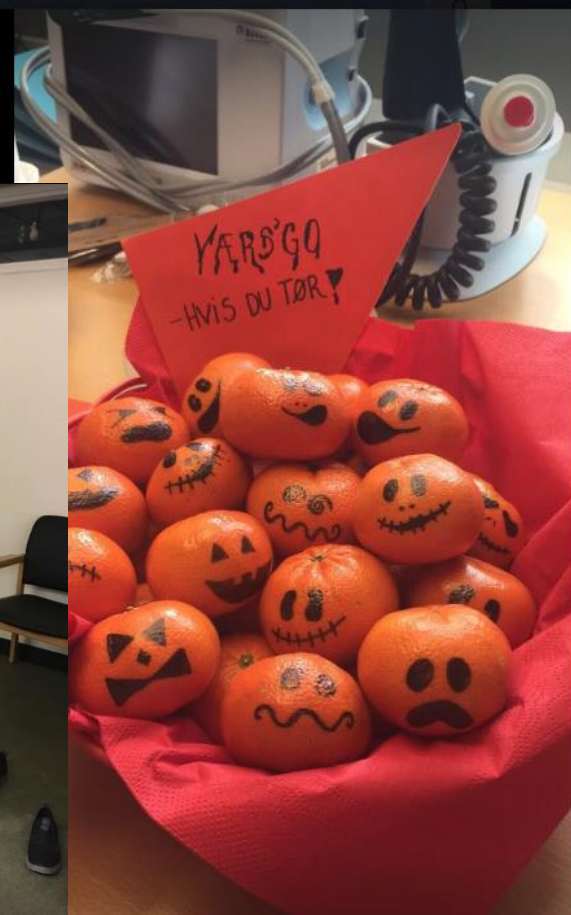
## Odense Child Cohort







Mobiloverførsler  
6 af 16



# 追跡期間      その期間で得られた情報とバイオマーカー

Time	Information and biomarkers obtained
10-16. weeks of gestation	Questionnaire incl. medicine intake and maternal education and lifestyle
	Serum PFAS, vitamin D
28. weeks of gestation	Urine phenols, parabens, phthalates, BPA, pesticides and fluorid
	Questionnaire incl. stress, medicine intake, lifestyle and infections
	24-hour urine
	Blood sample measured testosterone, cortisol and thyroid hormones
	Oral glucose tolerance test
	Urine cortisol
During pregnancy	Blood sample father
Delivery	Birth information
	Cord blood
	Cord sample
	Child hair
3 <sup>th</sup> months	Clinical examination incl. height, weight, anogenital distance, skin folds, blood pressure, head and abdominal circumference
	Questionnaire about child health incl. attachment and breastfeeding
	Blood sample child measured reproductive hormones during minipuberty and Total cholesterol, LDL, HDL, and triglyceride
	Breast milk sample
18 <sup>th</sup> months	Clinical examination incl. height, weight, anogenital distance, skin folds, blood pressure, head and abdominal circumference
	Questionnaire about attachment, teeth, health and breastfeeding
	Blood sample child measured PFAS and Total cholesterol, LDL, HDL, and triglyceride
3 years	Clinical examination incl. height, weight, anogenital distance, skin folds, blood pressure, head and abdominal circumference
	Questionnaire about sleep, health, medicine, screen time and breastfeeding
	Health visitor information on diet and attachment
	MacArthur-Bates language CDI-parent report every 3 months
	Symptoms of infection reported by text messages every second week (26 times) during one year.
	Parents and day care center completed information about behaviour by use of Child Behaviour Check List (CBCL) and teacher's report forms (C-TRF)
	Blood sample child

5 years	Clinical examination incl. height, weight, anogenital distance, skin folds, blood pressure, head and abdominal circumference
	Questionnaire about child health, screen time and sleep
	Parents and day care center completed information about behaviour by use of Child Behaviour Check List (CBCL) and teacher's report forms (C-TRF)
	Blood sample
	Urine sample measured pesticides and fluorid
	Faeces sample
7 years	Clinical examination incl. height, weight, anogenital distance, skin folds, blood pressure, head and abdominal circumference
	Questionnaire about child health, activity, diet, screen time and sleep and religion
	Kid screen questionnaire
	Blood sample
	Urine sample measured phthalates and bisphenols
	Faeces sample
	DXA scan
	Gross and fine motor skills (movement ABC-2), cardiorespiratory fitness (ergometer bicycle test to exhaustion) and handgrip and trunk muscle strength (maximal voluntary contraction of abdomen and back)
	Accelerometer test for a week at home
	Part of WISC V, IQ test
9 years	Clinical examination incl. height, weight, anogenital distance, skin folds, blood pressure, head and abdominal circumference
	Questionnaire about child health, activity, diet, screen time and sleep and religion
	Kid screen questionnaire
	Blood sample
	Urine sample measured phthalates and bisphenols
	DXA scan
	Gross and fine motor skills (movement ABC-2), cardiorespiratory fitness (ergometer bicycle test to exhaustion) and handgrip and trunk muscle strength (maximal voluntary contraction of abdomen and back)
	Accelerometer test for a week at home
	Part of WISC V, IQ test
planned	Puberty development
	Neuropsychological sex dimorphic tests

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277,000のサンプルが公開  
277,000 samples in OPEN



# 測定した内分泌かく乱化学物質

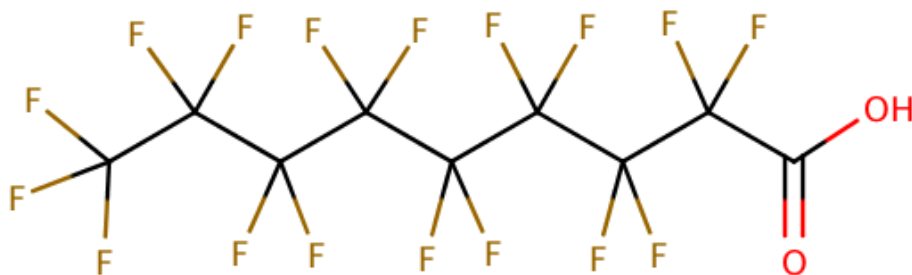
## Endocrine disruptors measured

測定時間 Time of measurement	化学物質 Chemical	検査数 N	サンプル Matrix
妊娠12週目 12 <sup>th</sup> week of gestation	有機フッ素化合物 Perfluoroalkyl substances (PFAS)	1599	血清 Serum
妊娠28週目 28 <sup>th</sup> week of gestation	フタル酸エステル類 Phthalates	877	尿 Urine
妊娠28週目 28 <sup>th</sup> week of gestation	ビスフェノールA Bisphenol A	877	尿 Urine
妊娠28週目 28 <sup>th</sup> week of gestation	ベンゾフェノン3 トリクロサン BP3 and triclosan	877	尿 Urine
妊娠28週目 28 <sup>th</sup> week of gestation	パラベン類 Parabens	565	尿 Urine
妊娠28週目 28 <sup>th</sup> week of gestation	農薬 Pesticides	1300	尿 Urine
生後8か月 18 months of age	有機フッ素化合物 PFAS	921	血清 Serum
5歳 5 years of age	農薬 Pesticides	860	尿 Urine
7歳 7years of age	ビスフェノール類（新規の代替物を含む） Bisphenols incl. new	300	尿 Urine
7歳 7 years of age	フタル酸エステル類（新規の代替物を含む） Phthalates incl new	300	尿 Urine

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# 有機フッ素化合物 PFAS



1940年代から生産されている  
Produced since 1940ties

最も使用されてきたのは  
**PFOAとPFOS**  
Most used PFOA and PFOS

ヒトの血清中の半減期は3.8～8.5年  
Half-life in human serum: 3,8 – 8,5 years

**PFAS**の耐油・耐水性 – とても有益だった  
PFASs grease and water resistant – very useful...



# PFAS



SDU 





# PFAS-どのようにばく露？

PFAS – HOW?

食品

Food



PFAA kan måles i blodet  
på alle mennesker

水

Water



Mid-Ohio Valley

ホコリ

Dust







A TODD HAYNES FILM

MARK  
RUFFALO

ANNE  
HATHAWAY

TIM  
ROBBINS

BILL  
CAMP

VICTOR  
GARBER

AND  
BILL  
PULLMAN

# DARK WATERS

ONE OF THE DEADLIEST COVER-UPS IN AMERICAN HISTORY

"A PERFECT FILM.  
RIVETING, POWERFUL  
AND IMPORTANT"

OBSERVER

"MARK RUFFALO'S  
BEST PERFORMANCE YET"

HOLLYWOOD NEWS



<https://www.youtube.com/watch?v=RvAOuhyunhY&feature=youtu.be>

SCREENPLAY BY MARIO CORREA AND MATTHEW MICHAEL CARNAHAN DIRECTED BY TODD HAYNES

PARTICIPANT PRESENTS A WOLFF HILL / KILLER CONTENT PRODUCTION A TODD HAYNES FILM "DARK WATERS" MARK RUFFALO ANNE HATHAWAY TIM ROBBINS BILL CAMP VICTOR GARBER MADE WINNINGHAM AND BILL PULLMAN PRODUCED BY LAURA ROSENTHAL CO-PRODUCED BY RANDALL POSTER EDITOR MARCELO ZARVOZ EXECUTIVE PRODUCERS CHRISTOPHER PETERSON  
WRITTEN BY ATTORSO GONCALVES PRODUCED BY HANNAH BEACHLER DIRECTED BY EDWARD LACHMAN EXECUTIVE PRODUCERS JEFF SKILL JONATHAN KING ROBERT KESSEL MICHAEL SLEED PRODUCED BY MARK RUFFALO CHRISTINE VACHON PAMELA KOFFLER CO-PRODUCED BY MARIO CORREA AND MATTHEW MICHAEL CARNAHAN DIRECTED BY TODD HAYNES



IN CINEMAS SOON

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# PFASばく露は以下のことに関連する

## PFAS exposure associated with

- 流産 Miscarriage
- 出生時体重減少 Birthweight
- 母乳育児期間 Duration of breastfeeding
- 成長と脂質の状態 Growth and lipid status
- 感染症にかかりやすくなる Infections
- ワクチンの効果低減・抗体生産減  
Vaccine antibodies
- 知能指数？ IQ?



# PFASによる影響について電子メールによる感染症症状の聞き取り

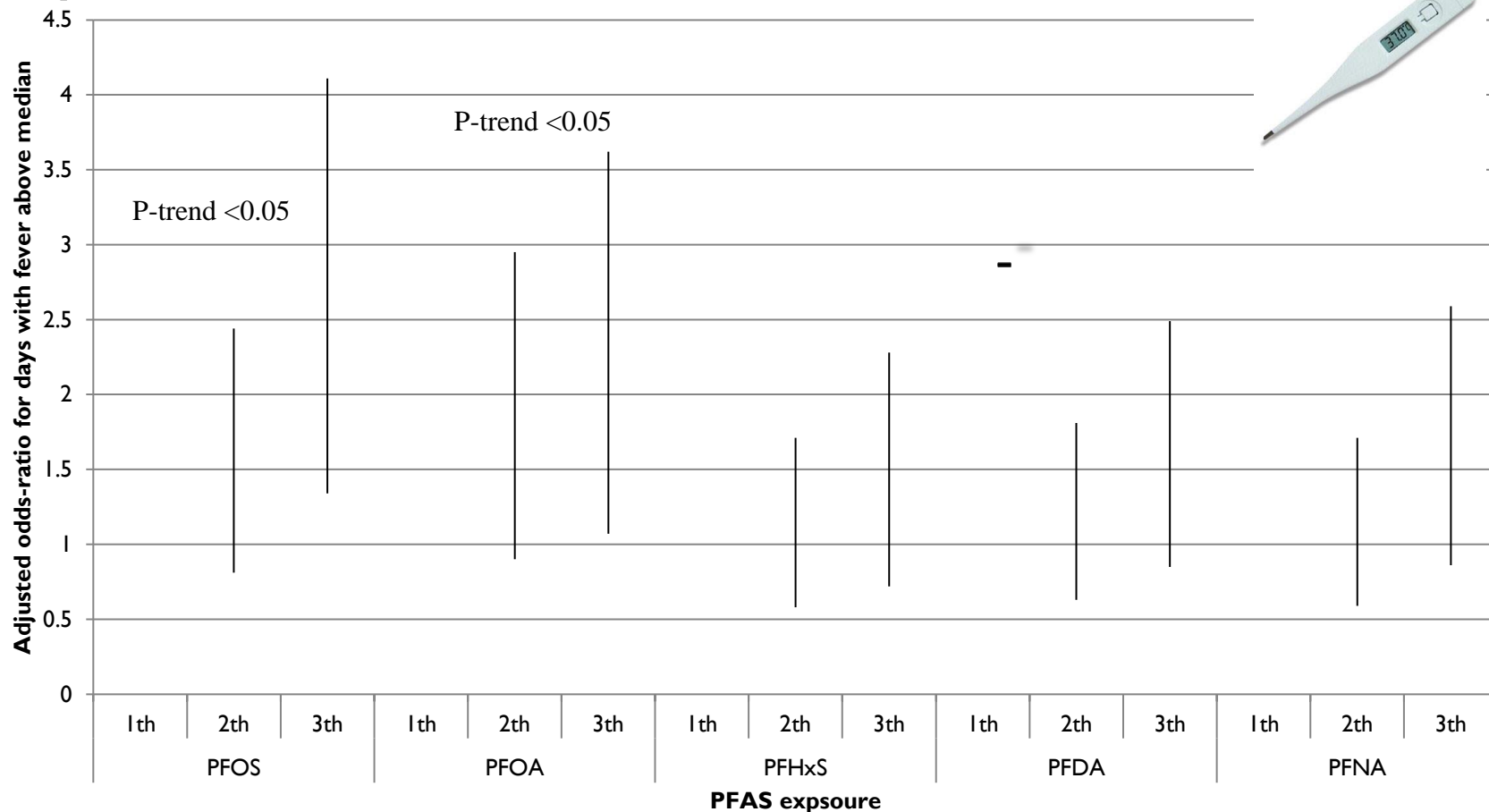
## Symptoms of infections by text message

- 2014年に、1,647世帯が招待され、1,540世帯(93%)が参加  
In 2014, 1,647 families invited 1,540 (93%) accepted
- 1年間、2週間に1回(26回)メールを送信  
Submitted text messages every second week (26 times) during one year
- 症状のない日、発熱、鼻づまり、咳、ゼーゼーヒューヒューという呼吸、目の炎症、  
耳の痛み、耳垂れ、下痢、嘔吐  
Days without symptoms, fever, stuffed or runny nose, cough, wheezy or whistling  
breathing, eye inflammation, ear pain, discharge from ear, diarrhea, and vomiting
- 発熱が最も関連性の高い症状であった。体温が38.5℃以上  
Fever was considered the most relevant outcome. Rectal temperature above 38.5° C



# 出生前のPFASばく露量が高いと 体温が38°Cを超える日数が増加

Odds-ratio days with temperature >38° according to prenatal PFAS exposure



Dalsager et al. Environ Int 2016.

母親の年齢、母親の教育レベル、分娩数、子どもの年齢で調整

Adjusted for maternal age, maternal educational level, parity and child age

# 入院のリスクも上昇

## Hospital admissions

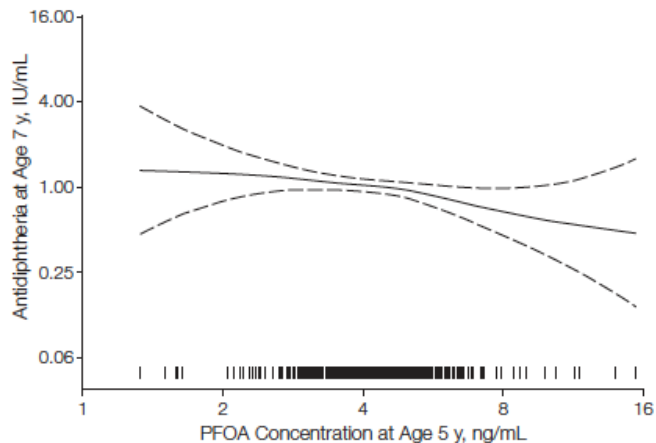
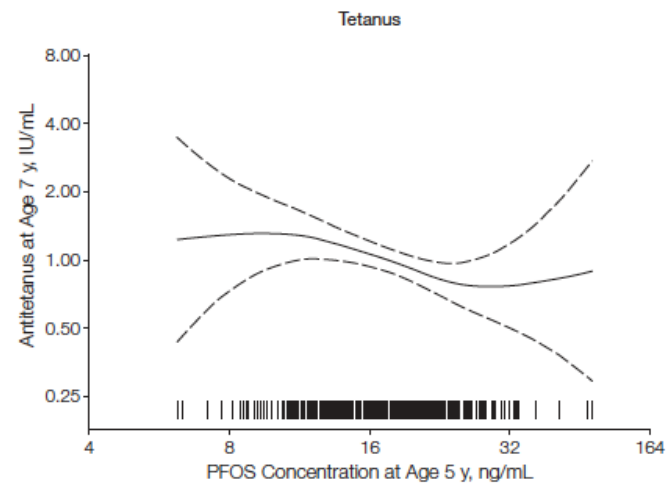
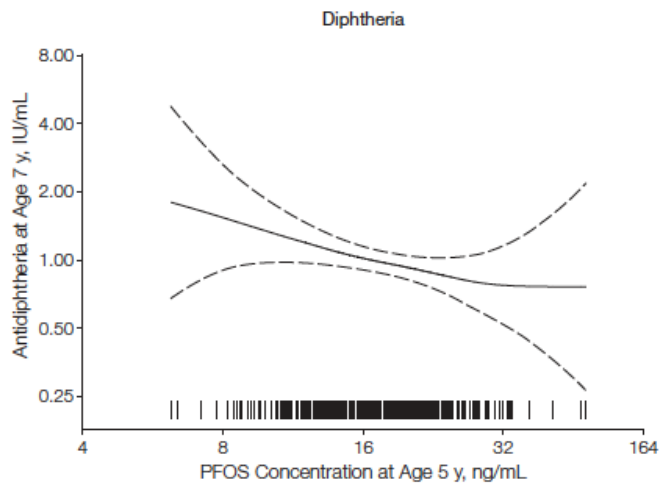
**Table 4**

Hazard ratios (HR's) and 95% confidence intervals (95% CI) for the association between maternal PFAS concentrations and the rate of hospitalization for infections (any and according to type)

	Any infection (N = 1472, events = 633)		Interaction, PFAS and child sex, p-value	URTI (N = 1472, events = 167)	LRTI (N = 1472, events = 151)	GI (N = 1472, events = 40)	Other (N = 1472, events = 275)
	Crude HR <sup>a</sup>	Adjusted <sup>b</sup> HR <sup>a</sup>		Adjusted <sup>b</sup> HR <sup>a</sup>	Adjusted <sup>b</sup> HR <sup>a</sup>	Adjusted <sup>b</sup> HR <sup>a</sup>	Adjusted <sup>b</sup> HR <sup>a</sup>
PFOs	1.18 (1.02, 1.36)	1.23 (1.05, 1.44)	0.067	1.25 (0.97, 1.61)	1.54 (1.11, 2.15)	0.77 (0.46, 1.29)	1.17 (0.98, 1.40)
PFOA	1.12 (0.97, 1.25)	1.13 (0.97, 1.29)	0.882	1.18 (0.93, 1.50)	1.27 (1.01, 1.59)	0.55 (0.32, 0.95)	1.12 (0.93, 1.35)
PFHxS	1.00 (0.89, 1.13)	1.02 (0.90, 1.16)	0.214	1.01 (0.83, 1.21)	1.01 (0.78, 1.32)	0.85 (0.50, 1.43)	1.07 (0.91, 1.25)
PFNA	1.04 (0.90, 1.21)	1.07 (0.92, 1.25)	0.592	1.18 (0.90, 1.53)	1.17 (0.89, 1.55)	0.80 (0.46, 1.40)	1.00 (0.82, 1.22)
PFDA	1.02 (0.89, 1.18)	1.06 (0.93, 1.22)	0.061	1.16 (0.95, 1.42)	1.06 (0.85, 1.32)	0.81 (0.46, 1.43)	1.04 (0.85, 1.27)

<sup>a</sup> The change in the instantaneous risk with every doubling of maternal serum PFAS concentration;

<sup>b</sup> adjusted for maternal age, parity, maternal educational level, child sex and child age



The generalized additive models have 3 *df* and were adjusted for age, sex, and vaccine  
the horizontal scale indicate individual observations.



# PFASばく露がワクチンの効果を低減

PFAS eksponering og vaccinationsrespons



# PF0AとPF0Sのばく露によるヒトの免疫学的健康状態に及ぼす影響に関する総説

## REVIEW ARTICLE

### A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and immunological health conditions in humans

Ellen T. Chang<sup>a,b</sup>, Hans-Olov Adami<sup>c</sup>, Paolo Boffetta<sup>d</sup>, H. James Wedner<sup>e</sup> and Jack S. Mandel<sup>a</sup>

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#### ABSTRACT

Whether perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS), two widely used and biopersistent synthetic chemicals, are immunotoxic in humans is unclear. Accordingly, this article systematically and critically reviews the epidemiologic evidence on the association between exposure to PFOA and PFOS and various immune-related health conditions in humans. Twenty-four epidemiologic studies have reported associations of PFOA and/or PFOS with immune-related health conditions, including ten studies of immune biomarker levels or gene expression patterns, ten studies of atopic or allergic disorders, five studies of infectious diseases, four studies of vaccine responses, and five studies of chronic inflammatory or autoimmune conditions (with several studies evaluating multiple endpoints). Asthma, the most commonly studied condition, was evaluated in seven studies. With few, often methodologically limited studies of any particular health condition, generally inconsistent results, and an inability to exclude confounding, bias, or chance as an explanation for observed associations, the available epidemiologic evidence is insufficient to reach a conclusion about a causal relationship between exposure to PFOA and PFOS and any immune-related health condition in humans. When interpreting such studies, an immunodeficiency should not be presumed to exist when there is no evidence of a clinical abnormality. Large, prospective studies with repeated exposure assessment in independent populations are needed to confirm some suggestive associations with certain endpoints.

#### ARTICLE HISTORY

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#### KEYWORDS

Asthma; autoimmune diseases; CAS No. 335-67-1; CAS No. 1763-23-1; epidemiology; hypersensitivity; immune system; immunization; immunological factors; infection; perfluoroalkyl substances; polyfluoroalkyl substances

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Supplemental data for this article can be accessed at <http://dx.doi.org/10.3109/1040844.2015.1122573>.

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**Table 1.** Results of epidemiologic studies of the association between exposure to perfluorooctanoic acid (PFOA) and/or perfluorooctanesulfonate (PFOS) and immune biomarkers or gene expression profiles.

Reference	Outcome	Number (%) with outcome	Estimate of association (95% confidence interval)	Adjustment factors
Olsen et al. 2003	White blood cell count	$n = 518$	"There were no significant mean differences between quartiles [of PFOA or PFOS] for ... hematology ... (data not shown)"	Age, body mass index, current daily alcohol consumption, current daily cigarette use, years worked at Antwerp or Decatur, and type of job (production vs. non-production)
Emmett et al. 2006b	White blood cell count	$n = 18$ (5%) abnormal	PFOA coefficient = 0.00039608, $r = 0.09$ , $p = 0.08$ No significant correlation in adults aged $\geq 19$ years or children aged $< 18$ years $t$ test $p = 0.64$ for PFOA in normal vs. abnormal	None
Emmett et al. 2006b	Neutrophils, percent	$n = 35$ (9%) abnormal	PFOA coefficient = 0.0004305, $r = 0.02$ , $p = 0.71$ No significant correlation in adults aged $\geq 19$ years or children aged $< 18$ years $t$ test $p = 0.02$ for PFOA in normal vs. abnormal (more abnormal with lower serum PFOA)	None
Emmett et al. 2006b	Neutrophils, absolute	$n = 12$ (3%) abnormal	PFOA coefficient = 0.00025301, $r = 0.07$ , $p = 0.17$ No significant correlation in adults aged $\geq 19$ years or children aged $< 18$ years $t$ test $p = 0.23$ for PFOA in normal vs. abnormal	None
Emmett et al. 2006b	Lymphocytes, percent	$n = 18$ (5%) abnormal	PFOA coefficient = -0.0006401, $r = 0.03$ , $p = 0.54$ No significant correlation in adults aged $\geq 19$ years or children aged $< 18$ years $t$ test $p = 0.01$ for PFOA in normal vs. abnormal (more abnormal with lower serum PFOA)	None
Emmett et al. 2006b	Lymphocytes, absolute	$n = 3$ (1%) abnormal	PFOA coefficient = 0.00009406, $r = 0.05$ , $p = 0.29$ No significant correlation in adults aged $\geq 19$ years or children aged $< 18$ years $t$ test $p = 0.59$ for PFOA in normal vs. abnormal	None
Emmett et al. 2006b	Monocytes, percent	$n = 39$ (11%) abnormal	PFOA coefficient = 0.00023119, $r = 0.04$ , $p = 0.44$ No significant correlation in adults aged $\geq 19$ years or children aged $< 18$ years $t$ test $p = 0.09$ for PFOA in normal vs. abnormal	None
Emmett et al. 2006b	Monocytes, absolute	$n = 7$ (2%) abnormal	PFOA coefficient = 0.00005008, $r = 0.13$ , $p = 0.01$ No significant correlation in adults aged $\geq 19$ years or children aged $< 18$ years $t$ test $p = 0.85$ for PFOA in normal vs. abnormal	None
Emmett et al. 2006b	Eosinophils, percent	$n = 19$ (5%) abnormal	PFOA coefficient = -0.0000652, $r = 0.01$ , $p = 0.82$ No significant correlation in adults aged $\geq 19$ years or children aged $< 18$ years $t$ test $p = 0.10$ for PFOA in normal vs. abnormal	None
Emmett et al. 2006b	Eosinophils, absolute	$n = 22$ (6%) abnormal	PFOA coefficient = 0.00000252, $r = 0.00$ , $p = 0.90$ No significant correlation in adults aged $\geq 19$ years or children aged $< 18$ years $t$ test $p = 0.85$ for PFOA in normal vs. abnormal	None
Emmett et al. 2006b	Basophils, percent	$n = 0$ (0%) abnormal	PFOA coefficient = 0.00003319, $r = 0.03$ , $p = 0.59$ No significant correlation in adults aged $\geq 19$ years or children aged $< 18$ years	None
Emmett et al. 2006b	Basophils, absolute	$n = 0$ (0%) abnormal	PFOA coefficient = 0.00000586, $r = 0.05$ , $p = 0.30$ No significant correlation in adults aged $\geq 19$ years or children aged $< 18$ years	None

(continued)



Table 1. Continued

Reference	Outcome	Number (%) with outcome	Estimate of association (95% confidence interval)	Adjustment factors
Costa et al. 2009	White blood cells ( $\times 10^9/L$ )	% outside reference range: Exposed: 2.6% Non-exposed: 5.6%	$t$ statistic = 0.10, $p \geq 0.05$ vs. matched non-exposed workers Exposed vs. non-exposed coefficient = 0.58 (−0.19, 1.35) PFOA coefficient = 0.029 (−0.011, 0.071)	Currently exposed and non-exposed pairs matched by age, job seniority, working hours, residential area, and housing and living conditions Regression analysis controlled for age, job seniority, body mass index, and alcohol consumption (+smoking for comparison of currently vs. never exposed workers; +year of observation for comparison by PFOA level in workers with concurrent PFOA and outcomes)
Costa et al. 2009	C-reactive protein (mg/L)	% outside reference range: Exposed: 5.1% Non-exposed: NR	PFOA coefficient = −0.020 (−0.268, 0.228)	Age, job seniority, body mass index, alcohol consumption, and year of observation
Costa et al. 2009	$\alpha 1$ globulins (%)	% outside reference range: Exposed: 0% Non-exposed: 0.9%	$t$ statistic = 0.59, $p \geq 0.05$ vs. matched non-exposed workers Exposed vs. non-exposed coefficient = −1.82 (−8.18, 4.54) PFOA coefficient = 0.026 (−0.001, 0.053)	Currently exposed and non-exposed pairs matched by age, job seniority, working hours, residential area, and housing and living conditions Regression analysis controlled for age, job seniority, body mass index, and alcohol consumption (+smoking for comparison of currently vs. never exposed workers; +year of observation for comparison by PFOA level in workers with concurrent PFOA and outcomes)
Costa et al. 2009	$\alpha 2$ globulins (%)	% outside reference range: Exposed: 12.8% Non-exposed: 14.0%	$t$ statistic = 0.20, $p \geq 0.05$ vs. matched non-exposed workers Exposed vs. non-exposed coefficient = 0.27 (−0.75, 1.28) PFOA coefficient = 0.026 (0.007, 0.045)	Currently exposed and non-exposed pairs matched by age, job seniority, working hours, residential area, and housing and living conditions Regression analysis controlled for age, job seniority, body mass index, and alcohol consumption (+smoking for comparison of currently vs. never exposed workers; +year of observation for comparison by PFOA level in workers with concurrent PFOA and outcomes)
Costa et al. 2009	$\beta$ globulins (%)	% outside reference range: Exposed: 0% Non-exposed: 0%	$t$ statistic = 0.49, $p \geq 0.05$ vs. matched non-exposed workers Exposed vs. non-exposed coefficient = −0.003 (−0.37, 0.36) PFOA coefficient = 0.011 (−0.008, 0.030)	Currently exposed and non-exposed pairs matched by age, job seniority, working hours, residential area, and housing and living conditions Regression analysis controlled for age, job seniority, body mass index, and alcohol consumption (+smoking for comparison of currently vs. never exposed workers; +year of observation for comparison by PFOA level in workers with concurrent PFOA and outcomes)
Costa et al. 2009	$\gamma$ globulins (%)	% outside reference range: Exposed: 0% Non-exposed: 0%	$t$ statistic = 0.10, $p \geq 0.05$ vs. matched non-exposed workers Exposed vs. non-exposed coefficient = −0.53 (−2.29, 1.24) PFOA coefficient = 0.013 (−0.005, 0.031)	Currently exposed and non-exposed pairs matched by age, job seniority, working hours, residential area, and housing and living conditions Regression analysis controlled for age, job seniority, body mass index, and alcohol

Table 1. Continued

Reference	Outcome	Number (%) with outcome	Estimate of association (95% confidence interval)	Adjustment factors
Costa et al. 2009	IgG (g/L)	% outside reference range: Exposed: 2.6% Non-exposed: NR	PFOA coefficient = -0.017 (-0.115, -0.080) [As reported, 95% confidence interval excludes -0.017; upper 95% confidence limit may be 0.080, since <i>p</i> -value is reported as non-significant.]	consumption (+ smoking for comparison of currently vs. never exposed workers; + year of observation for comparison by PFOA level in workers with concurrent PFOA and outcomes) Age, job seniority, body mass index, alcohol consumption, and year of observation
Costa et al. 2009	IgA (g/L)	% outside reference range: Exposed: 12.8% Non-exposed: NR	NR	Age, job seniority, body mass index, alcohol consumption, and year of observation
Costa et al. 2009	IgM (g/L)	% outside reference range: Exposed: 5.1% Non-exposed: NR	PFOA coefficient = 0.048 (-0.093, 0.190)	Age, job seniority, body mass index, alcohol consumption, and year of observation
Lin et al. 2011	Serum C-reactive protein (log mg/L)	NR	PFOA percentile: <50th (0.75–2.37 ng/mL): mean (SE) = 1.38 (0.14) 50th–74th (2.39–5.92 ng/mL): mean (SE) = 1.43 (0.14) 75th–89th (6.01–9.62 ng/mL): mean (SE) = 1.48 (0.18) ≥90th (9.64–28.13 ng/mL): mean (SE) = 1.41 (0.21) P-trend = 0.932 PFOS percentile: <50th (0.11–8.92 ng/mL): mean (SE) = 1.41 (0.13) 50th–74th (8.95–14.35 ng/mL): mean (SE) = 1.41 (0.16) 75th–89th (14.92–19.14 ng/mL): mean (SE) = 1.48 (0.17) ≥90th (19.98–67.26 ng/mL): mean (SE) = 1.36 (0.21) P-trend = 0.957	Age, gender, smoking status, drinking status, household income, systolic blood pressure, waist circumference, homeostasis model assessment of insulin resistance index, total cholesterol, and creatinine
Wang et al. 2011	Serum total IgE at age 2 years (kU/L, log-transformed)	<i>n</i> = 244 overall <i>n</i> = 133 males <i>n</i> = 111 females	Log PFOA (ng/mL): Overall coefficient = 0.027 (SE = 0.244), <i>p</i> = 0.870 Boys coefficient = 0.097 (SE = 0.345), <i>p</i> = 0.710 Girls coefficient = 0.001 (SE = 0.452), <i>p</i> = 0.998 Log PFOS (ng/mL): Overall coefficient = 0.251 (SE = 0.179), <i>p</i> = 0.147 Boys coefficient = 0.359 (SE = 0.255), <i>p</i> = 0.238 Girls coefficient = 0.095 (SE = 0.325), <i>p</i> = 0.723	Gender, gestational age, parity, maternal age, and prenatal environmental tobacco smoke exposure
Wang et al. 2011	Cord serum total IgE (kU/L, log-transformed)	<i>n</i> = 244 overall <i>n</i> = 133 males <i>n</i> = 111 females	Log PFOA (ng/mL): Overall coefficient = 0.134 (0.003, 0.458) Boys coefficient = 0.206 (0.047, 0.702) Girls coefficient = 0.067 (SE = 0.231), <i>p</i> = 0.823 Log PFOS (ng/mL): Overall coefficient = 0.161 (0.064, 0.642)	Gender, gestational age, parity, maternal age, and prenatal environmental tobacco smoke exposure

(continued)

REVIEW ARTICLE

A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and immunological health conditions in humans

Ellen T. Chang Declaration of interest

<sup>a</sup>Health Sciences  
Stanford University  
Boston, MA, USA;  
Immunology, Wa-

**ABSTRACT**  
Whether per-  
biopersistent  
systematicall  
exposure to f  
epidemiologi  
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ten studies o  
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seven studie  
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This manuscript was supported by the 3M Company. 3M was not involved in the preparation of the manuscript. The sponsors were provided the opportunity to review draft versions and to offer suggestions, whose inclusion in the manuscript was left to the discretion of the authors. The authors retained sole control of the manuscript content and the findings, and statements in this paper are those of the authors and not those of the author’s employer or the sponsors.

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H.J.W. declares no conflict of interest related to the subject of this manuscript. J.S.M. was a consultant to 3M and previously testified as an expert in legal proceedings related to PFOA and PFOS; he is now retired. E.T.C. is a consultant to 3M and other industry clients on issues related to perfluoroalkyl and polyfluoroalkyl substances, including PFOA and PFOS. P.B. was a consultant to other industry clients on issues related to PFOA. J.S.M., E.T.C., P.B., and H.O.A. co-authored a peer-reviewed, published manuscript on PFOA, PFOS, and cancer that was financially supported by 3M. None of the authors are currently engaged to testify as experts on behalf of the sponsors in litigation related to the compounds discussed in this manuscript.

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Public Health,  
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**E HISTORY**  
d 7 September 2015  
13 November 2015  
d 17 November 2015  
d online 12 January

**IRDS**  
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; 1763-23-1; epi-  
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; system; immuniza-  
munological factors;  
n; perfluoroalkyl  
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# 概要Outline

- 内分泌かく乱化学物質の定義  
Definition endocrine disrupting chemicals
- オーデンセ・子どもコホート疫学研究  
Odense Child Cohort
- 有機フッ素化合物(PFAS)  
Perfluoroalkyl substances
- フタル酸エステル類  
Phthalates
- 良いニュース、悪いニュース  
The good news, and the bad....
- 現在進行中の研究  
Ongoing research



# フタル酸エステル類

Phtalates



- 水溶性、短い半減期  
Water soluble, short half-life



SDU 





# どのようにばく露？ How?

空気中のホコリ  
Air dust



皮膚  
Skin



食品  
Food



# フタル酸エステル類のばく露は以下のことに 関連する Phtalate exposure associated with

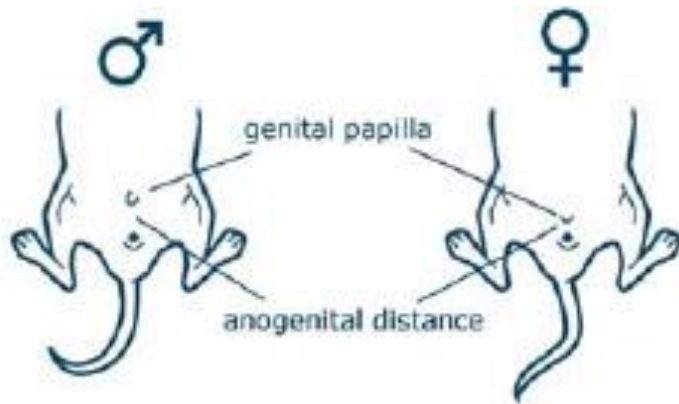
- 肛門性器間距離 Anogenital distance
- 思春期 Puberty
- ADHDを含む神経心理学的発達  
Neuropsychological development incl ADHD
- 喘息 Asthma
- 肥満 Obesity



# 肛門性器間距離 Anogenital distance

動物実験で検証された生殖器発達の性差の指標

Sexually dimorphic measure of genital development validated in animal studies



*Thankamony et al, Env Health Persp, 2009, Torres-Sanchez et al, Ann NY Acad Sci, 2008, Salazar-Martinez et al, Environ Health, 2004, Sathyanarayana et al, Int J Androl, 2010*

# BMJ Open Exposure to endocrine-disrupting chemicals and anthropometric measures of obesity: a systematic review and meta-analysis

Carolina Martins Ribeiro, Bruna Teles Soares Beserra, Nadyellem Graciano Silva, Caroline Lourenço Lima, Priscilla Roberta Silva Rocha, Michella Soares Coelho, Francisco de Assis Rocha Neves, Angélica Amorim Amato

## 内分泌かく乱化学物質へのばく露と肥満の人体測定指標: システマティックレビューとメタ解析

**Results** A total of 73 studies investigating bisphenol A (32 286 individuals), organochlorine compounds (34 567 individuals), phthalates (21 401 individuals), polybrominated biphenyls (2937 individuals), polycyclic aromatic hydrocarbons (5174 individuals), parabens (4097 individuals), benzoic acid (3671 individuals) and polyfluoroalkyl substances (349 individuals) met our inclusion criteria. Most had a cross-sectional design and low or medium risk of bias. In qualitative analysis, bisphenol A and phthalates were consistently associated with general and abdominal obesity, in children and adults, and some studies suggested this association was age-dependent and gender-dependent. Meta-analysis indicated a significant association between exposure to bisphenol A and overweight (OR 1.254, 95% CI 1.005 to 1.564), obesity (OR 1.503, 95% CI 1.273 to 1.774) and increased waist circumference (OR 1.503, 95% CI 1.267 to 1.783) in adults, and between exposure to 2,5-dichlorophenol and obesity in children (OR 1.8, 95% CI 1.1018 to 3.184).

ビスフェノールAとフタル酸エステル類は、小児および成人において一貫して肥満、特に腹部肥満と関連しており、いくつかの研究ではこの関連が年齢依存のおよび性別依存的事実であることが示唆された。

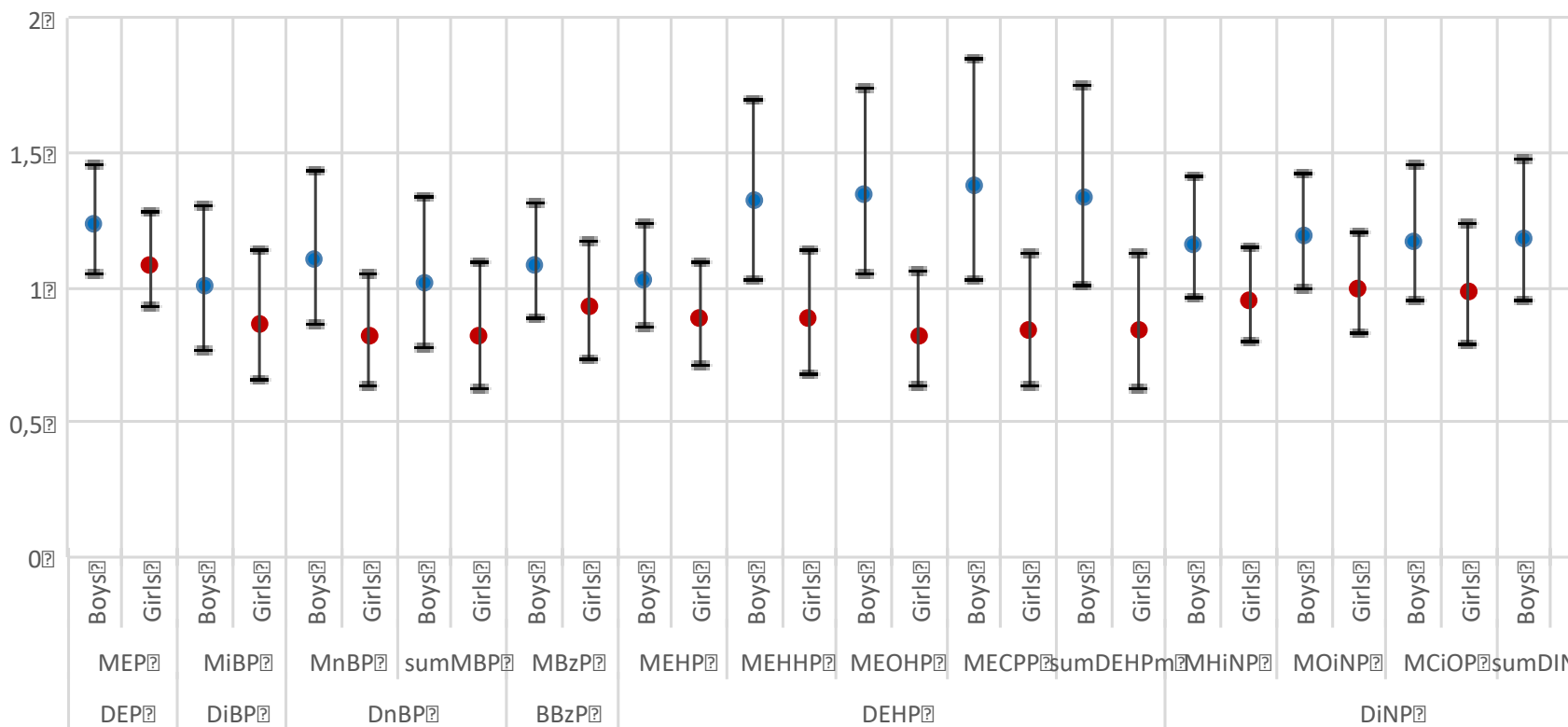
Nalgene - On the fly C



# 母親のフタル酸エステル類ばく露が2倍になると、子どもの語彙力に悪影響

Odds for being in lower 15% of vocabulary by doubling of maternal phthalate

Odds ratio of vocabulary





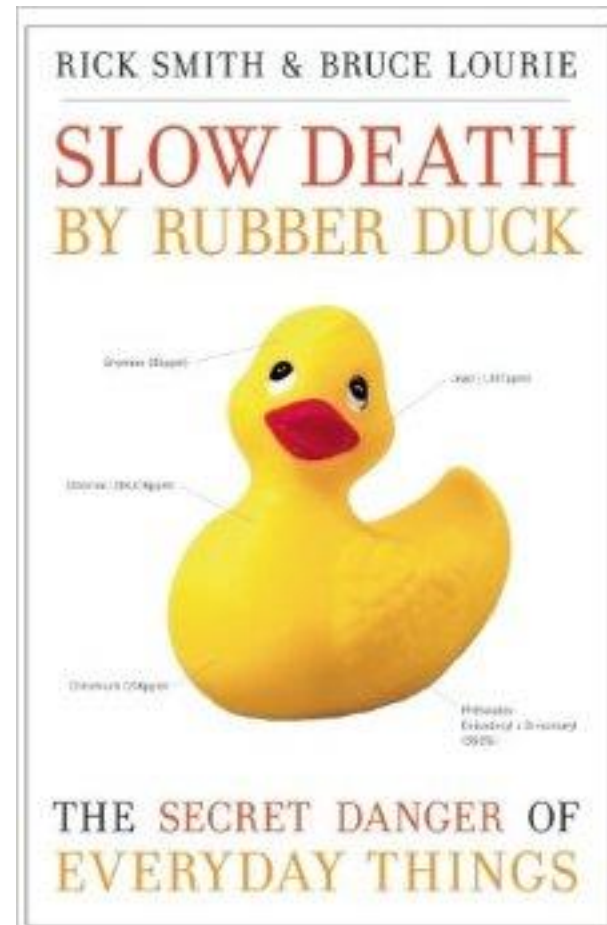
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The good news, and the bad....
- 現在進行中の研究  
Ongoing research

# 良いニュース

## The good news

- 消費者は影響力がある  
Consumers have power
- 欧州連合（EU）や世界保健機関（WHO）でも認められている問題  
The problem acknowledged in EU and WHO
- 規制が重要  
Regulation important



# デンマーク政府が食品包装材に含まれるPFASの使用を禁止

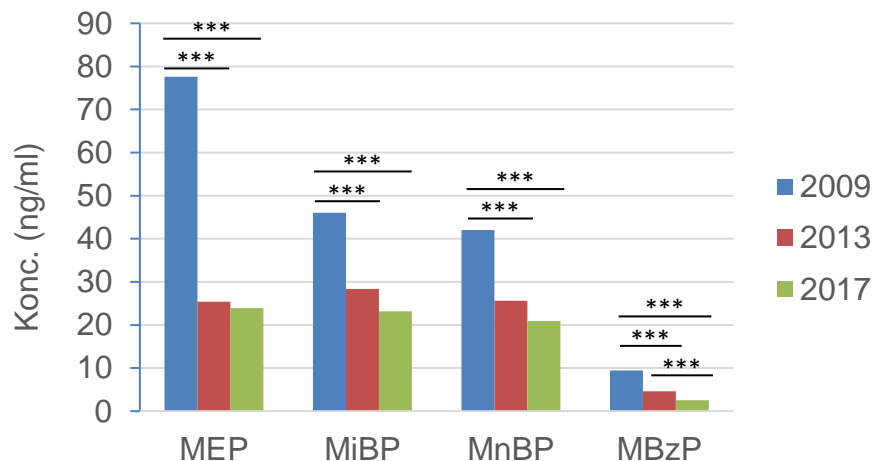
## Danish government bans PFAS in food packaging

- 2年間の自主的合意 Voluntary agreement for 2 years
- 包装材に含まれるPFASの合計濃度が規制値を超えた場合、管理する  
Controlling if combined concentration of PFAS in packaging is above limit
- PFASに含まれる各物質を個別に禁止するよりも良い  
Better than banning each compound
- デンマーク生協  
COOP Denmark
- EUの追随を期待  
Hopefully EU will follow

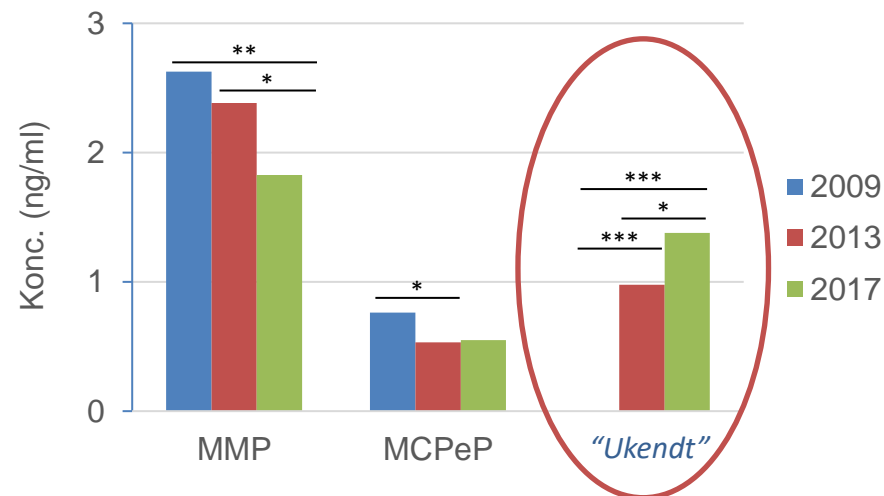
# 尿中のフタル酸エステル類と代替物

## Phthalats and substituents in urine

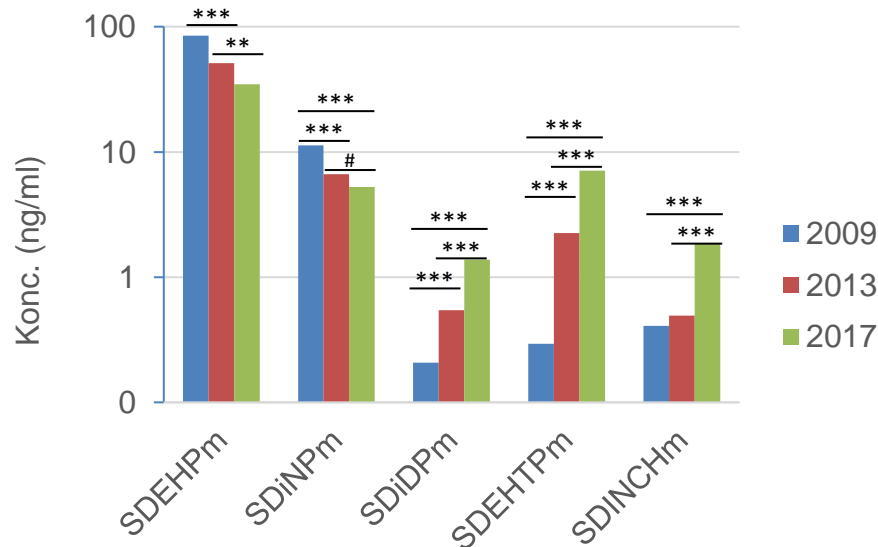
Lav molekylære phthalater



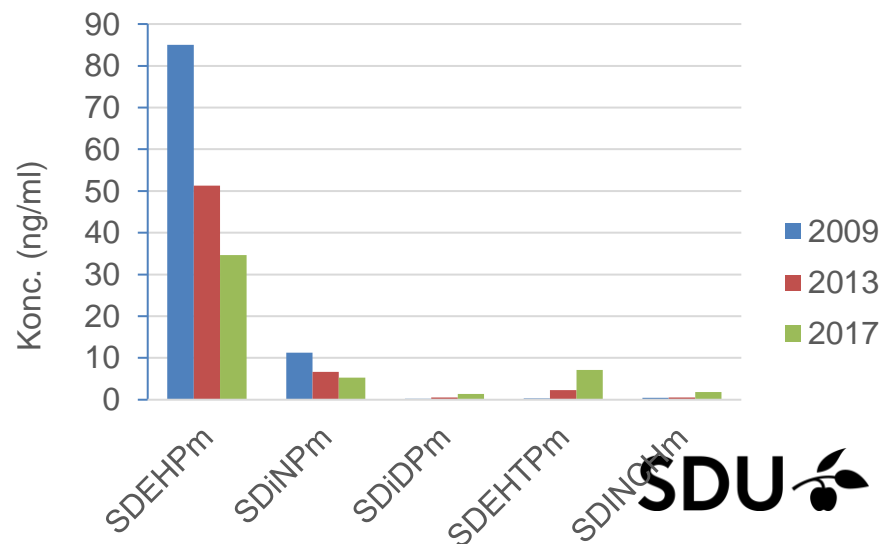
Phthalater i lave koncentrationer



Høj molekylære phthalater

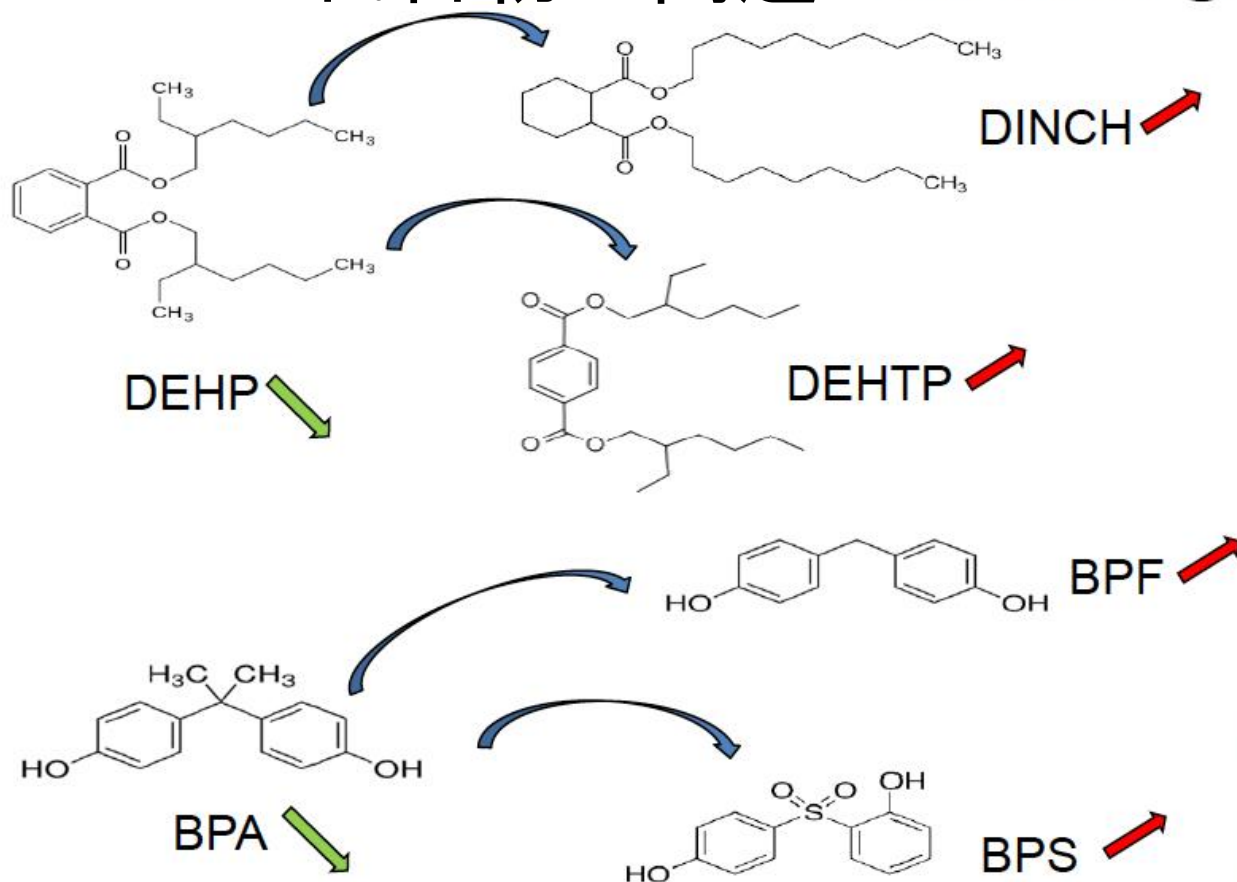


Høj molekylære phthalater



# 悪いニュース The BAD news

## 代替物の問題 Udfasning og substitution

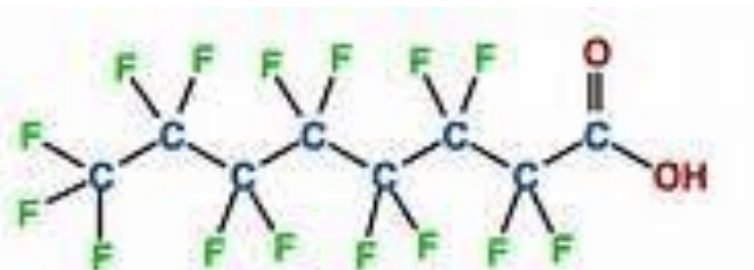


➤ Kræver nye metoder og nye analyser  
新しい分析方法が必要

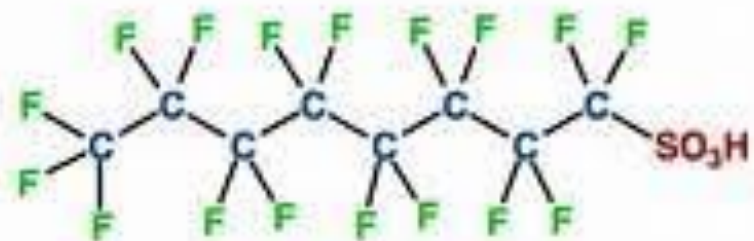




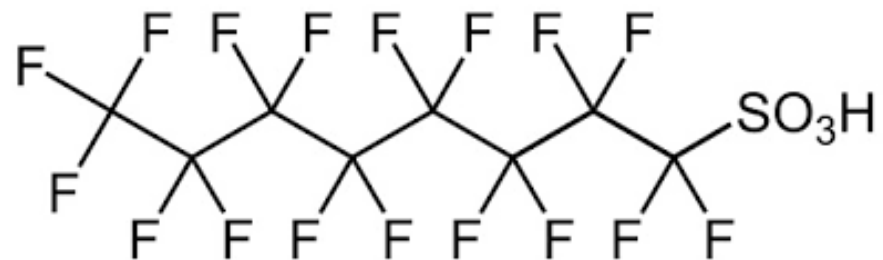
# 悪いニュース The bad news



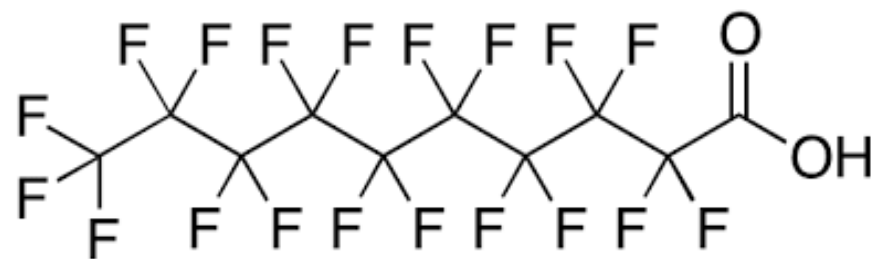
PFOA - perfluorooctanoic acid



PFOS - perfluorooctanesulfonic acid



PFHxS



PFDA

SDU 

# 現在進行中の研究

## Ongoing research

- 5歳段階での免疫反応（ワクチンの効果）  
Vaccination antibodies at age 5 years
- 農薬のばく露と神経発達への影響  
Pesticide exposure and neurodevelopment
- 思春期への影響 Puberty
- 性特異的な神経心理学的発達への影響  
Sex specific neuropsychological development
- パラセタモール（鎮痛・解熱剤：アセトアミノフェン）Paracetamol
- 7歳段階でのビスフェノール類、フタル酸エステル類濃度  
Bisphenols, phthalates measured at age 7 years
- DXAスキャン（低線量X線による骨密度や体組成の検査）  
DXA scans

# NHK・BSドキュメンタリー 「それでもプラスチックは必要ですか？ 人体をむしばむプラスチック」より

Documentary about plastic DR1

