Komplekse blandinger av persistente organiske miljøgifter, insulin resistens og fedme

Dr. Jérôme Ruzzin, Institutt for biologi, Universitet i Bergen.

jerome.ruzzin@bio.uib.no

Miljøgiftkonferansen 2012, Oslo.

Persistente organiske miljøgifter (POP-er)

wikipedia og www.miljostatus.no

POP-er kjennetegnes ved at de er giftige, lite nedbrytbare og bioakkumuleres i organismer.

Eksempler:

DIOKSINER som kan dannes i industrielle prosesser eller ved forbrenning når klor og karbon er tilstede. Den totale gruppen av miljøgiften dioksiner består da av 210 stoffer.

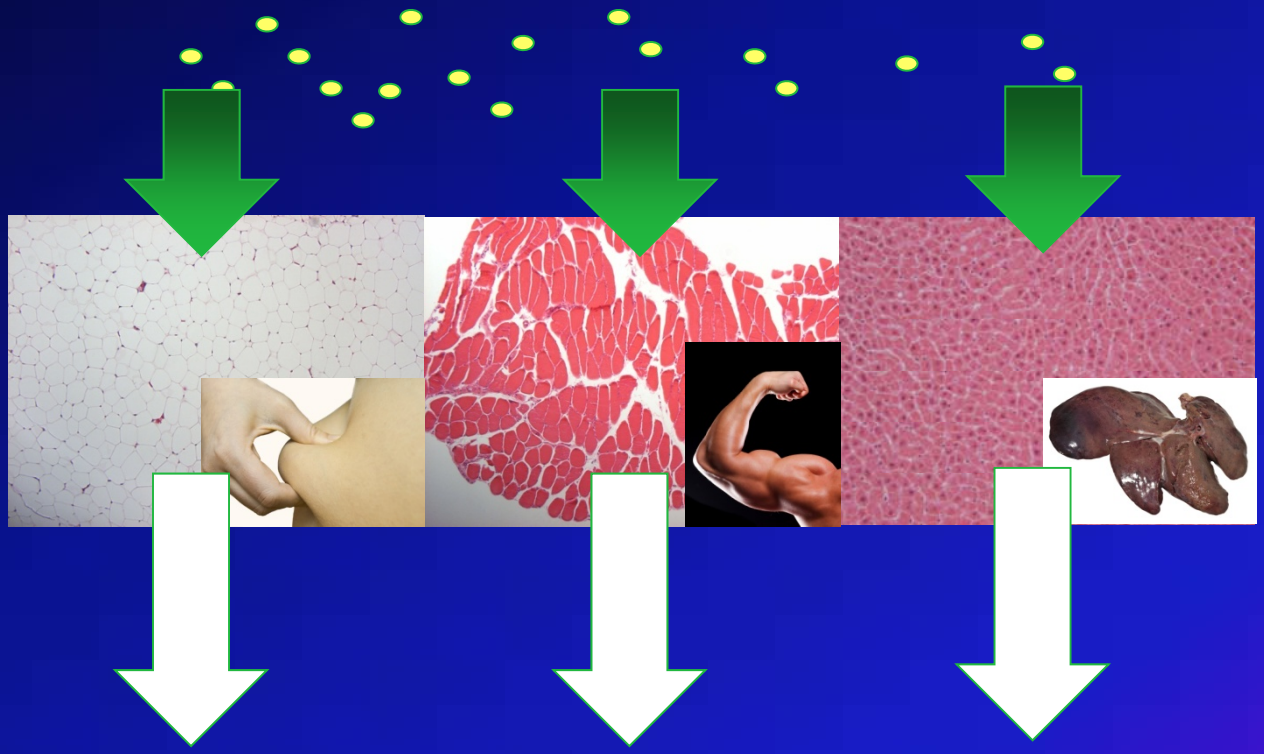
PCB (polyklorerte bifenyler). Stoff med god isolasjonsevne, lang holdbarhet, lav brennbarhet og god kjøleevne. Ble ofte brukt i elektronisk utstyr og byggprodukter.

KLORORGANISKE PESTICIDER: hexachlorobenzen (HCB), DDT, heptachlor, chlordane, aldrin, dieldrin, mirex…
Pesticider er beregnet til å kontrollere planter ("Herbicid"), sopp insekter ("Insektgift"), gnagere ("Rottegift") og andre organismer som kan være skadelige.

The Ukranian leader in front of a picture of his former, unblemished face. Viktor Yushchenko *Credit: Graeme Robertson/Getty Images*

Insulin resistens

Når celler ikke reagerer, eller reagerer lite på insulin



Ulike responser:

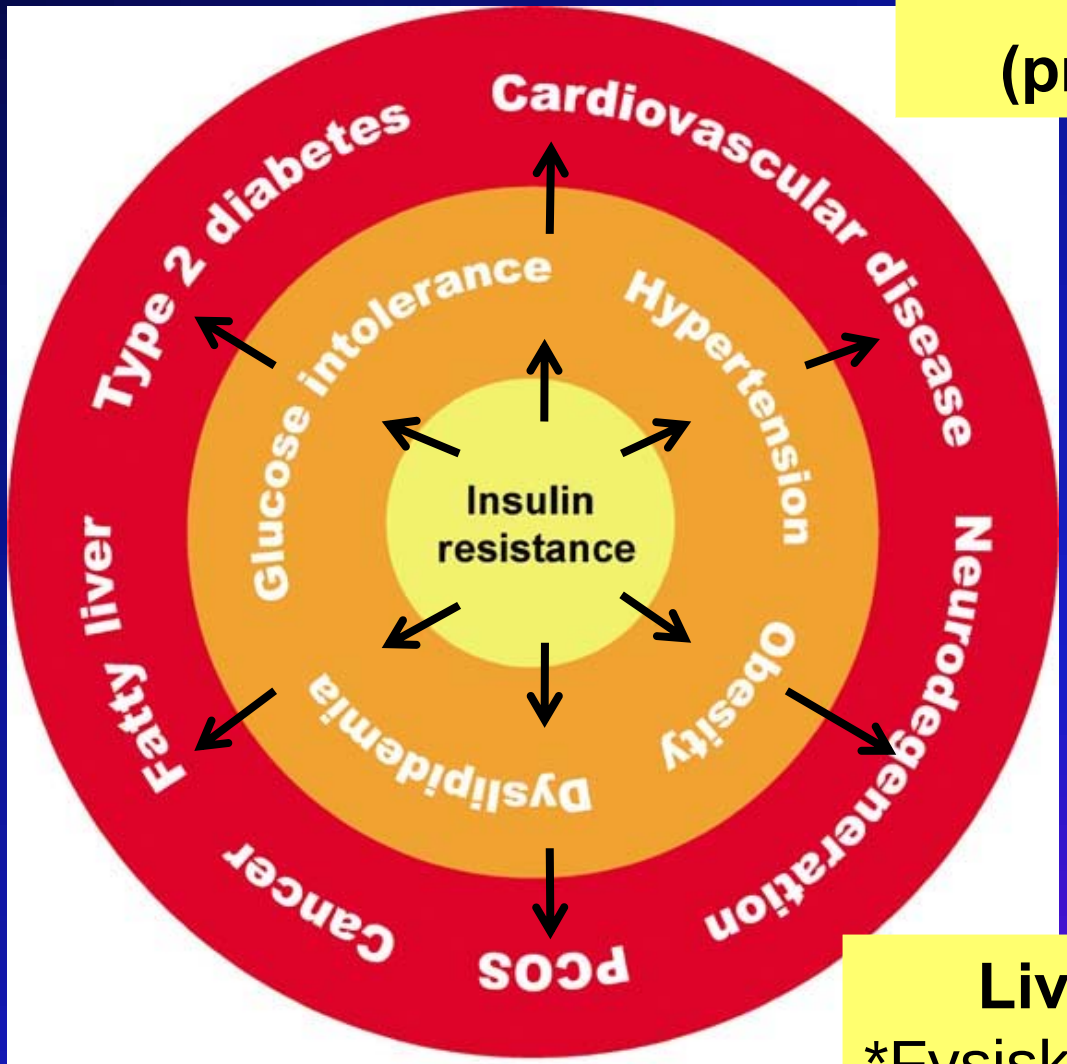
Cellulært opptak av visse næringstoffer, særlig glukose

Modifisering av aktiviteten til en rekke enzymer

Økning i DNA-replikasjon og proteinsyntese

Konsekvenser av insulin resistens

Andre faktorer ?



Biddinger SB, Kahn CR. 2006.
Annu. Rev. Physiol. 68:123–58

Genetisk (pre)disposisjon

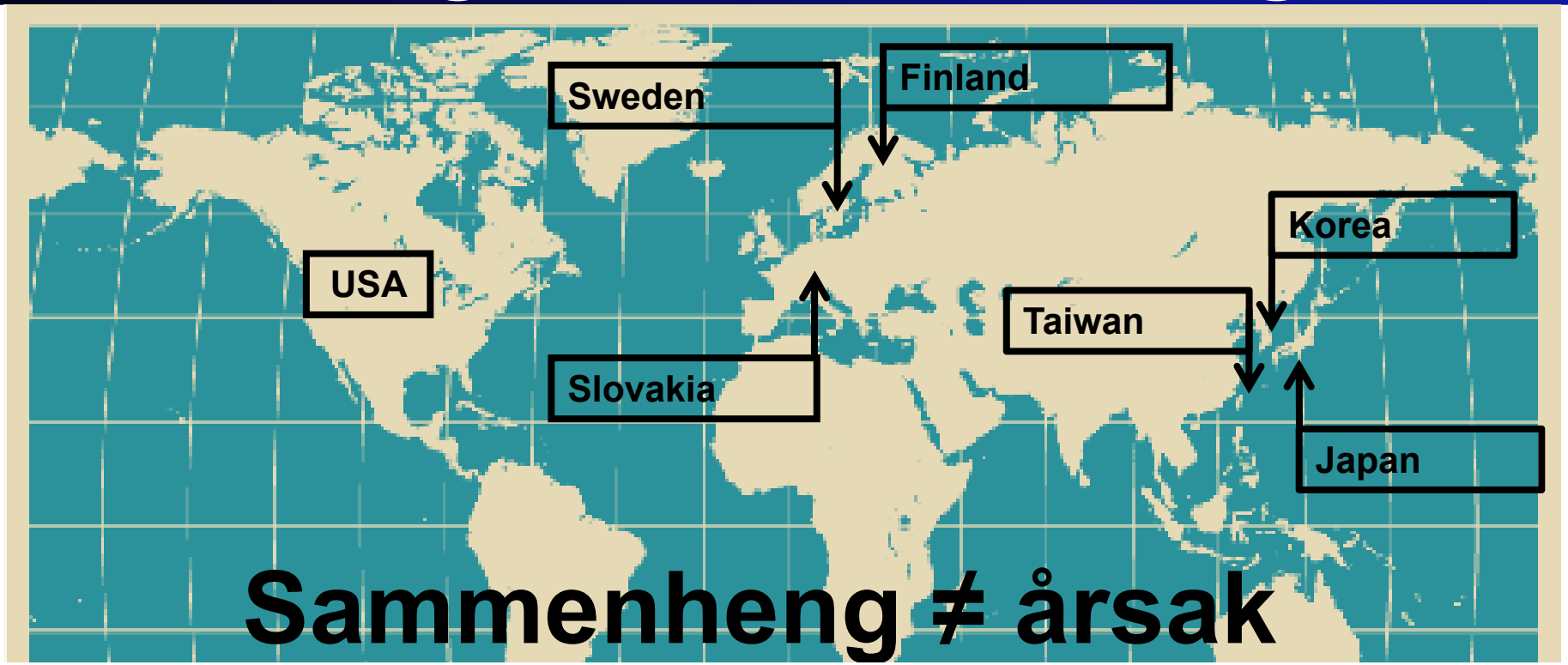
Hva er årsak(er) til at man utvikler insulin resistens?

Livsstilsfaktorer:

*Fysisk inaktivitet

*Overdrevent kaloriinntak

Sammenheng mellom POP-er og diabetes



Sammenheng ≠ årsak

Årsak: POP-er → Diabetes

Sammenheng: POP-er ↔ Diabetes

USA: Lee DH et al. *Diabetes Care* 2006; Turik M et al. *Chemosphere* 2009; Lee DH et al. *Environ Health Perspect* 2010
Europe: Rignell-Hydbom A et al. *Plos One* 2009; Ukropec J. et al. *Diabetologia* 2010; Airaksinen et al. *Diabetes Care* 2011; Lee DH et al. *Diabetes Care* 2011
Asia: Wang SL et al. *Diabetes Care* 2008. 6: Son HK et al. *Environ Inter* 2010. 7: Uemara H. *Environ Health Perspect* 2009

Er POP-er en viktig årsak til insulin resistens og metabolske forstyrrelser?

Hvordan er mennesker eksponert for POP-er?

Cirka 90% av eksponering kommer fra inntak av mat produkter

Levels of marker PCBs, PFCs, and organochlorine pesticides [ng/g ww or (LOD)].

From Schecter et al. *Environ Health Perspect*, 118:796-802, 2010

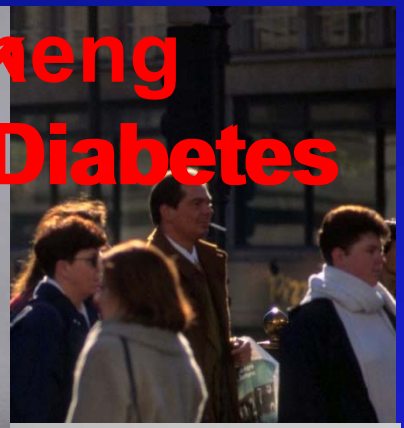
Marker	Hamburger	Bacon	Sausages	Whole milk	Ice cream	Eggs	Salmon	Cod
Lipid percent	21.70	36.10	23.90	3.8	16.2	10	11.90	0.30
PCB-52	ND (0.1)	ND (0.09)	ND (0.1)	ND (0.05)	ND (0.2)	ND (0.05)	0.28	ND (0.07)
PCB-101	ND (0.4)	ND (0.3)	ND (0.4)	ND (0.2)	ND (0.5)	ND (0.1)	0.51	ND (0.2)
PCB-118	ND (0.2)	ND (0.1)	ND (0.2)	ND (0.07)	ND (0.2)	ND (0.08)	0.43	ND (0.1)
PCB-153	1.2	ND (0.4)	ND (0.5)	ND (0.2)	ND (0.5)	ND (0.2)	1.21	ND (0.3)
PCB-138	ND (0.7)	ND (0.4)	ND (0.6)	ND (0.2)	ND (0.7)	ND (0.2)	0.93	ND (0.2)
PCB-180	0.21	ND (0.10)	ND (0.1)	ND (0.05)	0.091	ND (0.05)	0.44	ND (0.06)
PFOA	0.15	0.24	0.09	ND (0.02)	ND (0.03)	ND (0.04	0.23	0.10
PFBS	ND (0.04)	ND (0.05)	ND (0.04)	ND (0.02)	ND (0.03)	ND (0.04)	ND (0.07)	0.12
PFHxS	ND (0.04)	ND (0.05)	ND (0.04)	ND (0.02)	ND (0.03)	ND (0.04)	ND (0.07)	0.07
α-HCH	ND (0.08)	ND (0.03)	ND (0.03)	ND (0.02)	ND (0.02)	ND (0.03)	0.09	0.05
β-HCH	ND (0.09)	ND (0.03)	ND (0.03)	ND (0.02)	ND (0.02)	ND (0.03)	0.06	0.05
p,p´-DDT	0.08	ND (0.06)	0.17	ND (0.02)	0.038	ND (0.03)	0.45	ND (0.02)
p,p´-DDE	1.12	0.16	0.42	0.24	1.23	0.11	3.51	0.31
o,p-DDD	ND (0.03)	ND (0.03)	ND (0.03)	ND (0.02)	ND (0.02)	ND (0.01)	0.23	0.01
p,p´-DDD	0.053	ND (0.06)	0.037	ND (0.02)	0.02	ND (0.01)	1.92	0.09
Dieldrin	0.17	0.12	0.031	ND (0.02)	0.13	ND (0.03)	1.20	0.06
Endosulfan sulfate	0.17	ND (0.08)	ND (0.07)	ND (0.05)	ND (0.2)	ND (0.03)	1.85	ND (0.08)
Toxaphene-26	ND (0.2)	ND (0.08)	ND (0.08)	ND (0.06)	ND (0.06)	ND (0.05)	0.44	0.10
Toxaphene-50	ND (0.2)	ND (0.1)	ND (0.1)	ND (0.1)	ND (0.1)	ND (0.07)	0.92	0.10
α-Chlordane	ND (0.04)	ND (0.03)	ND (0.03)	ND (0.02)	ND (0.02)	ND (0.01)	0.44	0.11
Oxychlordane	ND (0.2)	ND (0.04)	ND (0.04)	ND (0.04)	0.029	ND (0.04)	0.07	0.05
trans-Nonachlor	0.05	ND (0.03)	ND (0.03)	ND (0.02)	0.035	ND (0.01)	0.56	0.19
cis-Heptachlor epoxide	0.07	ND (0.03)	0.052	ND (0.02)	0.069	ND (0.02)	0.22	0.02
Pentachlorobenzene	0.06	ND (0.03)	ND (0.03)	ND (0.02)	ND (0.04)	ND (0.03)	0.04	ND (0.03)
Hexachlorobenzene	0.18	ND (0.1)	ND (0.1)	ND (0.07)	ND (0.1)	ND (0.07)	0.64	0.57

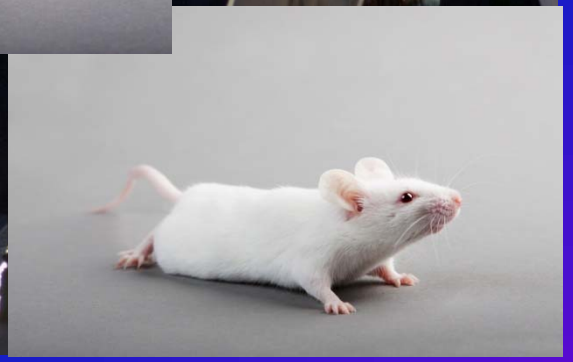
ND, not detected.

POP-er

Samanhengen

POP-er ⟷ Diabetes





Insulin resistens, diabetes, fedme…

Research

Persistent Organic Pollutant Exposure Leads to Insulin Resistance Syndrome

Jérôme Ruzzin,[1] Rasmus Petersen,[2,3] Emmanuelle Meugnier,[4] Lise Madsen,[1,3] Erik-Jan Lock,[1] Haldis Lillefosse,[1] Tao Ma,[2,3] Sandra Pesenti,[4] Si Brask Sonne,[3] Troels Torben Marstrand,[5] Marian Kjellevold Malde,[1] Zhen-Yu Du,[1] Carine Chavey,[6] Lluis Fajas,[6] Anne-Katrine Lundebye,[1] Christian Lehn Brand,[7] Hubert Vidal,[4] Karsten Kristiansen,[3] and Livar Frøyland[1]

[1]National Institute of Nutrition and Seafood Research (NIFES), Bergen, Norway; [2]Department of Biochemistry and Molecular Biology, University of Southern Denmark, Odense, Denmark; [3]Department of Biology, University of Copenhagen, Copenhagen, Denmark; [4]INSERM U-870, INRA (Institut national de la recherche agronomique) U-1235, Lyon 1 University, Institut National des Sciences Appliquées de Lyon and and Hospices Civils de Lyon, Oullins, France; [5]The Bioinformatics Centre, Department of Biology and Biotech Research and Innovation Centre, University of Copenhagen, Copenhagen, Denmark; [6]Institut de Recherche en Cancérologie de Montpellier, INSERM U896 Metabolism and Cancer Laboratory, Montpellier, France; [7]Department of Insulin Pharmacology, Histology and Delivery, Novo Nordisk A/S, Maaloev, Denmark

Environ Health Perspect 118:465–471 (2010). doi:10.1289/ehp.0901321 [Online 19 November 2009]

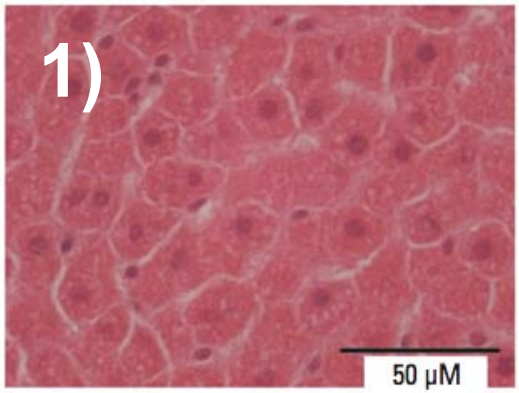
POP-er:
~9.5pg WHO 1998 TEQ -PCDD/F-PCB/g fett
Maksimum nivå I EU er 10.0pg WHO 1998 TEQ

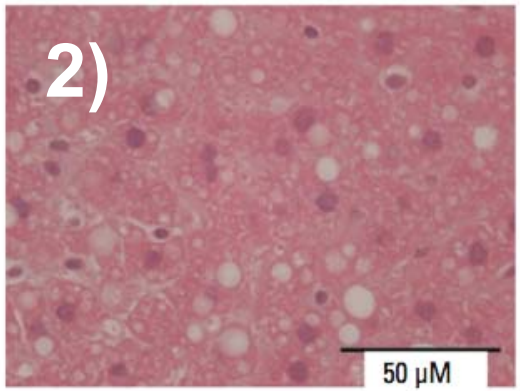
Uraffinert olje
Rå

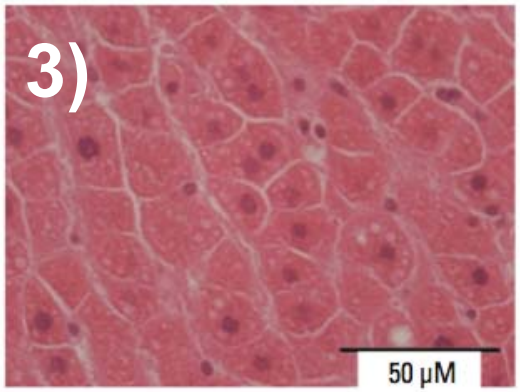
"Raffinering"

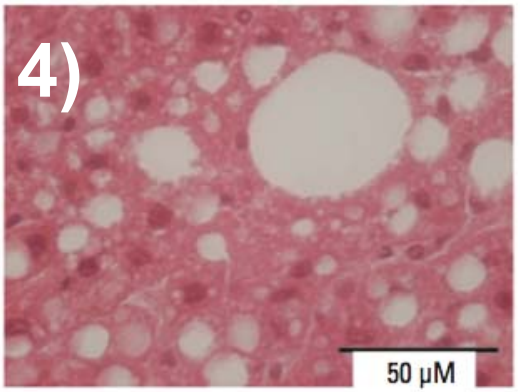
Raffinert olje

POP-er:
~0.5pg WHO 1998 TEQ -PCDD/F-PCB/g fett









1) Kontrollfôr

2) Høyfettfôr → Type 2 diabetes, Obesity

3) Høyfettfôr med raffinert lakseolje → Utviklet ikke type 2 diabetes og obesity

4) Høyfettfôr med rå lakseolje → Alvorlige metabolske forstyrrelser. Mer enn 2)

POP-er:
~9.5pg WHO 1998 TEQ -PCDD/F-PCB/g fett
Maksimum nivå I EU er 10.0pg WHO 1998 TEQ

Uraffinert olje
Rå

"Raffinering"

Raffinert olje

POP-er:
~0.5pg WHO 1998 TEQ -PCDD/F-PCB/g fett

OPEN ACCESS Freely available online

PLoS one

Chronic Consumption of Farmed Salmon Containing Persistent Organic Pollutants Causes Insulin Resistance and Obesity in Mice

Mohammad Madani Ibrahim[1,2], Even Fjære[1,3], Erik-Jan Lock[1], Danielle Naville[4], Heidi Amlund[1], Emmanuelle Meugnier[4], Brigitte Le Magueresse Battistoni[4], Livar Frøyland[1], Lise Madsen[1,3], Niels Jessen[5], Sten Lund[6], Hubert Vidal[4], Jérôme Ruzzin[1,7]*

1 National Institute of Nutrition and Seafood Research, Bergen, Norway, **2** Institute of Biomedicine, University of Bergen, Bergen, Norway, **3** Department of Biology, University of Copenhagen, Copenhagen, Denmark, **4** INSERM U-1060, INRA U-1235, CarMeN Laboratory, Lyon1 University, Oullins, France, **5** Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark, **6** Department of Internal Medicine and Diabetes and Institute of Experimental Clinical Research, Aarhus University Hospital, Aarhus, Denmark, **7** Department of Biology, University of Bergen, Bergen, Norway

PLoS ONE 6(9): e25170. doi:10.1371/journal.pone.0025170

56 dager

1) **Kontrollfôr**

2) **Ekstrem høyfettfôr** → **Type 2 diabetes**

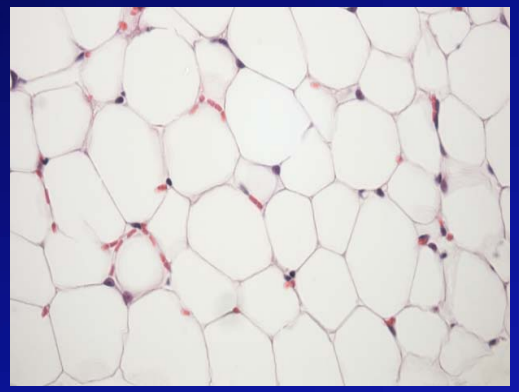
3) **Ekstrem høyfettfôr med oppdrettslaks-fillet (som fås kjøpt i vanlig dagligvarebutikk)** → **Type 2 diabetes. Mer enn 2) Obesity**

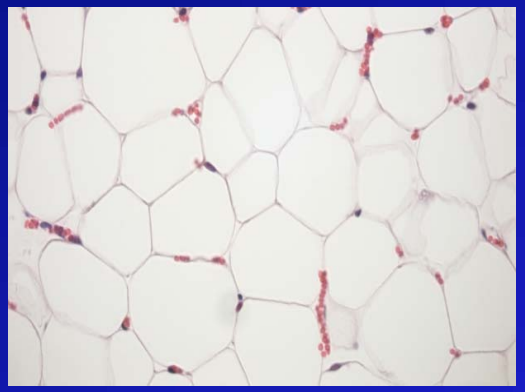
Vil det samme skje hvis mus spiser en annen type fôr ?

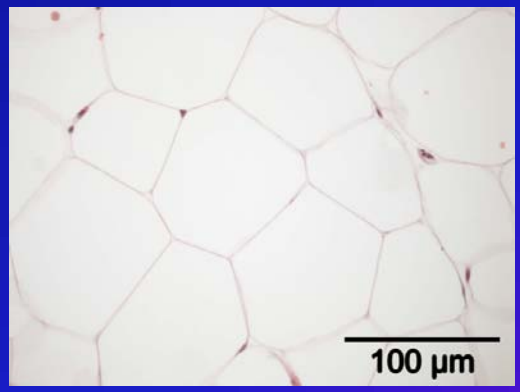
Kontrollfôr

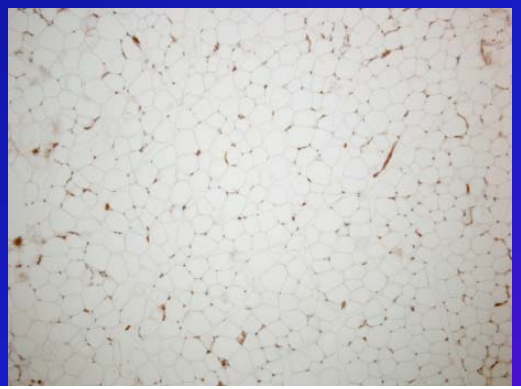
Western Diet

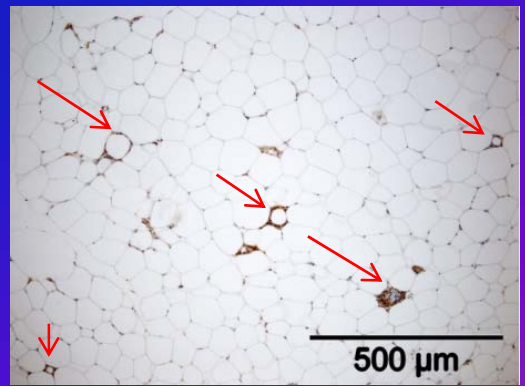
Western Diet
med oppdrettslaks-fillet











KONKLUSJON

Inntak av oppdrettslaks-fillet gir insulin resistens og andre metabolske forstyrrelser i både "ekstrem høyfettfôr" og "Western diet"

Hva vil skje dersom vi reduserer

POP nivåer i oppdrettslaks-fillet?

3) Ekstrem høyfettfôr med oppdrettslaks-fillet (som fås kjøpt i vanlig dagligvarebutikk)

→Vanlige nivåer av POP-er

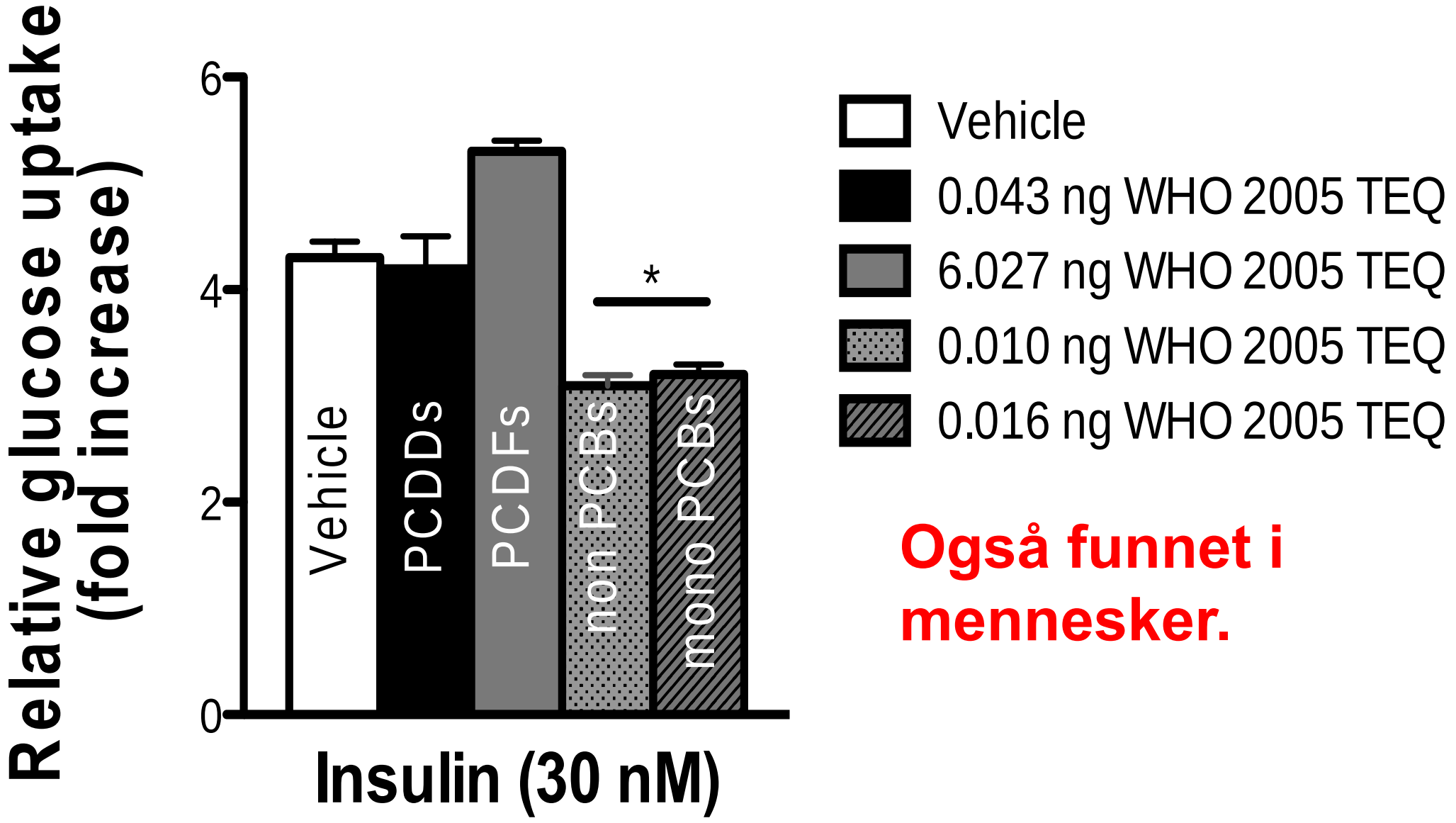
Insulin resistens…

4) Ekstrem høyfettfôr med oppdrettslaks-fillet

→Lave nivåer av POP-er (~50% mindre POP-er)

Mindre metabolske forstyrrelser

In vitro studier



Også funnet i mennesker.

POP-er / Humant perspektiv

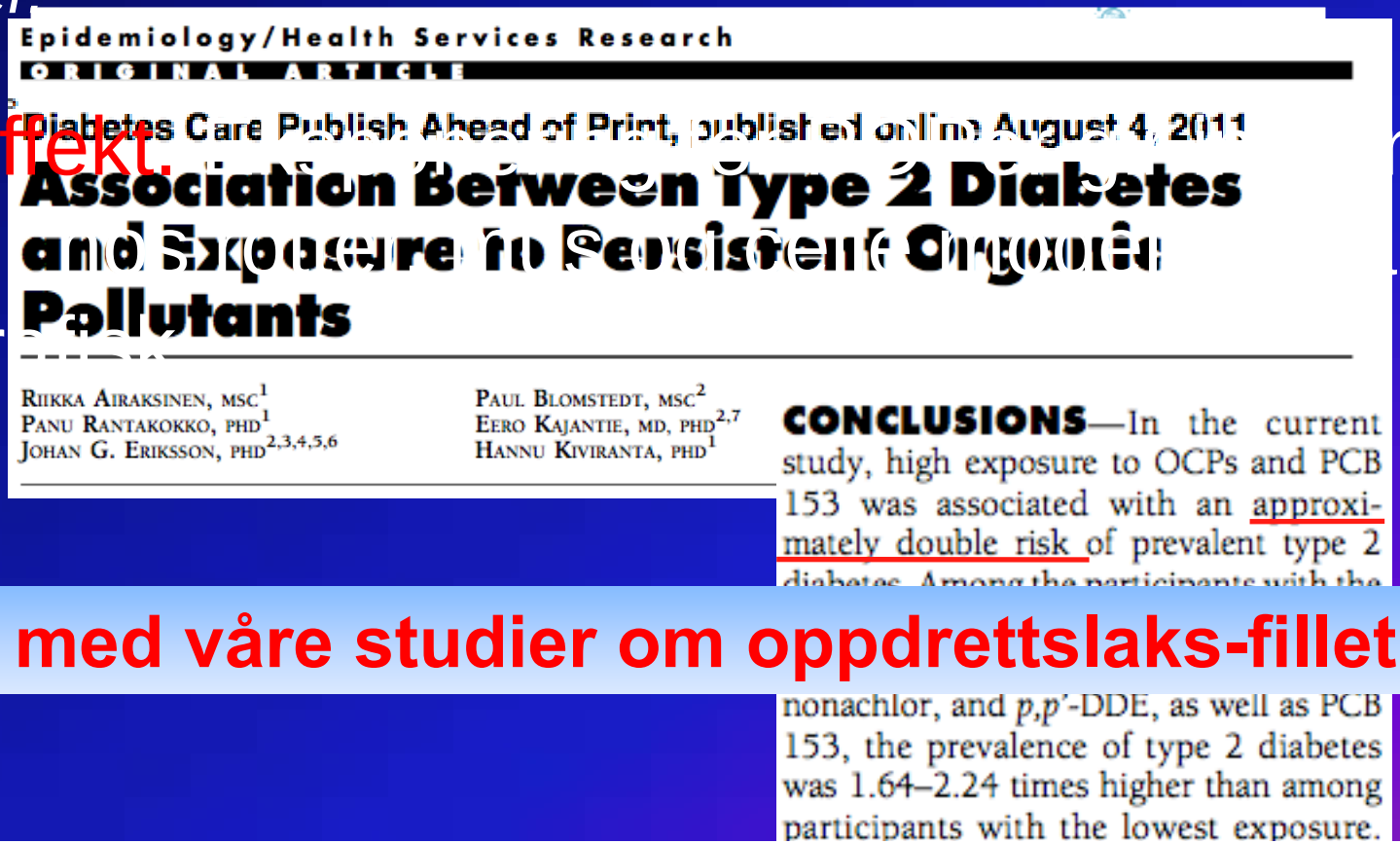
-> Sammenheng mellom POPer / diabetes og andre metabolske sykdommer. *Cirka 30 cross-sectional human studier.*

-> Prospective studier POPer / diabetes. *4 prospective human studier.*

-> Årsak effekt.

resistens..

funn i zebr



Epidemiology/Health Services Research

ORIGINAL ARTICLE

Diabetes Care Publish Ahead of Print, published online August 4, 2011

Association Between Type 2 Diabetes and Exposure to Persistent Organic Pollutants

Riikka Airaksinen, msc[1]
Panu Rantakokko, phd[1]
Johan G. Eriksson, phd[2,3,4,5,6]
Paul Blomstedt, msc[2]
Eero Kajantie, md, phd[2,7]
Hannu Kiviranta, phd[1]

CONCLUSIONS—In the current study, high exposure to OCPs and PCB 153 was associated with an approximately double risk of prevalent type 2 diabetes. Among the participants with the

nonachlor, and *p,p'*-DDE, as well as PCB 153, the prevalence of type 2 diabetes was 1.64–2.24 times higher than among participants with the lowest exposure.

Hva med våre studier om oppdrettslaks-fillet?

POP-er / Humant perspektiv

Med hensyn til

*** Musens vekt**

*** Fôring periode (56 dager)**

➡ Voksen (70kg) som spiser 250g laks / uke

Fra 20 til 44 år

➡ ELLER (Barn/Ungdom)

Fra 6 til 19 år

Total inntak av oppdrettslaks-fillet: cirka 180g

abetes, fedme…

Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes[1–4]

Luc Djoussé, J Michael Gaziano, Julie E Buring, and I-Min Lee

Am J Clin Nutr 2011;93:143-50

[1] From the Divisions of Aging (LD, JMG, and JEB) and Preventive Medicine (JMG, JEB, and I-ML), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; the Massachusetts Veterans Epidemiology and Research Information Center and Geriatric Research, Education, and Clinical Center, Boston Veterans Affairs Healthcare System, Boston, MA (LD and JMG); the Department of Ambulatory Care and Prevention, Harvard Medical School, Boston, MA (JEB); and the Department of Epidemiology, Harvard School of Public Health, Boston, MA (I-ML).

1992-1995

2008

Prospective study (average:12.4 years) of 36,328 women (mean age of 54.6 years) Women's Health Study Cohort

TABLE 4
Type 2 diabetes according to median fish consumption[1]

Quintiles of fish consumption	No. of cases	Crude	Model 1	Model 2
1 (0.47 servings of fish/wk)	464	1.0	1.0	1.0
2 (0.93 servings of fish/wk)	450	1.10 (0.97,1.25)[2]	1.11 (0.98,1.27)	1.11 (0.98,1.27)
3 (1.47 servings of fish/wk)	402	1.06 (0.92,1.21)	1.16 (1.01,1.32)	1.17 (1.02,1.34)
4 (1.93 servings of fish/wk)	503	1.12 (0.99,1.27)	1.32 (1.17,1.50)	1.35 (1.19,1.54)
5 (3.93 servings of fish/wk)	551	1.38 (1.28,1.56)	1.41 (1.25,1.60)	1.49 (1.30,1.70)
P for trend	—	<0.0001	<0.0001	<0.0001

[1] Model 1 was adjusted for age, BMI, parental history of diabetes, smoking (never, former, or current), exercise (quintiles of metabolic equivalent task hours per week), alcohol intake (4 categories), and menopausal status (not sure or pre- or postmenopausal) by using Cox proportional hazard models. Model 2 was adjusted for age, BMI, parental history of diabetes, smoking (never, former, or current), exercise (quintiles of metabolic equivalent task hours per week), alcohol intake (4 categories), menopausal status (not sure or pre- or postmenopausal), red-meat intake, and quintiles of energy intake, linoleic acid, α-linolenic acid, dietary magnesium, *trans* fat, saturated fat, cereal fiber, and glycemic index by using Cox proportional hazard models.

[2] Hazard ratio; 95% CI in parentheses (all such values).

Long-chain omega-3 fatty acids, fish intake, and the risk of type 2 diabetes mellitus[1–3]

Am J Clin Nutr 2009;90:613–20. Printed in USA. © 2009 American Society for Nutrition

Manas Kaushik, Dariush Mozaffarian, Donna Spiegelman, JoAnn E Manson, Walter C Willett, and Frank B Hu

[1] From the Departments of Nutrition (MK, WCW, and FBH), Biostatistics (DS), and Epidemiology (MK, DS, DM, JEM, WCW, and FBH), Harvard School of Public Health, Boston, MA, and the Channing Laboratory (DM, JEM, WCW, and FBH) and the Division of Preventive Medicine (JEM), Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA.

Conclusions: We found no evidence that higher consumption of LCFAs and fish reduces the risk of T2DM. Instead, higher intakes may modestly increase the incidence of this disease.

KONKLUSJONER

* Sterke bevis på at POP-eksponering kan gi insulin resistens og andre metabolske sykdommer.

* Alle mennesker (voksne, barn, spedbarn) bør unngå å bli eksponert for POP-er.

* Innhold av POP-er i mat MÅ reduseres.

International Collaborators:

- Hubert Vidal and his team

National Institute of Health and Medical Research (INSERM), Oullins,

The Research Council of Norway

* The Leiv Eiriksson mobility programme
* Grant for establishing research project
* Canadian Advanced Food and Materials Network

* Miljø, gener & helse program
* Matprogrammet

UNIVERSITAS BERGENSIS