Integrating lifecourse, environmental, molecular and epigenetic epidemiology.

any chances?

EPI 2008 18th World Congress of Epidemiology www.epi2008.com

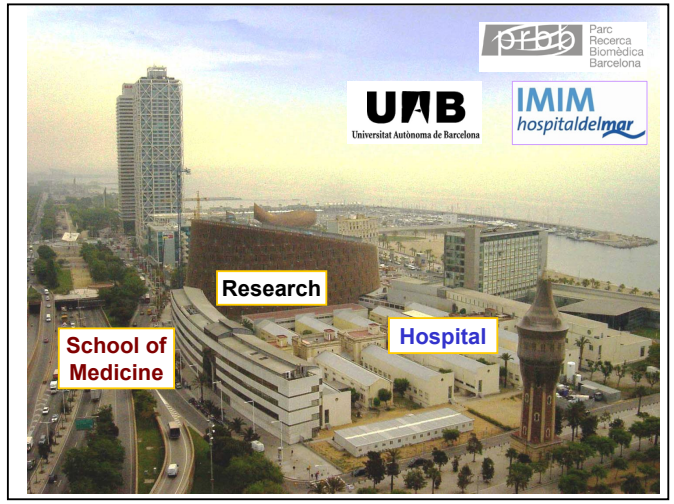
XVIII IEA World Congress of Epidemiology
VII Brazilian Congress of Epidemiology
Epidemiology in the construction of health for all: tools for a changing world
September 20 - 24, 2008 - FIERGS - Porto Alegre - RS - Brazil

Miquel Porta, MD, MPH, PhD
Institut Municipal d'Investigació Mèdica,
Universitat Autònoma de Barcelona, and
University of North Carolina at Chapel Hill.

Porto Alegre
Wed., Sept. 24, 2008

IEA Hosted and supported by the International Epidemiological Association

ABRASCO
Associação Brasileira de Pós-Graduação em Saúde Coletiva



XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology

www.imim.es

Home > Research programmes > Epidemiology and public health >

Clinical and Molecular Epidemiology of Cancer
Scientific documents

- Accumulation of genetic and epigenetic alterations: a key causal process between the environment and the occurrence of cancer
- Between molecules and the environment: keeping patients in the picture
- B. Conferencia: "¿Deberíamos analizar los compuestos tóxicos persistentes que tenemos en la sangre?"
- A. Encuentro de trabajo: "Concentraciones de compuestos tóxicos persistentes (CTPs) en la población general española: información disponible y posibles estudios para un diagnóstico de la situación"

IMIM hospitaldelmar
Parc Recerca Biomèdica Barcelona
UAB Universitat Autònoma de Barcelona

→ integrate...

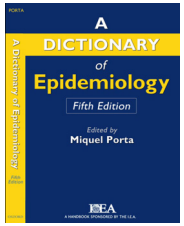
Integrative research

Yes.

INTEGRATIVE RESEARCH Research that integrates knowledge, data, methods, techniques, reasoning and cultural referents from several disciplines, approaches and levels of analysis to generate knowledge that no discipline alone could achieve.

e.g., analyses of the relationships among gene structure, expression and function; on the relationships among molecular pathways, pathophysiology and clinical phenotypes, as in clinical pharmacology and clinical genetics; research that asseses interactions among environmental, genetic & epigenetic processes.

To integrate: to make a new whole; to combine parts into a new system and get them to interact so that the system expresses functions unavailable to the parts.



Oxford University Press, 2008.

Journal of Clinical Epidemiology 60 (2007)

"Omics" research, monetization of intellectual property and fragmentation of knowledge: can clinical epidemiology strengthen integrative research?

Miquel Porta[a,b,c,*], Ildefonso Hernández-Aguado[c,d], Blanca Lumbreras[c,d]

this paper also sketches methodological proposals that may help *integrate* microbiological, clinical, and environmental evidence.

Clinical and epidemiological reasoning, knowledge, and methods need to be applied on a much wider scale than until now by "omics" studies that aim at making inferences relevant for human beings.

"omics research" could apply a diversity of clinicoepidemiological models favoring *integrative research*.

+ Porta M. In: Von Hoff DD et al. Pancreatic cancer. Boston: Jones & Bartlett, 2005.
+ *Clinical Biochemistry* 2008 ... + *Proteomics Clinical Applications* 2009

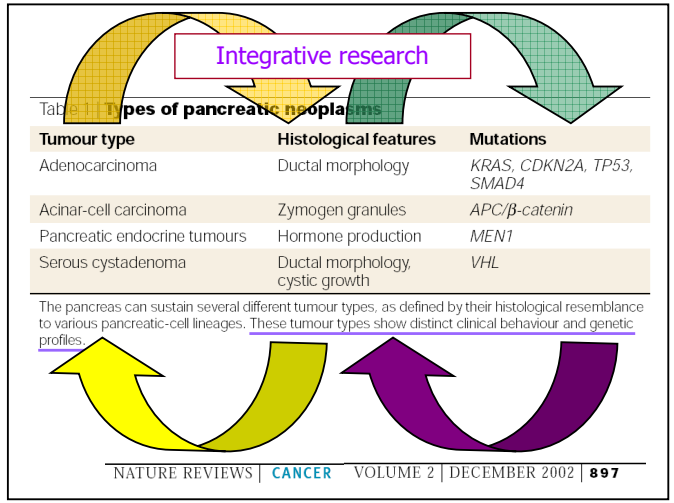


Table 1 | Types of pancreatic neoplasms

Tumour type	Histological features	Mutations
Adenocarcinoma	Ductal morphology	*KRAS, CDKN2A, TP53, SMAD4*
Acinar-cell carcinoma	Zymogen granules	*APC/β-catenin*
Pancreatic endocrine tumours	Hormone production	*MEN1*
Serous cystadenoma	Ductal morphology, cystic growth	*VHL*

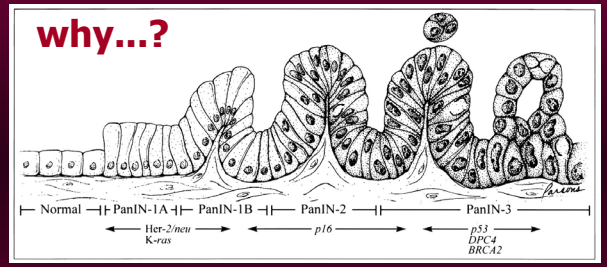
The pancreas can sustain several different tumour types, as defined by their histological resemblance to various pancreatic-cell lineages. These tumour types show distinct clinical behaviour and genetic profiles.

NATURE REVIEWS | CANCER VOLUME 2 | DECEMBER 2002 | 897

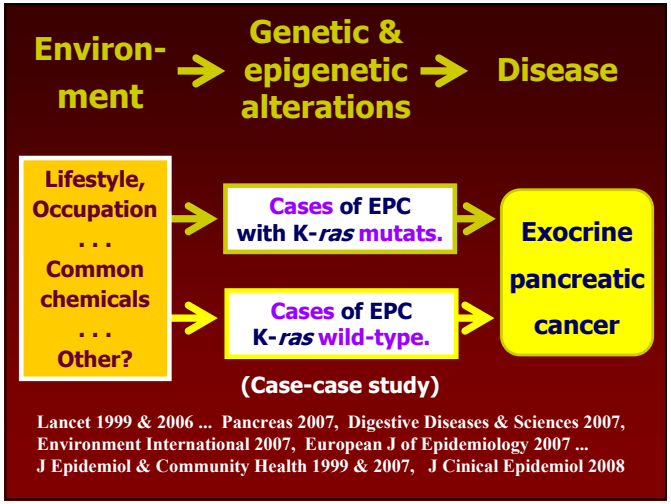
XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

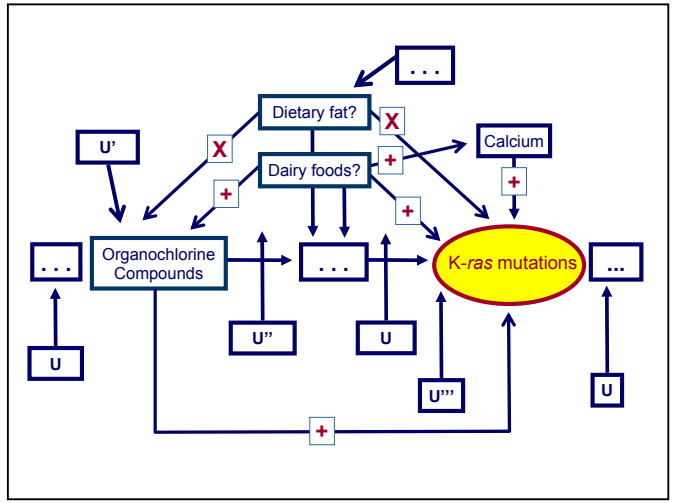
Integrating lifecourse...
environmetal, epigetic epidemiology

a progression model (i.e., hypothesis) for EPC:



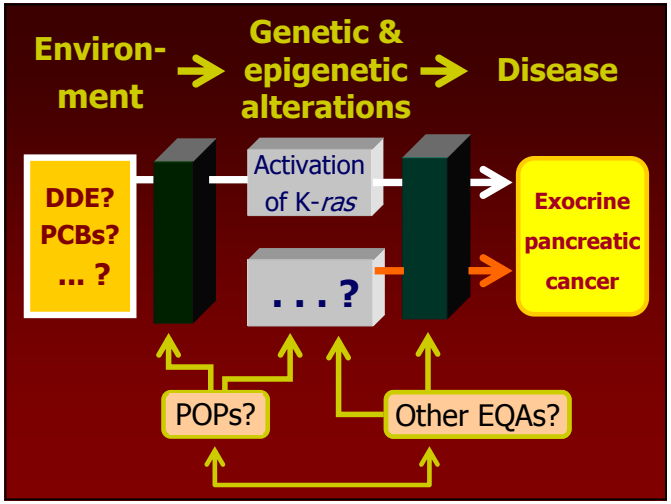
Hruban RH, Goggins M, Parsons J, Kern SE.
Progression model for pancreatic cancer.
Clin Cancer Res 2000.

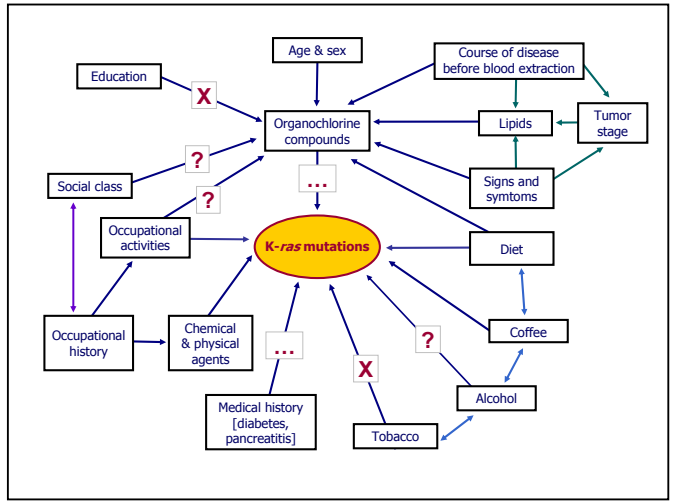




XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology





Accumulation
of genetic & epigenetic alterations:
is a key causal process
between the environment
and the occurrence of cancer.

EDITORIAL

La acumulación de alteraciones genéticas y epigenéticas:
un proceso causal clave entre el medio ambiente
y las enfermedades de etiología compleja

Gac Sanit. 2005;19(4):273-6

(Accumulation of genetic and epigenetic alterations: a key causal process between the environment and diseases of complex etiology)

EPIGENETICS:
heritable changes in gene expression
that are not regulated by
the DNA nucleotide sequence
e.g., gene silencing by promoter
hypermethylation or histone modification.

Information heritable during cell division
other than the DNA sequence itself.

Andreas Luch
FEBRUARY 2005
NATURE REVIEWS | CANCER

NATURE AND NURTURE – LESSONS
FROM CHEMICAL CARCINOGENESIS

XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology

Epigenetic
Refers to mitotically or
meiotically heritable changes
in gene expression that do
not involve a change in DNA
sequence.

Information heritable during cell division
other than the DNA sequence itself.

NATURE REVIEWS | GENETICS | APRIL 2007

EPIGENETICS:
heritable changes in gene expression
that are not regulated by
the DNA nucleotide sequence
e.g., gene silencing by promoter
hypermethylation or histone modification.

Impressive rediscovery of the lifelong
influence of environmental agents
on gene expression.

Andreas Luch
FEBRUARY 2005
NATURE REVIEWS | CANCER

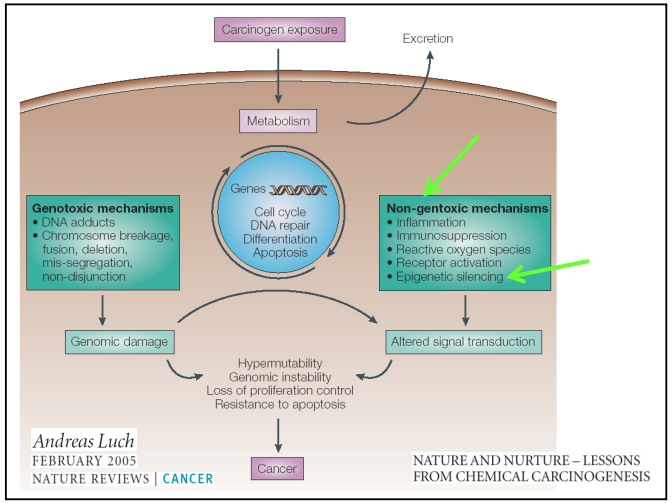
NATURE AND NURTURE – LESSONS
FROM CHEMICAL CARCINOGENESIS

e.g.: Nickel, Cadmium, Arsenic: carcinogenicity also involves DNA hypermethylation and histone deacetylation, both of which contribute to heterochromatin condensation and the epigenetic silencing of some genes.

Impressive rediscovery of the lifelong influence of environmental agents on gene expression.

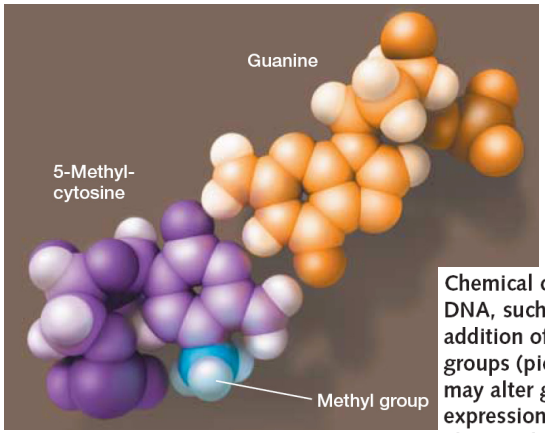
Andreas Luch
FEBRUARY 2005
NATURE REVIEWS | CANCER

NATURE AND NURTURE – LESSONS FROM CHEMICAL CARCINOGENESIS



XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology



Chemical changes to DNA, such as the addition of methyl groups (pictured), may alter gene expression without altering the gene's DNA sequence.

JAMA, March 19, 2008

FOCUS ON EPIGENETICS

REVIEWS

Environmental epigenomics and disease susceptibility

Randy L. Jirtle and Michael K. Skinner‡*

Abstract | Epidemiological evidence increasingly suggests that environmental exposures early in development have a role in susceptibility to disease in later life. In addition, some of these environmental effects seem to be passed on through subsequent generations. Epigenetic modifications provide a plausible link between the environment and alterations in gene expression that might lead to disease phenotypes. An increasing body of evidence from animal studies supports the role of environmental epigenetics in disease susceptibility. Furthermore, recent studies have demonstrated for the first time that heritable environmentally induced epigenetic modifications underlie reversible transgenerational alterations in phenotype. Methods are now becoming available to investigate the relevance of these phenomena to human disease.

NATURE REVIEWS | GENETICS | APRIL 2007

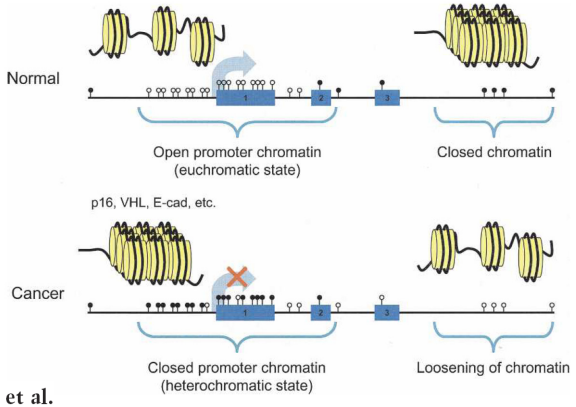
REVIEWS

Box 2 | **Key questions for environmental epigenetics**

- Which human genes result in enhanced disease susceptibility when they are epigenetically deregulated by environmental factors?
- What environmental factors deleteriously alter the epigenome, and at what doses?
- What role does the epigenome have in reproduction, development and disease aetiology?
- Are there nutritional supplements that can reduce the harmful effects of chemical and physical factors on the epigenome?
- Can epigenetic biomarkers be identified that will allow for the detection of early-stage diseases?
- Can detection technologies be developed that will allow for a quick and accurate genome-wide assessment of epigenome?
- Can epigenetics be integrated into systems biology as an important regulatory mechanism?

NATURE REVIEWS | GENETICS | APRIL 2007

The normal versus cancer epigenome



Ting et al.
GENES & DEVELOPMENT 2006

XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre
Integrating lifecourse...
environmetal, epigetic epidemiology

Environmental Epigenomics in Human Health and Disease

Dana C. Dolinoy and Randy L. Jirtle*

The epigenome consists of the DNA methylation marks and histone modifications involved in controlling gene expression. It is accurately reproduced during mitosis and can be inherited transgenerationally. The innate plasticity of the epigenome also enables it to be reprogrammed by nutritional, chemical, and physical factors. Imprinted genes and metastable epialleles represent two classes of genes that are particularly susceptible to environmental factors because their regulation is tightly linked to epigenetic mechanisms. To fully understand the etiology of the most devastating diseases that plague humans, the full complexity of the human epigenome will ultimately need to be characterized. Moreover, the elucidation of the interaction of the environment with the epigenome should allow for the development of novel epigenetic-based diagnostic, prevention, and therapeutic strategies for human diseases. Herein, we introduce the emerging field of environmental epigenomics, discuss the importance of imprinted genes and metastable epialleles as epigenetically labile genomic targets, and endorse the genome-wide identification of the full suite of epigenetically labile targets in both the mouse and human genomes.

Environmental and Molecular Mutagenesis 49:4–8 (2008)

The history of cancer epigenetics

Andrew P. Feinberg and Benjamin Tycko

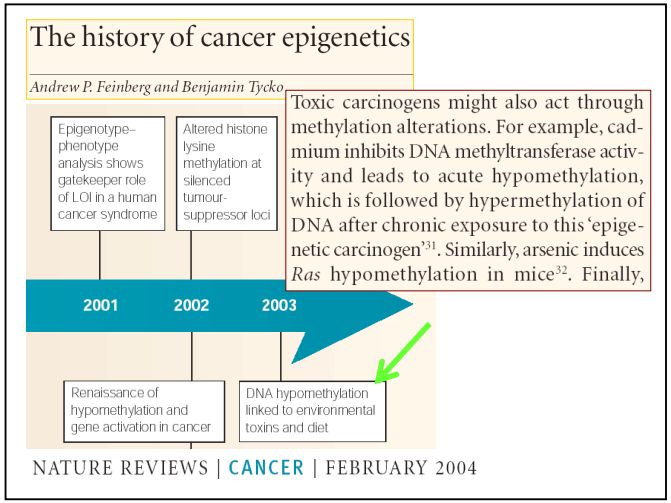
Box 1 | **The three main types of epigenetic information**

Cytosine DNA methylation is a covalent modification of DNA, in which a methyl group is transferred from *S*-adenosylmethionine to the C-5 position of cytosine by a family of cytosine (DNA-5)-methyltransferases. DNA methylation occurs almost exclusively at CpG nucleotides and has an important contributing role in the regulation of gene expression and the silencing of repeat elements in the genome.

Genomic imprinting is parent-of-origin-specific allele silencing, or relative silencing of one parental allele compared with the other parental allele. It is maintained, in part, by differentially methylated regions within or near imprinted genes, and it is normally reprogrammed in the germline.

Histone modifications — including acetylation, methylation and phosphorylation — are important in transcriptional regulation and many are stably maintained during cell division, although the mechanism for this epigenetic inheritance is not yet well understood. Proteins that mediate these modifications are often associated within the same complexes as those that regulate DNA methylation.

NATURE REVIEWS | CANCER | FEBRUARY 2004



International Journal of Epidemiology 2004;**33**:929–935

Epigenetic epidemiology

Eva Jablonka

Almost by definition complex diseases depend on the intricate interplay of genetic and environmental factors that lead to changed epigenetic states,

Transgenerational epigenetic inheritance

the patterns of transmission of complex hereditary diseases may reflect the actions of non-mutagenic environmental agents and nutritional conditions on gene expression in ancestral generations, as well as the effects of the DNA that individuals actually inherited.

International Journal of Epidemiology 2004;**33**:929–935

Epigenetic epidemiology

Eva Jablonka

Effective disease prevention and treatment will have to overcome the inertia caused by the persistence of epigenetic effects that are the result of exposure to toxicants and pollutants in earlier generations: removing present offending environmental factors may not be enough—it may need active and specific compensation for past epigenetic programming.[49]

XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

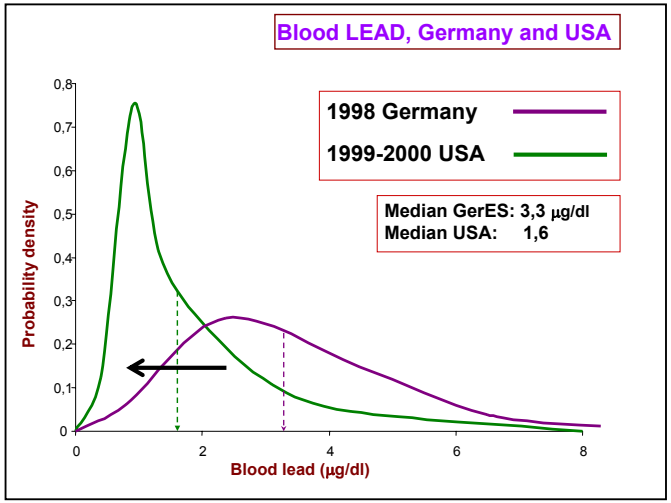
Integrating lifecourse...
environmetal, epigetic epidemiology

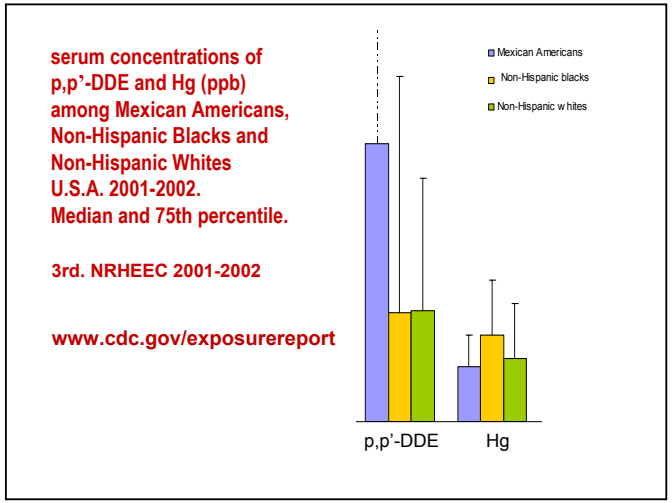
Attention to mechanisms
interactions
indirect effects
(e.g., epigenetic effects)

YES, very difficult to detect:
subtle, low RR, long-term effects. But...

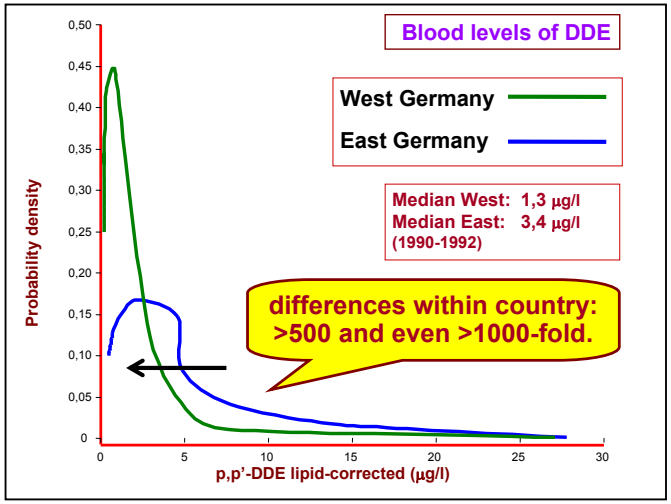
NOT negligible: 1) mechanistic interest.

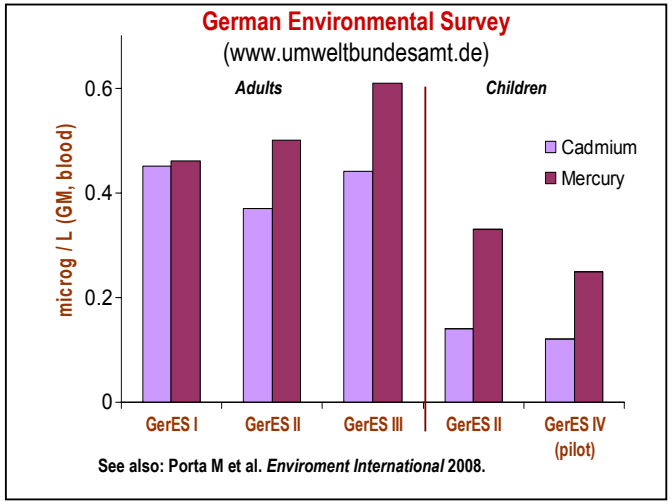
2) ↑↑↑ number of individuals exposed to environmental chemical agents.



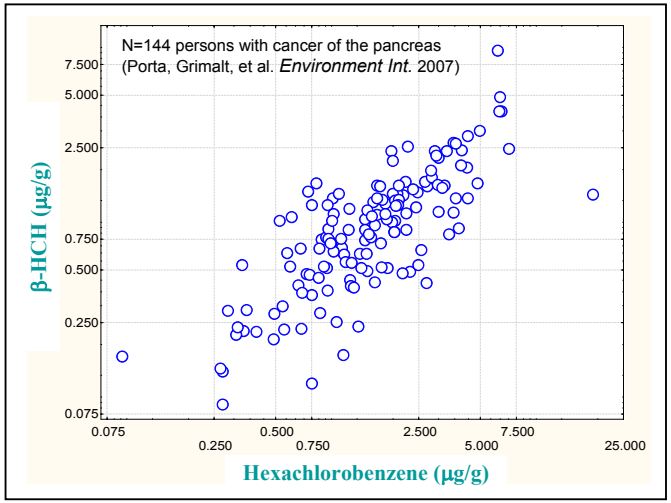


XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre
Integrating lifecourse...
environmetal, epigetic epidemiology





See also: Porta M et al. *Enviroment International* 2008.



Association of Urinary Bisphenol A Concentration With Medical Disorders and Laboratory Abnormalities in Adults

Iain A. Lang, PhD
Tamara S. Galloway, PhD
Alan Scarlett, PhD

JAMA, September 17, 2008

Context Bisphenol A (BPA) is widely used in epoxy resins lining food and beverage containers. Evidence of effects in animals has generated concern over low-level chronic exposures in humans.

David Melzer, MB, PhD

Results Higher urinary BPA concentrations were associated with cardiovascular diagnoses in age-, sex-, and fully adjusted models (OR per 1-SD increase in BPA concentration, 1.39; 95% confidence interval [CI], 1.18-1.63; $P=.001$ with full adjustment). Higher BPA concentrations were also associated with diabetes (OR per 1-SD increase in BPA concentration, 1.39; 95% confidence interval [CI], 1.21-1.60; $P<.001$) but not with other studied common diseases. In addition, higher BPA concentrations were associated with clinically abnormal concentrations of the liver enzymes γ-glutamyltransferase (OR per 1-SD increase in BPA concentration, 1.29; 95% CI, 1.14-1.46; $P<.001$) and alkaline phosphatase (OR per 1-SD increase in BPA concentration, 1.48; 95% CI, 1.18-1.85; $P=.002$).

XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology

Arsenic Exposure and Prevalence of Type 2 Diabetes in US Adults

Ana Navas-Acien, MD, PhD
Ellen K. Silbergeld, PhD
Roberto Pastor-Barriuso, PhD
Eliseo Guallar, MD, DrPH

JAMA, August 20, 2008

Design, Setting, and Participants Cross-sectional study in 788 adults aged 20 years or older who participated in the 2003-2004 National Health and Nutrition Examination Survey (NHANES) and had urine arsenic determinations.

Results

After adjustment for diabetes risk factors and markers of seafood intake, participants with type 2 diabetes had a 26% higher level of total arsenic (95% confidence interval [CI], 2.0%-56.0%) than participants without type 2 diabetes

After similar adjustment, the odds ratios for type 2 diabetes comparing participants at the 80th vs the 20th percentiles were 3.58 for the level of total arsenic (95% CI, 1.18-10.83).

PNAS

Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development

Dana C. Dolinoy*†‡, Dale Huang*, and Randy L. Jirtle

2007

The hypothesis of fetal origins of adult disease posits that early developmental exposures involve epigenetic modifications, such as DNA methylation, that influence adult disease susceptibility. *In utero* or neonatal exposure to bisphenol A (BPA), a high-production-volume chemical used in the manufacture of polycarbonate plastic, is associated with higher body weight, increased breast and prostate cancer, and altered reproductive function.

evidence that epigenetic patterning during early stem cell development is sensitive to BPA exposure. Moreover, maternal dietary supplementation, with either methyl donors like folic acid or the phytoestrogen genistein, negated the DNA hypomethylating effect of BPA. Thus, we present compelling evidence that early developmental exposure to BPA can change offspring phenotype by stably altering the epigenome, an effect that can be counteracted by maternal dietary supplements.

Clinical and Experimental Allergy, **36**, 1236–1241 2006

Early exposure to dichlorodiphenyldichloroethylene, breastfeeding and asthma at age six

J. Sunyer*†, M. Torrent‡, R. Garcia-Esteban*, N. Ribas-Fitó*, D. Carrizo§, I. Romieu¶, J. M. Antó*† and J. O. Grimalt§

Results At birth and 4 years of age, all children had detectable levels of DDE (median 1 ng/mL and 0.8 ng/mL, respectively). From birth to age 4, the mean DDE level among children with artificial feeding decreased by 72%, while among breastfed children it increased by 53%. Diagnosed asthma and persistent wheezing were associated with DDE at birth [odds ratio (OR) for an increase in 1 ng/mL, OR = 1.18, 95% confidence interval (95% CI) = 1.01–1.39 and OR = 1.13, 95% CI = 0.98–1.30, respectively], but not with DDE at 4 years. Neither breastfeeding nor atopy modified these associations ($P > 0.3$). Breastfeeding protected against diagnosed asthma (OR = 0.33, 95% CI = 0.08–0.87) and wheezing (OR = 0.53, 95% CI = 0.34–0.82) in children with low and high DDE levels at birth.
Conclusion In a community without known dichlorodiphenyltrichloroethane environmental releases, this study strengthens the evidence for an effect of DDE on asthma by measuring the disease at age 6 and does not support the hypothesis that DDE modifies the protective effect of breastfeeding on asthma.

EDITORIAL

Could low-level background exposure to persistent organic pollutants contribute to the social burden of type 2 diabetes?

Duk-Hee Lee, David R Jacobs Jr, Miquel Porta

Persistent organic pollutants may contribute to cause diabetes

J Epidemiol Community Health 2006;**60**:1006–1008.

XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology

Association Between Serum Concentrations of Persistent Organic Pollutants and Insulin Resistance Among Nondiabetic Adults

Results from the National Health and Nutrition Examination Survey 1999–2002

DUK-HEE LEE *Diabetes Care* 30:622–628, 2007

OC pesticides and nondioxin-like PCBs may be associated with type 2 diabetes risk by increasing insulin resistance,

POPs may interact with obesity to increase the risk of type 2 diabetes.

Response to Porta DIABETES CARE, NOVEMBER 2006

THE LANCET
Vol 368 August 12, 2006 *Miquel Porta*

Persistent organic pollutants and the burden of diabetes

When assessing the mechanisms linking diet, fat intake, obesity, and diabetes, persistent organic pollutants should also be considered. We need a better understanding of the burden of diabetes that these pollutants might contribute to cause.

Molecular Endocrinology March 2006

Michelle M. Tabb and Bruce Blumberg

New Modes of Action for Endocrine-Disrupting Chemicals

EDC affect the transcriptional activity of nuclear receptors by modulating proteasome-mediated degradation of nuclear receptors and their coregulators. Xenobiotics and environmental contaminants can act as hormone sensitizers by inhibiting histone deacetylase activity and stimulating mitogen-activated protein kinase activity. Some endocrine disrupters can have genome-wide effects on DNA methylation status. Others can modulate lipid metabolism and adipogenesis, perhaps contributing to the current epidemic of obesity.

- Perinatal exposure to environmental estrogens and the development of obesity. [Mol Nutr Food Res. 2007]
- Developmental exposure to endocrine disruptors and the obesity epidemic. [Reprod Toxicol. 2007]
- Adverse effects of the model environmental estrogen diethylstilbestrol are transmitted to subsequent generations. [Endocrinology. 2006]
- Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. [Endocrinology. 2006]
- Estrogenic environmental endocrine-disrupting chemical effects on reproductive neuroendocrine function and dysfunction across [Rev Endocr Metab Disord. 2007]

Environmental Obesogens: Organotins and Endocrine Disruption via Nuclear Receptor Signaling

Felix Grün and Bruce Blumberg

Endocrinology 147(6) (Supplement):S50–S55

XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology

international journal of andrology 2008

Effects of endocrine disruptors on obesity

Retha R. Newbold, Elizabeth Padilla-Banks, Wendy N. Jefferson

Environmental chemicals with hormone-like activity can disrupt the programming of endocrine signalling pathways that are established during perinatal life and result in adverse consequences that may not be apparent until much later in life. Increasing evidence implicates developmental exposure to environmental hormone mimics with a growing list of adverse health consequences in both males and females. Most recently, obesity has been proposed to be yet another adverse health effect of exposure to endocrine disrupting chemicals (EDCs) during critical stages of development.

Together, these data suggest new targets (i.e. adipocyte differentiation and mechanisms involved in weight homeostasis) of abnormal programming by EDCs, and provide evidence that support the scientific term 'the developmental origins of adult disease'. The emerging idea of an association of EDCs and obesity expands the focus on obesity from intervention and treatment to include prevention and avoidance of these chemical modifiers.

Toxicokinetic model for OCs in adipose tissue

Improving Organochlorine Biomarker Models for Cancer Research

Mary S. Wolff

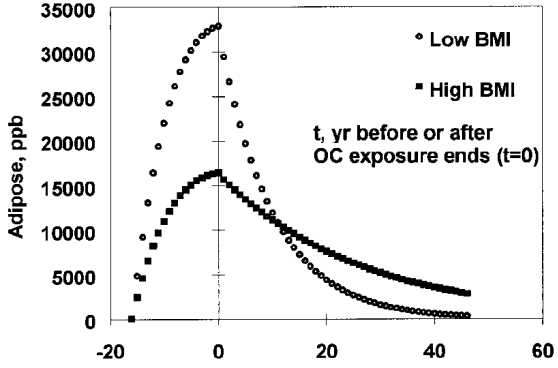
Cancer Epidemiol Biomarkers Prev 2005;14(9).

After adjusting for covariates, DDE and PCB were both positively associated with BMI and inversely with BMI-gain; they were lowest with low BMI, high BMI-gain, and longer lactation. This pattern is consistent with a pharmacokinetic model that predicts higher body burdens during windows of highest uptake, faster elimination of organochlorine compounds in leaner women, and lowered levels accompanying BMI-gain.

Cancer Epidemiology, Biomarkers & Prevention *October 1999*

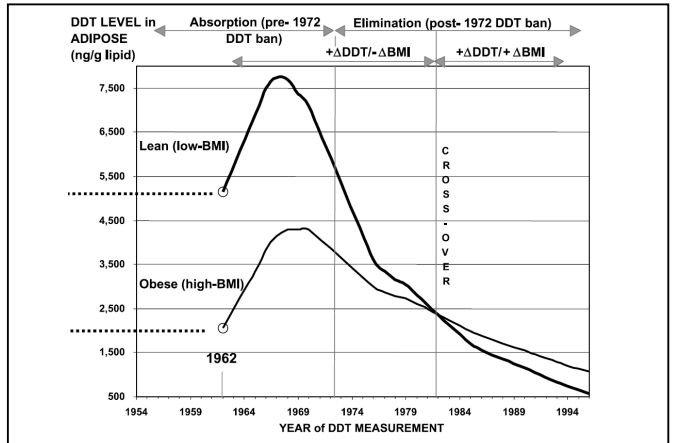
Mary S. Wolff[1] and Henry A. Anderson

Toxicokinetic model for OCs in adipose tissue



Cancer Epidemiology, Biomarkers & Prevention *October 1999*

Mary S. Wolff[1] and Henry A. Anderson



single birth-cohort model of DDT with two extremes of BMI where first exposure starts in 1962 (modified from ref. 8). DDT levels in adipose lipids for a lean BMI (~ 23 kg/m^2) are in the upper DDT curve. Levels for an obese BMI (~ 35 kg/m^2) are in the lower curve.

XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology

Toxicokinetic model for OCs in adipose tissue

Pharmacokinetic Variability and Modern Epidemiology- The Example of Dichlorodiphenyltrichloroethane, Body Mass Index, and Birth Cohort

Cancer Epidemiol Biomarkers Prev 2007

Mary S. Wolff,[1] Henry A. Anderson,[2] Julie A. Britton,[3] and Nat Rothman[4]

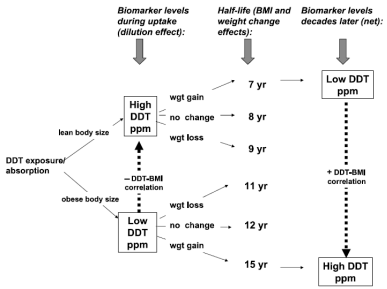


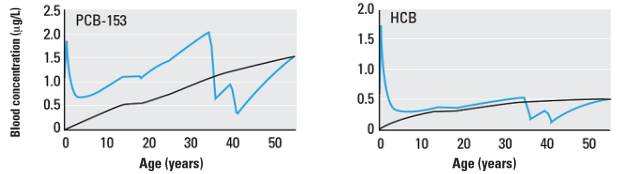
Figure 1. Summary of body size effects on DDT levels in lipids. Early effect is dilution (*Biomarker levels during uptake*). Subsequent postexposure effects on DDT levels decades later result from DDT half-life, including weight change alteration of elimination rate (*Biomarker levels decades later*); half-life estimates are based on those from Thomaseth and Salvan (12).

July 2008 • Environmental Health Perspectives

Physiologically Based Pharmacokinetic Modeling of Persistent Organic Pollutants for Lifetime Exposure Assessment: A New Tool in Breast Cancer Epidemiologic Studies

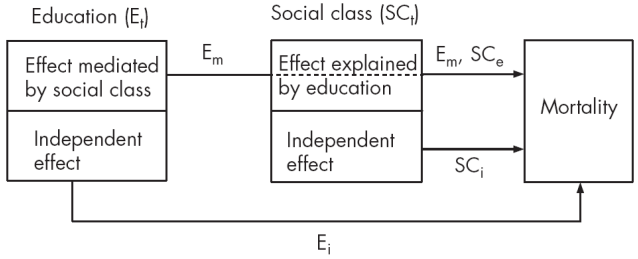
Marc-André Verner,[1] Michel Charbonneau,[2] Lizbeth López-Carrillo,[3] and Sami Haddad[1]*

[1]Département des sciences biologiques, Université du Québec à Montréal, Montréal, Québec, Canada; [2]INRS-Institut Armand-Frappier, Université du Québec, Laval, Québec, Canada; [3]Instituto Nacional de Salud Publica, Cuernavaca, Mexico

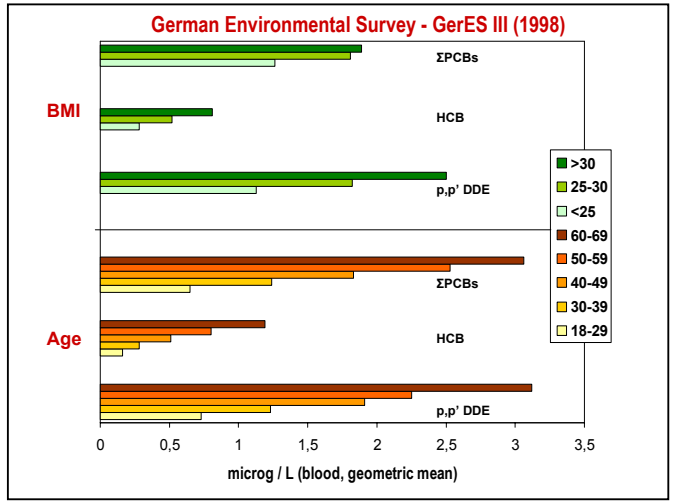


Toxicokinetic profiles for normal body weight history for a woman who was exposed to 10 ng/kg/day of each of the chemicals and had no pregnancy (black line) or was breast-fed for 6 months in childhood, was exposed to 18.7 ng/kg/day PCB-153, 11.6 ng/kg/day HCB, and who had two pregnancies at 35 and 40 years of age followed by 12-month lactation periods (blue line).

Figure 1 Pathways from education and social class to mortality. E_i = effect of education independent of social class; E_m = effect of education mediated by social class; E_t = total effect of education; SC_i = effect of social class independent of education; SC_e = effect of social, class explained by education; SC_t = total effect of social class.

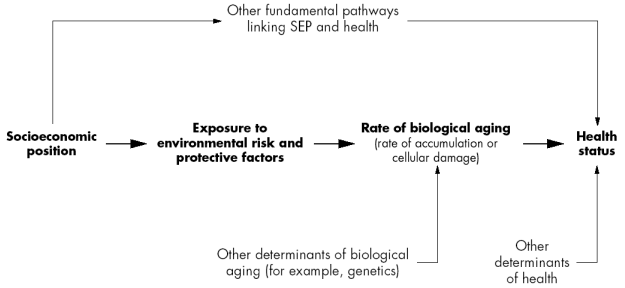


Pekka Martikainen et al. – *J Epidemiol Community Health* 2007.

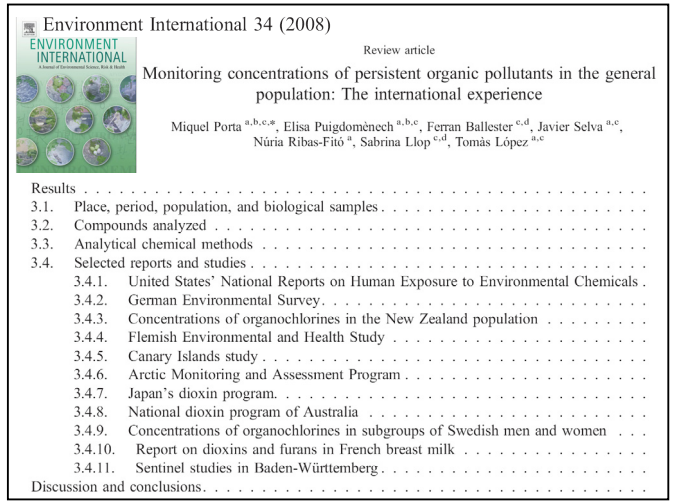


XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology



Adams J et al. – *J Epidemiol Community Health* 2005.


Environment International 34 (2008)

ENVIRONMENT INTERNATIONAL

Review article

Monitoring concentrations of persistent organic pollutants in the general population: The international experience

Miquel Porta [a,b,c,*], Elisa Puigdomènech [a,b,c], Ferran Ballester [c,d], Javier Selva [a,c], Núria Ribas-Fitó [a], Sabrina Llop [c,d], Tomàs López [a,c]

Environment International 34 (2008)

Review article

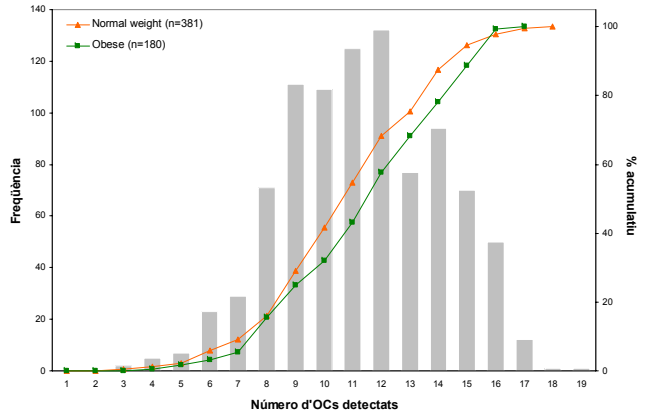
Monitoring concentrations of persistent organic pollutants in the general population: The international experience

Miquel Porta [a,b,c,*], Elisa Puigdomènech [a,b,c], Ferran Ballester [c,d], Javier Selva [a,c], Núria Ribas-Fitó [a], Sabrina Llop [c,d], Tomàs López [a,c]

Abstract

Assessing the adverse effects on human health of persistent organic pollutants (POPs) and the impact of policies aiming to reduce human exposure to POPs warrants monitoring body concentrations of POPs in representative samples of subjects. While numerous *ad hoc* studies are being conducted to understand POPs effects, only a few countries are conducting nationwide surveillance programs of human concentrations of POPs, and even less countries do so in representative samples of the general population. We tried to identify all studies worldwide that analyzed the distribution of concentrations of POPs in a representative sample of the general population, and we synthesized the studies' main characteristics, as design, population, and chemicals analyzed. The most comprehensive studies are the National Reports on Human Exposure to Environmental Chemicals (USA), the German Environmental Survey, and the Arctic Monitoring and Assessment Programme. Population-wide studies exist as well in New Zealand, Australia, Japan, Flanders (Belgium) and the Canary Islands (Spain). Most such studies are linked with health surveys, which is a highly-relevant additional strength. Only the German and Flemish studies analyzed POPs by educational level, while studies in the USA offer results by ethnic group. The full distribution of POPs concentrations is unknown in many countries. Knowledge gaps include also the interplay of age, gender, period and cohort effects on the prevalence of exposures observed by cross-sectional surveys. Local and global efforts to minimize POPs contamination, like the Stockholm convention, warrant nationwide monitoring of concentrations of POPs in representative samples of the general population. Results of this review show how such studies may be developed and used.

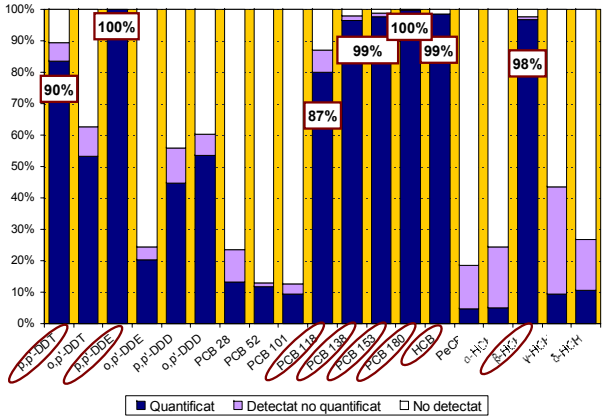
Catalonia, 2002 (N = 919). Detection and quantification of POPs



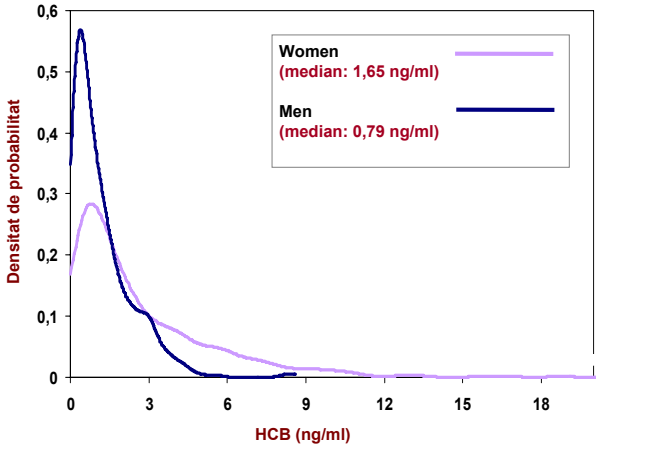
XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

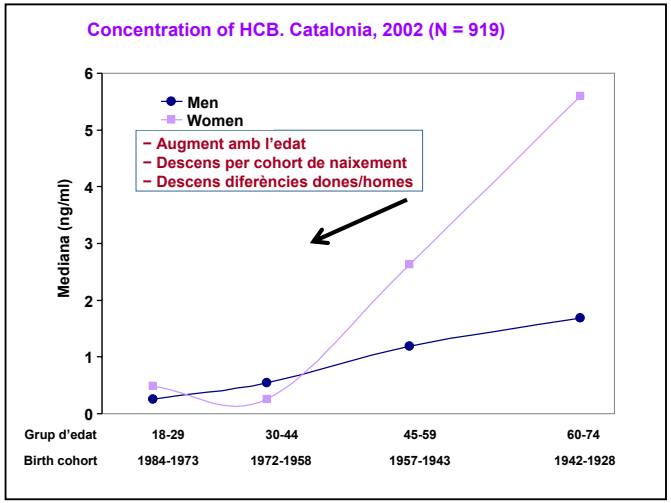
Integrating lifecourse...
environmetal, epigetic epidemiology

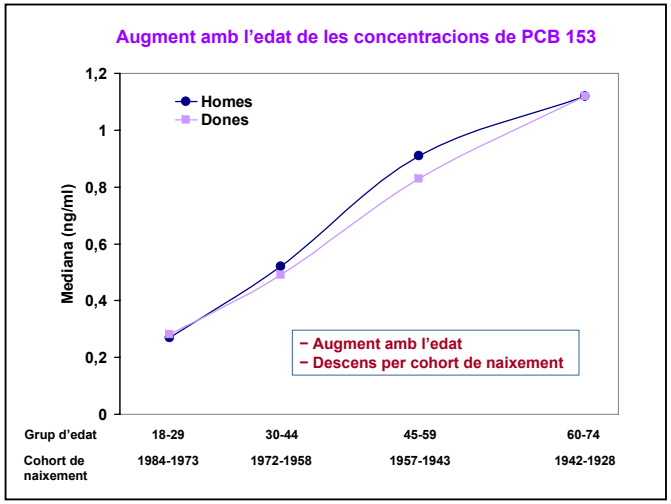
Catalonia, 2002 (N = 919). Detection and quantification of POPs

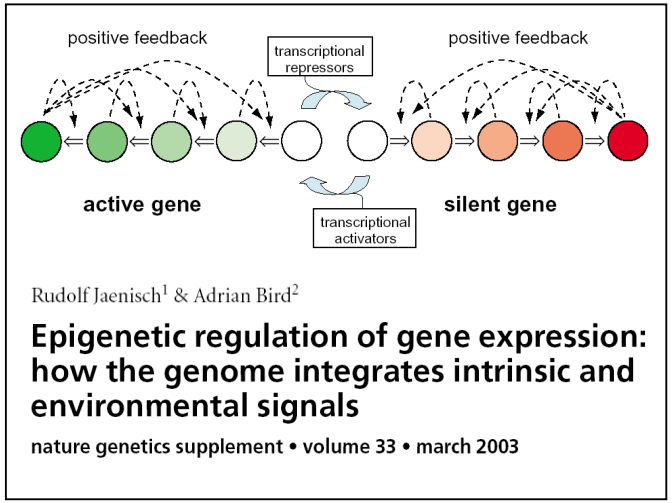


Population distribution of HCB. Catalonia, 2002 (N = 919)









XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology

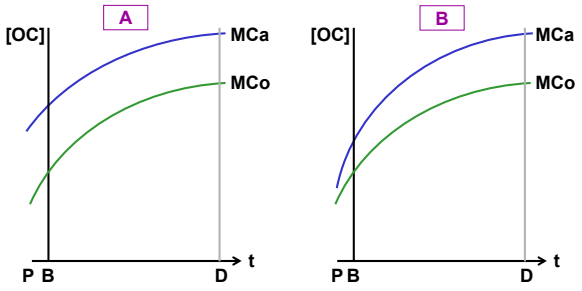
- **Underestimation of causal complexity.**
  i.e., common underestimation of the complexity of gene-environment interactions and of environmental epigenomics:
  - wide changes in fluxes of exposure and excretion during lifetime or causally relevant 'exposure-window',
  - different effects at different doses for same agent (saturation and hormesis...),
  - dynamics of gene-gene and exposure-exposure (mixtures) interactions...

Increased Concentrations of Polychlorinated Biphenyls, Hexachlorobenzene, and Chlordanes in Mothers of Men with Testicular Cancer

Lennart Hardell,[1,2] Bert van Bavel,[2] Gunilla Lindström,[2] Michael Carlberg,[1] Ann Charlotte Dreifaldt,[1] Hans Wijkström,[3] Hans Starkhammar,[4] Mikael Eriksson,[5] Arne Hallquist,[6] and Torgny Kolmert[7]

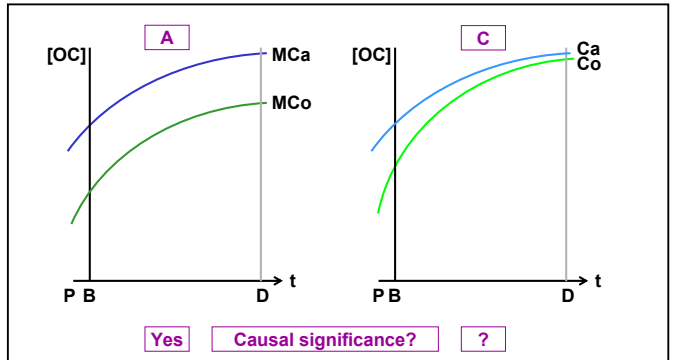
Table 6. OR (95% CI) for mothers of cases with testicular cancer, all types combined.[a]

	Cases/controls	OR (95% CI)
Sum of PCBs[b]	34/20	3.8 (1.4–10)
HCB	35/22	4.4 (1.7–12)
p,p´-DDE	22/22	1.3 (0.5–3.0)
cis-Heptachlordane	27/21	2.1 (0.8–5.0)
cis-Chlordane	22/15	2.5 (0.99–6.1)
Oxychlordane	28/22	2.6 (0.9–7.1)
MC6	25/22	1.3 (0.5–3.2)
trans-Nonachlordane	34/22	4.1 (1.5–11)
cis-Nonachlordane	32/22	3.1 (1.2–7.8)
Sum of chlordanes	27/22	1.9 (0.7–5.0)



[OC]=Organochlorine concentration.
P=pregnancy. B=birth. D=diagnosis of the cancer and measurement of OC.
MCa=Mothers of Cases. MCo=Mothers of Controls.

Hardell L. et al. Environ Health Perspect 2003



[OC]=Organochlorine concentration. Ca=Cases. Co=Controls.
P=pregnancy. B=birth. D=diagnosis of the cancer and measurement of OC.
MCa=Mothers of Cases. MCo=Mothers of Controls.

Hardell L. et al. Environ Health Perspect 2003

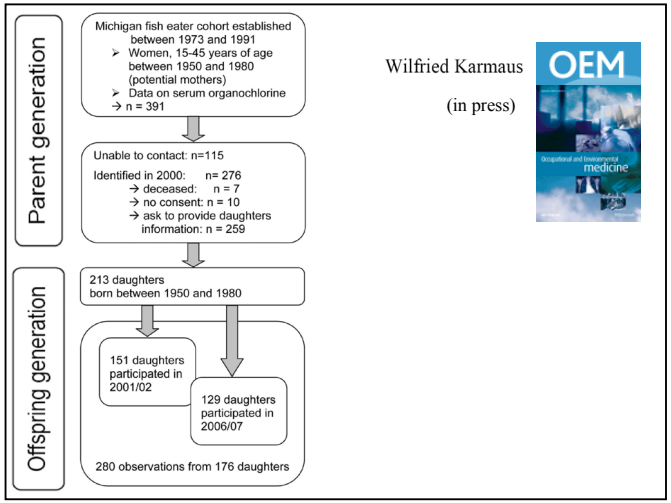
XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre
Integrating lifecourse...
environmetal, epigetic epidemiology

Maternal levels of dichlorodiphenyl-dichloroethylene (DDE) may increase weight and body mass index in adult female offspring

Wilfried Karmaus

(in press)

Objectives: To investigate the effect of prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyl-dichloroethylene (DDE) on weight, height, and body mass index (BMI) in adult female offspring of the Michigan fisheater cohort examined between 1973 and 1991.



Wilfried Karmaus

(in press)

Problems are not just methodological, but conceptual (epistemological & ontological) as well:

- **Underestimation of causal complexity.**

Oversimplification in the design of the "object of the study"
(Miettinen; Bolúmar & Porta, Eur J Epidemiol 2004)

e.g., genotypes are not static "exposures", but dynamic sources of proteins;

"robustness" and "redundancy"...
1 gene → **> 1** protein...
1 genotype → **> 1** phenotype...

XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology

Results: Maternal height and BMI were significant predictors of their daughters' height, weight, and BMI. Low birth weight (<2,500 g) was significantly associated with reduced adult offspring weight and BMI. Weight and BMI of adult offspring were statistically significantly associated with the extrapolated prenatal DDE levels of their mothers. Controlling for confounders and compared to maternal DDE levels below 1.502 µg/L, there was an increase in offspring BMI of 1.65 when prenatal DDE levels were between 1.502 – 2.9 µg/L and an increase of 2.88 if maternal serum DDE was greater than 2.9 µg/L. Prenatal PCB levels showed no effect.

Conclusion: Prenatal exposure to the estrogenic endocrine-disrupting chemical DDE may be one of the factors contributing to the epidemic of obesity in women.

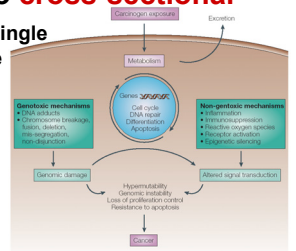
Problems are not just methodological, but conceptual (epistemological & ontological) as well:

- **Underestimation of causal complexity.**

Underestimation of time dynamics or time-related events.

Studies are much too cross-sectional

e.g., too often there is just 1 single measurement of the exposure or of the "biomarker", no consideration of intermediate processes, compensatory mechanisms, epigenetic processes, reversible effects...



Problems are not just methodological, but conceptual (epistemological & ontological) as well:

- **Underestimation of causal complexity.**
  - **We need studies**
  - **– with a much stronger biological rationale**
  - **– with a much stronger clinical rationale**
  - **– truly longitudinal**
  - **– with repeated measures for each individual**
  - **– with more public health "sense & sensitivity".**

Epigenome

The global epigenetic patterns that distinguish or are variable between cell types. These patterns include DNA methylation, histone modifications and chromatin-associated proteins.

Epigenome:
The overall epigenetic state of a cell.

NATURE REVIEWS | GENETICS | APRIL 2007

XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre
Integrating lifecourse...
environmetal, epigetic epidemiology

DISEASES OF COMPLEX ETIOLOGY

result from complex interactions between social, environmental, clinical, genetic and epigenetic processes over long periods of life. Common diseases with late-onset phenotypes often result from interactions between the EPIGENOME, the GENOME and the environment.

Phenotypic plasticity and the epigenetics of human disease

Andrew P. Feinberg

It is becoming clear that epigenetic changes are involved in human disease as well as during normal development. A unifying theme of disease epigenetics is defects in phenotypic plasticity — cells' ability to change their behaviour in response to internal or external environmental cues. This model proposes that hereditary disorders of the epigenetic apparatus lead to developmental defects, that cancer epigenetics involves disruption of the stem-cell programme, and that common diseases with late-onset phenotypes involve interactions between the epigenome, the genome and the environment.

Epigenome:
The overall epigenetic state of a cell.

NATURE|24 May 2007

Epigenetics and the environment

The epigenome is an important target of environmental modification. Environmental toxins such as heavy metals disrupt DNA methylation and chromatin[82]. Oestrogenic and anti-androgenic toxins that decrease male fertility alter DNA methylation, and these changes are inherited by subsequent generations[83]. Dietary modification also can have a profound effect on DNA methylation and genomic imprinting. Deficiency in folate and methionine

The common disease genetic and epigenetic (CDGE) hypothesis argues that in addition to genetic variation, epigenetics provides an added layer of variation that might mediate the relationship between genotype and internal and external environmental factors[90]. This epigenetic component could help to explain the marked increase in common diseases with age, as well as the frequent discordance of diseases such as bipolar disorder between monozygotic twins[76].

The overall epigenetic state of a cell.

NATURE|24 May 2007

GLOSSARY *J Epidemiol Community Health* 2003

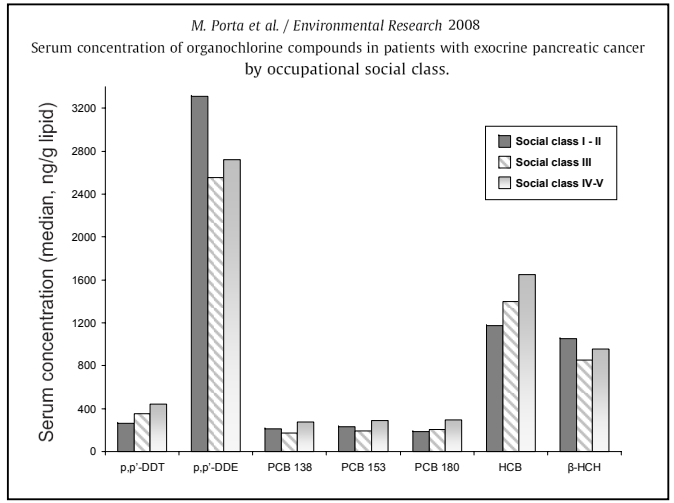
Life course epidemiology

D Kuh, Y Ben-Shlomo, J Lynch, J Hallqvist, C Power

GLOSSARY *J Epidemiol Community Health* 2004

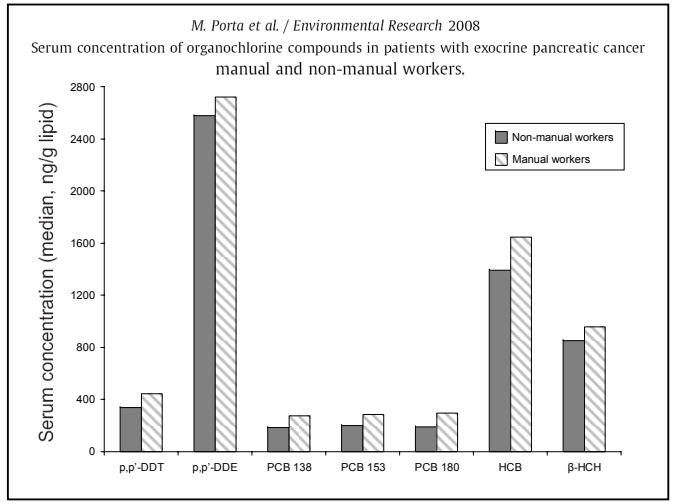
Developmental origins of adult health

D J P Barker



XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology

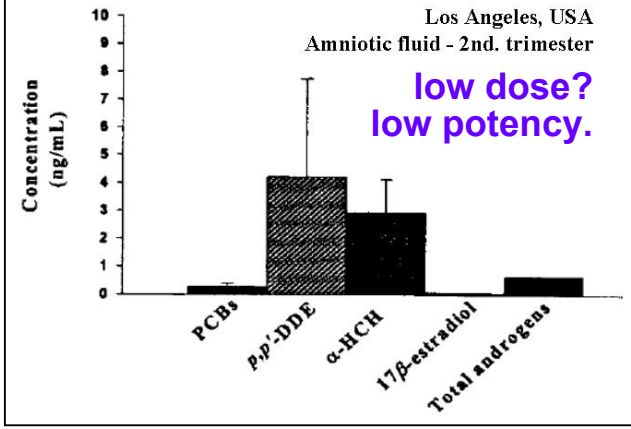


M. Porta et al. / Environmental Research 2008

Differences in serum concentrations of organochlorine compounds by occupational social class in pancreatic cancer☆

Background: The relationships between social factors and body concentrations of environmental chemical agents are unknown in many human populations. Some chemical compounds may play an etiopathogenic role in pancreatic cancer.
Objective: To analyze the relationships between occupational social class and serum concentrations of seven selected organochlorine compounds (OCs) in exocrine pancreatic cancer: dichlorodiphenyltrichloroethane (p,p′-DDT), dichlorodiphenyldichloroethene (p,p′-DDE), 3 polychlorinated biphenyls (PCBs), hexachlorobenzene, and β-hexachlorocyclohexane.
Methods: Incident cases of exocrine pancreatic cancer were prospectively identified, and interviewed face-to-face during hospital admission ($n = 135$). Serum concentrations of OCs were analyzed by high-resolution gas chromatography with electron-capture detection. Social class was classified according to occupation.
Results: Multivariate-adjusted concentrations of all seven compounds were higher in occupational social classes IV–V (the less affluent) than in classes I–II; they were higher as well in class III than in classes I–II for four compounds. Concentrations of six OCs were higher in manual workers than in non-manual workers ($p < 0.05$ for PCBs). Social class explained statistically between 3.7% and 5.7% of the variability in concentrations of PCBs, and 2% or less variability in the other OCs.
Conclusions: Concentrations of most OCs were higher in the less affluent occupational social classes. In pancreatic cancer the putative causal role of these persistent organic pollutants may not be independent of social class. There is a need to integrate evidence on the contribution of different social processes and environmental chemical exposures to the etiology of pancreatic and other cancers.

Foster W, et al. J Clin Endocrinol Metab 2000; 85: 2954-7.

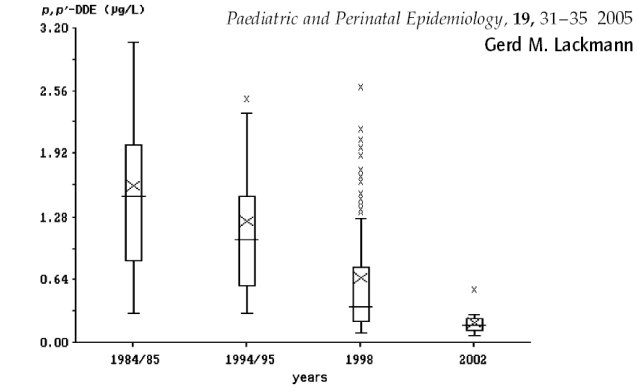


XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre
Integrating lifecourse...
environmetal, epigetic epidemiology

M. Porta et al. / Environmental Research 2008

Differences in serum concentrations of organochlorine compounds by occupational social class in pancreatic cancer☆

Ubiquitous as they are, social class and environmental pollutants seldom talk to each other: studies on the influence of social position on health rarely include biological measurements of environmental chemical agents–and vice versa (Porta et al., 2008a; United Nations Environment Programme, 2003; Alcock et al., 2003; Borrell et al., 2004a; Davey Smith et al., 1998; Martikainen et al., 2007). Evidence on the relationships between social factors and human concentrations of pollutants could contribute to an improved understanding of health patterns by socioeconomic position. It could also advance knowledge on social mechanisms of exposure to environmental compounds, and strengthen policies that aim to narrow social disparities in health.



Paediatric and Perinatal Epidemiology, **19**, 31–35 2005
Gerd M. Lackmann

Figure 1. Box & Whisker-diagram of *p,p′*-DDE concentrations (µg/L) in full-term German neonates from the mid-1980s to 2002.

Environmental Research 98 (2005) 8–13

Breastfeeding and concentrations of HCB and *p,p′*-DDE at the age of 1 year

Núria Ribas-Fitó,[a,*] Joan O. Grimalt,[b] Esther Marco,[b] Maria Sala,[a] Carlos Mazón,[c] Jordi Sunyer[a]

Exposure to organochlorine compounds (OCs) occurs both in utero and through breastfeeding. Levels of hexachlorobenzene (HCB) in the cord serum of newborns from a population located in the vicinity of an electrochemical factory in Spain are among the highest ever reported. We aimed to assess the degree of breast milk contamination in this population and the subsequent exposure of children to these chemicals through breastfeeding. A birth cohort including 92 mother–infant pairs (84% of all births in the study area) was recruited between 1997 and 1999 in five neighboring villages. OCs were measured in cord serum, colostrum, breast milk, and children's serum at 13 months of age. Concentrations of OCs were detected and quantified in all colostrum and milk samples. The concentrations in mature milk were lower than those encountered in colostrum. At 13 months of age the highest concentration of OC was found for dichlorodiphenyl dichloroethane (*p,p′*-DDE), in contrast to what these children presented at birth, where HCB was the highest compound. Those infants who were breastfed had higher concentrations at the age of 1 than those who were formula fed (2.13 ng/mL of HCB among formula feeders vs 4.26 among breast feeders, and 1.95 of *p,p′*-DDE vs 6.00 ($P<0.05$)). Long-term breastfeeding leads to a dose–response increase of the concentrations in children's serum during the first year of life.

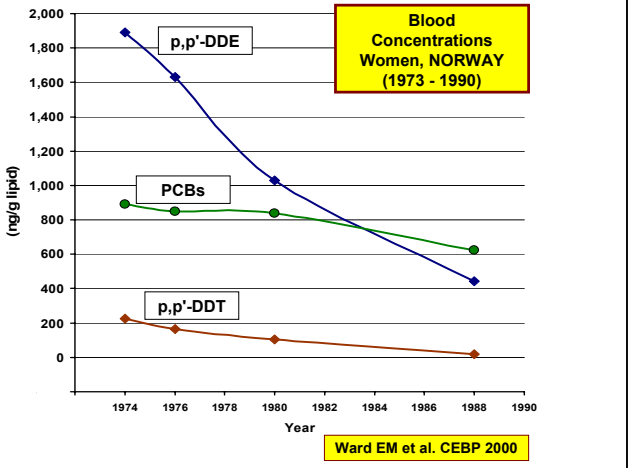
OCs were detected and quantified in all colostrum and milk samples.

At 13 months of age the highest concentration

(*p,p′*-DDE), in contrast to what these children presented at birth, where HCB

XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

Integrating lifecourse...
environmetal, epigetic epidemiology



Spraying it about — in 1946, whole districts of Athens were sprayed with DDT from low-flying aircraft in attempts to halt the spread of a cholera epidemic by flies.
NATURE 1995; 375: 538-9.

www.sciencemag.org SCIENCE VOL 308 3 JUNE 2005

Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility

Matthew D. Anway, Andrea S. Cupp,* Mehmet Uzumcu,† Michael K. Skinner‡

Transgenerational effects of environmental toxins require either a chromosomal or epigenetic alteration in the germ line. Transient exposure of a gestating female rat during the period of gonadal sex determination to the endocrine disruptors vinclozolin (an antiandrogenic compound) or methoxychlor (an estrogenic compound) induced an adult phenotype in the F_1 generation of decreased spermatogenic capacity (cell number and viability) and increased incidence of male infertility. These effects were transferred through the male germ line to nearly all males of all subsequent generations examined (that is, F_1 to F_4). The effects on reproduction correlate with altered DNA methylation patterns in the germ line. The ability of an environmental factor (for example, endocrine disruptor) to reprogram the germ line and to promote a transgenerational disease state has significant implications for evolutionary biology and disease etiology.

www.sciencemag.org SCIENCE VOL 308 3 JUNE 2005

DEVELOPMENTAL BIOLOGY

Endocrine Disrupters Trigger Fertility Problems in Multiple Generations

"We're mostly describing a new phenomenon," acknowledges Skinner. But he is worried nonetheless. "The hazards of environmental toxins are much more pronounced than we realized," he asserts.

...really?

XVIII IEA World Congress of Epidemiology
Miquel Porta - 23 Sept. 2008 - Porto Alegre

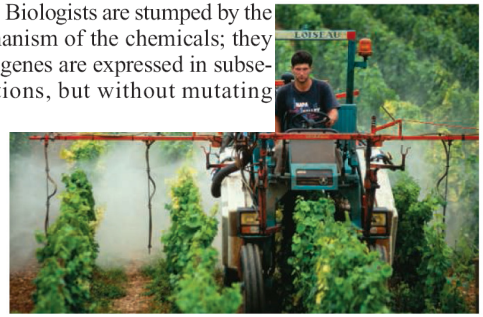
Integrating lifecourse...
environmetal, epigetic epidemiology

www.sciencemag.org SCIENCE VOL 308 3 JUNE 2005

DEVELOPMENTAL BIOLOGY

Endocrine Disrupters Trigger Fertility Problems in Multiple Generations

Biologists are stumped by the apparent mechanism of the chemicals; they may alter how genes are expressed in subsequent generations, but without mutating DNA.



Unfertile ground. The fungicide vinclozolin, which is sprayed on vineyards like these, can cause fertility problems in male offspring of exposed rats.

www.imim.es/programesrecerca/epidemiologia/en_documentsgrecm.html

THANK YOU FOR YOUR ATTENTION

IMIM hospitaldelmar

prbb Parc Recerca Biomèdica Barcelona

UAB Universitat Autònoma de Barcelona