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Biomonitoring and biomarkers to unravel prenatal risk factors for later health outcomes

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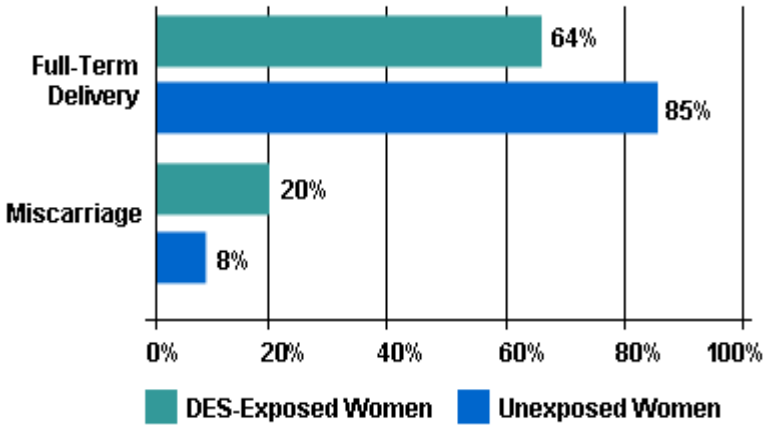
Outline

- Prenatal exposure to environmental chemicals and health outcomes later in life
- Biomarkers and biomonitoring
- Biomarkers of exposure
- Biomarkers of effect
- Conclusions

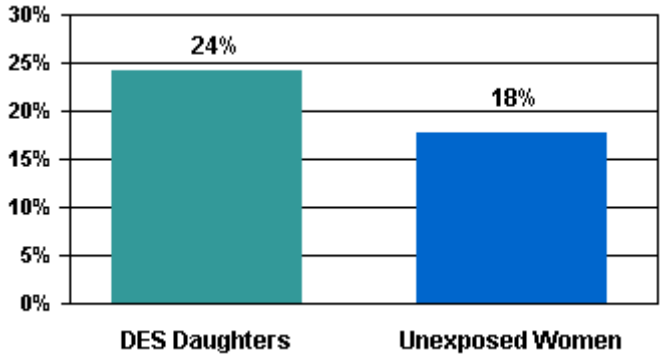
Prenatal exposures and late health outcomes

- **The story of DES (diethylstilbestrol) 1938-1950**
- **DES: a** synthetic form of estrogen (female hormone) prescribed to women to prevent pregnancy complications
- **DES Daughters :**
  - 40 times more likely to develop CCA of the vagina and cervix than women not exposed to DES
  - Pregnancy complications and fertility problems
- **DES sons**: genital abnormalities



* Kaufman, 2000

infertility

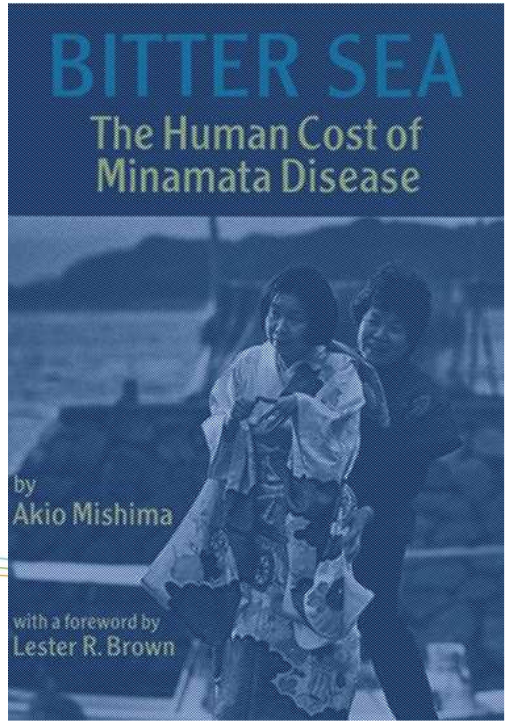


Palmer,2001

Prenatal exposures and late health outcomes : methylmercury

Minamata Disease: methylmercury poisoning in Japan 1950's

- methylmercury was being dumped into the bay by a plant of the Chisso Corporation
- "…in every case the mother was healthy, and it was not until more than three months after birth that the symptoms were recognized " Shoji Kitamura (1959)
- 10-12% of villagers developed the disease
- Formal recognition of the Minamata disease causation1963/68



Prenatal exposures and late health outcomes : methylmercury

Fish intake : Faroe island cohort

Table 1. Mercury effects on neurobehavioral tests at 7 and 14 years of age, as determined in structural equation analysis with covariate adjustment before and after addition of the frequency of maternal fish dinners during pregnancy.

	Mercury without adjustment for fish intake		Mutual adjustment			
			Fish intake		Mercury	
Age/test group	Effect[a]	*p*-Value	Effect	*p*-Value	Effect	*p*-Value
7 Years						
Motor	–9.74	0.034	25.1	0.010	–12.2	0.0092
Verbal	–10.4	0.0018	3.62	0.61	–10.8	0.0017
14 Years						
Motor	–7.41	0.033	19.9	0.006	–9.37	0.0082
Attention	–8.40	0.029	12.2	0.13	–9.54	0.016
Spatial	2.60	0.50	17.3	0.031	1.04	0.79
Verbal	–5.97	0.080	9.85	0.16	–6.87	0.049
Memory	–2.86	0.39	3.15	0.64	–3.05	0.37

[a]Effect of true exposure doubling expressed in percent of SD of latent response.

Grandjean , Weihe

Prenatal exposures and late health outcomes
Sufficient evidence, limited evidence

- Developmental milestones: Methylmercury, PCBs
- Cognitive function 0-2 yrs: Methylmercury, PCBs, lead
- Cognitive function > 2 yrs: Methylmercury, PCBs, lead, ETS
- Behavioral problems: PCBs
- Motoric function: Methylmercury, PCBs,
- Auditory function: Methylmercury, lead, PCBs
- Visual function: Methylmercury,
- Childhood lung infections: PCBs
- Childhood middle ear infections: PCBs, DDE (lactational exposure)
- Childhood cancers
  - Lymphoma: ETS
  - Leukemia: herbicides, insecticides,ETS, unspecified solvents
  - Brain: insecticides
- Child growth &Pubertal development: PCBs (post natal growth in height)
- Sudden death infant syndrome: **active smoking**

Wigle et al., J. Tox. Env. Health, Part B,11:373-517,2008

Prenatal exposure and health outcomes

- Food contaminants (PCBs, methylHg)
- Chemicals in consumer products (bisphenol A, PFOS)
- Air pollution (PM, PAHs)

DOSE ?

- Neurobehaviour,
- Sexual development,
- Immune effects
- Increased cancer incidence
- Changes in growth curves

EFFECT ?

Human biomonitoring: direct measurement in human tissues

Environmental monitoring → **biomarkers of exposure** → **biomarkers effects** → **adverse health effects**

air

dust

Consumer products

water

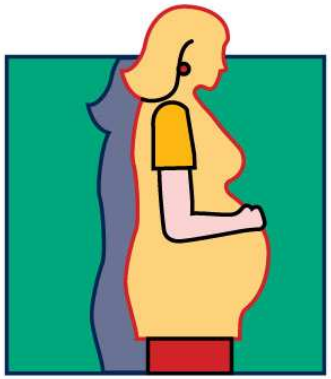
soil

Blood lead

Cotinine in urine

MeHg in hair

…



Hormone levels

DNA damage

Gene expression

Epigenetic changes

Birth weight
Growth

IQ
behaviour

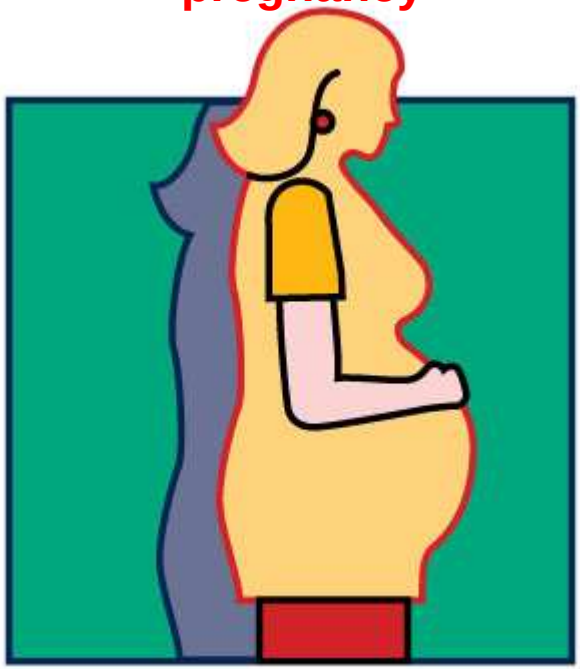
puberty

Asthma

Cancer

Human biomonitoring:
direct measurement in human tissues

Preconception **pregnancy** **post natal**



Mothers / fathers
Blood
Urine
Hair

Breast milk

Mothers
Blood
Urine
Hair

Cord blood
Placenta
meconium
Urine

Flemish human biomonitoring campaign Environmental health

Monitoring for action…

2002-2006-2011

Commissioned, financed , steered by the Ministry of the Flemish Community (Dept of Science, Public Health and Environment)

Goals

Develop a surveillance program for environmental health → policy support

- » Identify “base line values” or “reference values” for environmental pollutants in the Flemish population
- » Has the area of residence an impact on the internal pollutant levels and potential biological effects?
- » Early signaling of environmental health risks ?

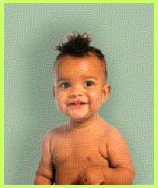
Biomarkers

1600 youngsters

Oct 2003- July 2004

42 schools

18 mL blood, 50 mL urine



1200 newborns

Sept 2002- Dec 2003

25 maternities + 2 stem cell banks

50 mL cord blood

1600 adults

Sept 2004- June 2005

43 municipalities

35 mL blood, 5 urine

Biomarker analysis in FLEHS

	Newborns: 1200	Teenagers: 1600 (14-15y)	Adults: 1600 (50-65y)
Markers of exposure	cadmium, lead marker PCBs, pesticides, dioxine-activity	cadmium, lead marker PCBs, pesticides 1-OH pyrene, tt-muconic acid	cadmium marker PCBs, pesticides, dioxine-activity 1-OH pyrene, tt-muconic acid
Markers of effect	Biometry, TSH (heel prick), Apgar score, time to pregnancy ***Questionnaire***: asthma & allergy *Follow- up of part of children*	comet test hormone balance Biometry, sexual development ***Questionnaire***: asthma & allergy	comet test, micronuclei gene-expression tumour markers 8-OH dG ***Questionnaire:*** asthma & allergy
Covariates and confounders **Markers of susceptibility**	***Questionnaire:*** general+ food *Biochemical analyses:* cholesterol, iron status cord blood	***Questionnaire:*** general + food *Biochemical analyses:* cholesterol, ferritin, urinary creatinine	***Questionnaire***: general + food *Biochemical analyses:* cholesterol, ferritin, urinary creatinine

Results:

pollutants in the perinatal period of life

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child's health

A. Neurobehavioral & cognitive development 0-3y (led by Dr Viaene- OPZ)
B. Respiratory health 0-3y (led by Dr. Desager-UA)
C. Biometry (lenghth , weight): at birth, 1-3y
D. Thyroid hormone levels

Neurological behaviour follow-up

Info on pregnancy
Postnatal depression

0 1 12 24 36 **months**

Cord blood
(Pb, Cd, PCB's, dioxins, TSH,FT3, FT4),nutrition, covariates

Behaviour child, emotional status mother, life-events

Cognitive and Behavioural tests child, IQ-test mother, Observation Home Environment, Cortisol

- - - - - *monthly quesionnaire on food & development*

- · - · - *3-monthly " " "*

Follow-up:
birth weight and growth curves

Birth weight/lenght

0 1 12 24 36 **months**

Cord blood
(Pb, Cd, PCB's, dioxins, TSH,FT3, FT4),nutrition, covariates

Weight
BMI sds

BMIsds= Child 'sBMI-population mean BMI/ population standard deviation

- - - - - *monthly quesionnaire on food & development*

-·-·- *3-monthly " " "*

Biometry:

- 138 mother infant pairs
- Exposures in cord blood: pp'-DDE, PCBs, HCB, dioxins
- Health outcomes:
  - PCBs negative effect on birth weight and birth length
  - DDE had no effect on birth weight or length
  - DDE and PCBs is associated with increased BMI during early childhood

    Verhulst et al., 2009, EHP 117, 122-126

BMI during pre-school age, correlated with adult BMI (Nader et al., 2006; Sachdev et al., 2005).

Higher BMI at that age associated with increased obesity risk in adult life (Whitaker et al. 1998).

PCBs in cord blood vs. BMI_{SDS} between 1-3 years of child's age

Parameter	β ± standard error	p
Intercept	0.758 ± 0.588	0.2
Birth Weight standard deviation score	0.333 ± 0.045	0.001
Maternal smoking ever	0.368 ± 0.172	0.03
Maternal BMI (kg/m^2)	0.046 ± 0.022	0.04
PCBs (ng/g lipids)	0.003 ± 0.001	0.03
Age of the child	-0.766 ± 0.069	< 0.001

Similar follow-up studies:
- DDE and/or PCBs ~ height in boys (Gladen et al., 2000)
- DDE ~ weight & BMI in adult females (Karmaus and Eneli, 2004)
- PCB ~ smaller height (Sagiv et al., 2007)
- PCB ~ increased growth in 5-year-old girls (Hertz-Picciottto et al., 2005)

Effects on birth weight

chemical	N	biomarker		author
PFOS	428 Japan	Maternal serum	per log10 unit: beta = -148.8 g	Washino et al, 2009
PFOA	1400 Denmark	Maternal plasma	adjusted beta = -10.63 g;	Fei et al 2007
PCB	100 Denmark	Maternal plasma	P75-P25 was 155g	Halldorson et al, 2008
HCB	300 Norway	breastmilk	beta = -90 g per 8 microg/kg milk fat	Eggesbo et al, 2009
Phtalates (DBP and DEHP)	201 China	Maternal blood		Zhang et al 2009

Negative relation between POPs and thyroid hormones measured in cord blood

Multiple linear regression model /contaminant , 200 participants
adjusted for plasma total lipids, gestational age, gender, alcohol consumption during pregnancy, and age of the mother. MAERVOET et al, , Environmental Health Perspectives (2007)

	ln fT3 (pmol/L)			ln fT4 (pmol/L)			ln TSH (mIU/L)		
	β	*p*	*n*	β	*p*	*n*	β	*p*	*n*
Polychlorinated biphenyls									
∑ 5 PCBs (ng/ml)	-0.198	**0.01**	195	-0.345	**< 0.001**	196	-0.055	0.50	196
Organochlorinated pesticides									
HCB (ng/ml)	-0.154	**0.03**	195	-0.287	**< 0.001**	196	-0.061	0.42	196
p,p´-DDE (ng/ml)	-0.074	0.29	195	-0.146	**0.04**	196	-0.048	0.51	196
Dioxin-like compounds									
Calux-TEQ (pg/ml)	-0.154	**0.04**	138	-0.165	**0.04**	138	-0.018	0.83	138
Heavy Metals									
Cadmium (ng/ml)	-0.084	0.23	186	-0.041	0.58	187	-0.035	0.63	187
Lead (ng/ml)	-0.100	0.15	186	0.064	0.37	187	0.041	0.57	187

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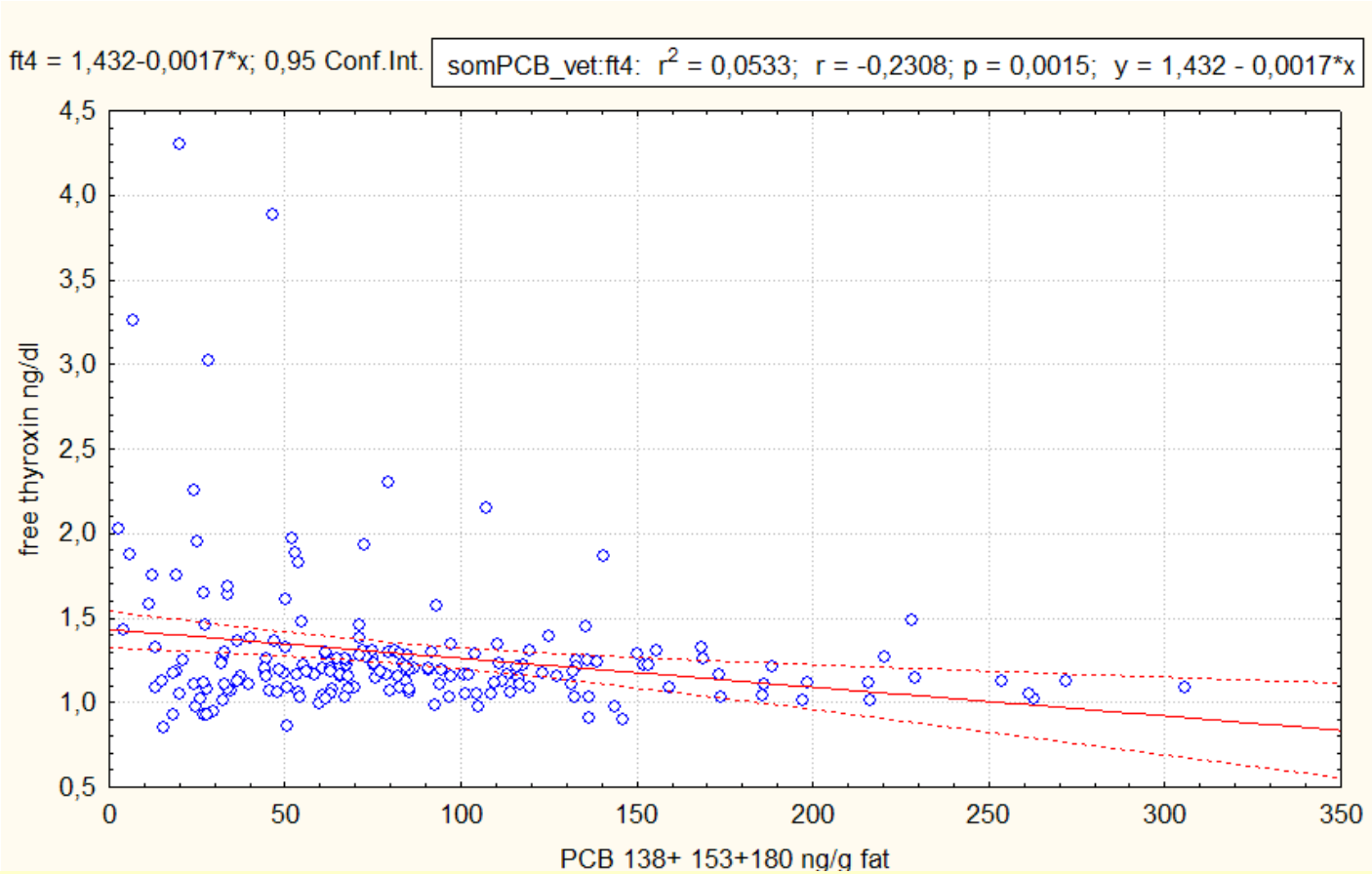
Free thyroxin vs concentration of sum marker PCB's in cord blood



Clinically irrelevant? (Kimbrough and Krouskas, 2001)

Very subtible changes in T_4/TSH homeostasis may affect development of human fetus (Boas et al., 2006; Zöller, 2001)

Asthma/allergy follow-up

Cord blood:
Pb, Cd, PCBs, dioxinlike comp
Questionnaires

Questionnaires nutrition, infections, Medication, home environment, vaccination, Airway/allergy complaints, pets, hygiene

Gut flora (faeces: 3wk, 6m, 12m)

Exhaled breath:
- condensate proteins
- Gas phase VOC

8-oxodG urine
mAPI index
Exhaled NO
Skin prick tests

0 1 2 3 4 5 6 ……..12……..……24……36 months

Conc. NO_2, PM_{10} (4x4 km): 3 trim pregnancy, 3m, 1y

Emissions benzene, NOx (1x1 km): average of 1y

Distance to motorways

Definitions

Allergy

positieve reaction on 1 allergen in skin prick test (3y)

->egg milk, grass, house dust mite

Respiratory complaints

- Coughing during day (1,2 en 3y): “last 6 m regularly coughing during day”
- Wheezing (1, 2 en 3 y): “last 6 m regularly wheezing ”
- Frequent wheezing (3y): mAPI index

Outdoor air pollutants

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Symptoms

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Pollutants cord blood

DDE - wheeze

	Wheeze 2 y
Family history asthma or allergy	+
Birth weight	+
Birth height	+
Sex	+
Pb cord blood	+
DDE cord blood	+
Antibiotics	+

Effect	OR	95% Confidence Limits	
Birth height	1,603	1,196	2,149
DDE (fat, LOG)	1,930	1,078	3,454
Number of days antibiotics	1,093	1,038	1,150

DDE - wheeze

Table 4. Adjusted RR (95% CI) between DDE in cord serum and wheezing at 4 years of age. *Sunyer, 2005*

Characteristic	All	Nonatopic
p,p′-DDE[a]	1.32 (1.13–1.54)	1.30 (1.05.1.62)
Maternal asthma	2.62 (1.46–4.71)	3.45 (1.18–10.10)
Maternal smoking	1.48 (0.89–2.47)	1.03 (0.51–2.10)
Parity (≥ second child)	1.18 (0.69–2.02)	1.54 (0.74–3.24)
Maternal education		
Primary	0.62 (0.26–1.46)	0.36 (0.13–1.04)
Secondary	0.80 (0.32–1.98)	0.37 (0.11–1.19)
High	0.29 (0.08–1.12)	0.17 (0.03–0.89)
Male	2.03 (1.15–3.57)	2.84 (1.21–6.68)
Gestational age (weeks)	0.87 (0.81–0.95)	0.90 (0.82–1.00)
Breast-feeding	0.57 (0.33–0.99)	0.34 (0.17–0.69)
p,p′-DDE in quartile (ng/mL)[b]		
< 0.57	1	1
0.57–1.03	1.00 (0.41–2.43)	1.32 (0.37–4.70)
1.03–1.90	1.62 (0.70–3.74)	2.63 (0.96–7.20)
> 1.90	2.36 (1.19–4.69)	2.49 (1.00–6.19)

- *associated with changes in immune system*
  - *immune cells (Vine 2001)*
  - *immunoglobulins (Cooper et al. 2004; Vine 2001)*
  - *cytokines (Bilrha 2003; Daniel 2002)*
- *hormone-like activity of DDE*
  - *DDE in TH_2 immune differentiation: interfere with mast cells in airways (express estrogen/progesterone receptors)*
  - *Direct effect on airway through altering b2-adrenergic responsiveness & increasing production of prostaglandins*

Outdoor air pollutants

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Symptoms

↖

Pollutants cord blood

Impact of air quality in perinatal period on airway problems in young children

perinatal NO_2, PM_{10}	**Wheezing 1y**
PM_{10} first 3 m	**Coughing 3y**
perinatl NO_2 , benzeen	**Allergy 3y**

- *Miller et al. ('04):* PAK's 3th trim pregnancy -> ↑coughing on 1y
- TRAPCA study: modelled concentrations $PM_{2.5}$, NO_2 or soot in first year of life:
  - coughing on 1y: *German cohort (Gehring et al., '02)*
  - dd astma, air way infections, cold on 2y: cohort of the Netherlands *(Brauer et al., '07)*
  - Asthma symptoms (nt sign): Swedish cohorte *(Gehring et al., '02)*

Overall conclusion…

Flemish birth cohort data support hypotheses exposure to **environmental factors early in life**, affect young child's health (0-3y)

Biometry	BMI, 3y	PCBs
Behavioural & cognitive tests	3y	Pb PCBs
Respiratory health	wheezing, 2y wheezing 1y, allergy 3y	DDE Outdoor pollutants

Mechanisms of late effects?

- hormone levels,
- oxidative stress
- epigenetic changes?

Biomarkers of effect ?

→ mechanistic

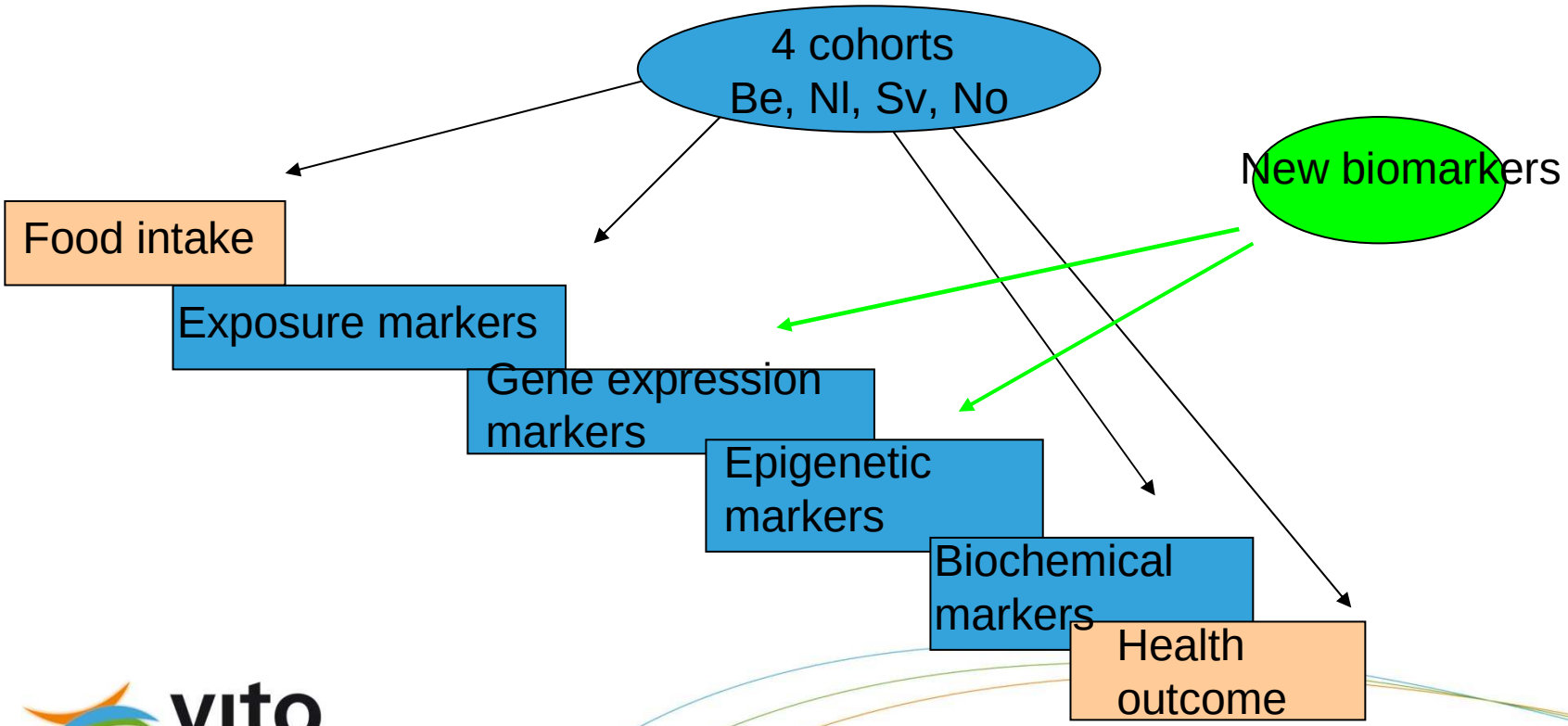
→early warning

Epigenetic changes as biomarkers for environmental exposures: human studies?

exposure	N	Biomarker matrix	effect	author
Traffic related PAH exposure	56 children	Umbilical Cord white blood cells	Increased DNA Methylation of 59-CpG Island of ACSL3	Perera et al, 2009
Sum of POPs	70 Greenlandic Inuit	Blood samples	DNA Hypomethylation	Rusiecki et al, 2009
Peak exposures to,traffic particles	718 elderly Boston	Blood leucocyt DNA methylation	DNA hypomethylation	Baccarelli 2009
benzene	213 adults Milan	Blood DNA samples	DNA hypomethylation	Bollati et al, 2007

OBELIX
ENDOCRINE DISRUPTORS AND OBESITY

OBELIX: OBesogenic Endocrine disrupting chemicals: LInking prenatal eXposure to the development of obesity later in life



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