Integrating biomarkers of internal dose
of environmental chemical pollutants
in basic and clinical research
on the etiopathogenesis of human diseases

why bother?

Miquel Porta, MD, MPH, PhD
Professor & Scientist,
Hospital del Mar Research Institute - IMIM,
Universitat Autònoma de Barcelona,
University of North Carolina at Chapel Hill

prbb,
Barcelona,
13 June 2012

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
- Integrating lifecourse, environmental, molecular and epigenetic epidemiology
- Environmental toxic substances: exposed individuals and exposed populations
- Between molecules and the environment: keeping patients in the picture

facebook Miquel Porta Video YouTube Miquel Porta (miquelporta) on Twitter

Baja la 'contaminación interior'

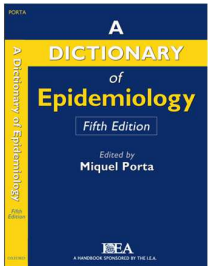
Por primera vez disminuyen los niveles en sangre de los compuestos tóxicos persistentes ● Aun así solo el 4% de la población tiene cantidades reducidas

Las razones de la disminución no están claras. Lo más verosímil es que se deba primordialmente a las políticas de control de los CTP en alimentos desarrolladas durante décadas por las autoridades y empresas que operan en la ciudad.

Solo al medirlos todos juntos se obtiene una idea real de su extensión

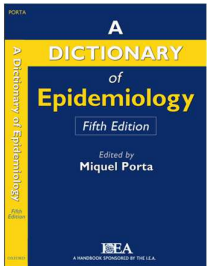
Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

EPIGENETICS
EPIGENOME
EPIGENETIC INHERITANCE
INHERITANCE
INHERITANCE, CULTURAL
DISEASES OF COMPLEX ETIOLOGY
DETERMINISM, GENETIC
GENETIZATION
GENE EXPRESSION
INTEGRATIVE RESEARCH
PLASTICITY
BIRTH COHORT
DEVELOPMENTAL ORIGINS HYPOTHESIS
DEVELOPMENTAL AND LIFE COURSE EPIDEMIOLOGY
GENETIC, CLINICAL, MOLECULAR EPIDEMIOLOGY
EMBODIMENT



Oxford University Press, 2008.

LEAD TIME
SCREENING
GENETIC SCREENING
PRIMARY PREVENTION
SECONDARY PREVENTION
TERTIARY PREVENTION
QUATERNARY PREVENTION
ZERO-TIME SHIFT
LENGTH BIAS
CASE FINDING
NUMBER NEEDED TO SCREEN (NNS)
NUMBER NEEDED TO TREAT (NNT)
EARLY DETECTION OF DISEASE
DETECTABLE PRECLINICAL PERIOD (SOJOURN TIME)



Oxford University Press, 2008.

Science of the Total Environment 423 (2012)

Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Barcelona in 2006, and comparison with levels in 2002

Miquel Porta [a,b,c,*], Tomàs López [a,b,c], Magda Gasull [a,c], Maica Rodríguez-Sanz [c,d,e], Mercè Garí [f], José Pumarega [a,c], Carme Borrell [c,d,e], Joan O. Grimalt [f]

International Journal of Epidemiology 2012;1–3
Advance Access published March 15, 2012 doi:10.1093/ije/dys014

Commentary: A step towards more comprehensive analyses of life course effects of mixtures of environmental factors

Miquel Porta,[1,2,3]* Magda Gasull[1,2,3] and José Pumarega[1,2,3]

Environment International 44 (2012)

Number of persistent organic pollutants detected at high concentrations in a general population

Miquel Porta [a,b,c,*], José Pumarega [a,c], Magda Gasull [a,c]

International Journal of Epidemiology 2012;1–3
Advance Access published March 15, 2012 doi:10.1093/ije/dys014

Commentary: A step towards more comprehensive analyses of life course effects of mixtures of environmental factors

Miquel Porta,[1,2,3]* Magda Gasull[1,2,3] and José Pumarega[1,2,3]

3 types of reasons / 3 suggestions for you to think about (if you wish):

There are 3 strong scientific reasons to integrate biomarkers of internal dose of environmental factors in basic, clinical and epidemiological research on the etiopathogenesis of human diseases of complex etiology;

i. Most individuals accumulate complex mixtures of persistent toxic substances throughout the life course, both at high and low concentrations;

Integrating biomarkers of internal dose
of environmental chemical pollutants
in basic and clinical research
on the etiopathogenesis of human diseases

why bother?

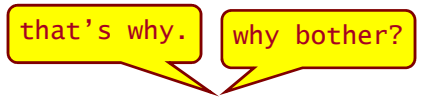
3 types of reasons / 3 suggestions for you to think about (if you wish):

There are 3 strong scientific reasons to integrate biomarkers of internal dose of environmental factors in basic, clinical and epidemiological research on the etiopathogenesis of human diseases of complex etiology;

i. Most individuals accumulate complex mixtures of persistent toxic substances throughout the life course, both at high and low concentrations;

ii. Knowledge on **the joint effects of such 'cocktails'** (including alterations of metabolic functions and gene expression) ought to be assessed more often when **building causal scenarios that aim at being relevant for human health**; and

iii. It may be scientifically unfounded to study mechanisms of diseases of complex etiology without considering environmental mixtures and the hypothesis that **key causal processes involve contamination by toxic pollutants and the ensuing accumulation of genetic and epigenetic alterations.**



We know quite a lot about
→ generalized human contamination
→ toxic effects of environmental pollutants

i. Most individuals accumulate complex mixtures of persistent toxic substances throughout the life course, both at high and low concentrations;

ii. Knowledge on **the joint effects of such 'cocktails'** (including alterations of metabolic functions and gene expression) ought to be assessed more often when **building causal scenarios that aim at being relevant for human health**; and

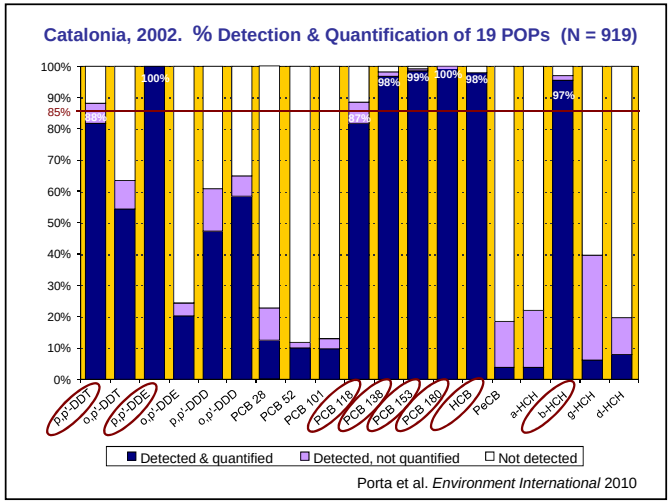
iii. It may be scientifically unfounded to study mechanisms of diseases of complex etiology without considering environmental mixtures and the hypothesis that **key causal processes involve contamination by toxic pollutants and the ensuing accumulation of genetic and epigenetic alterations.**

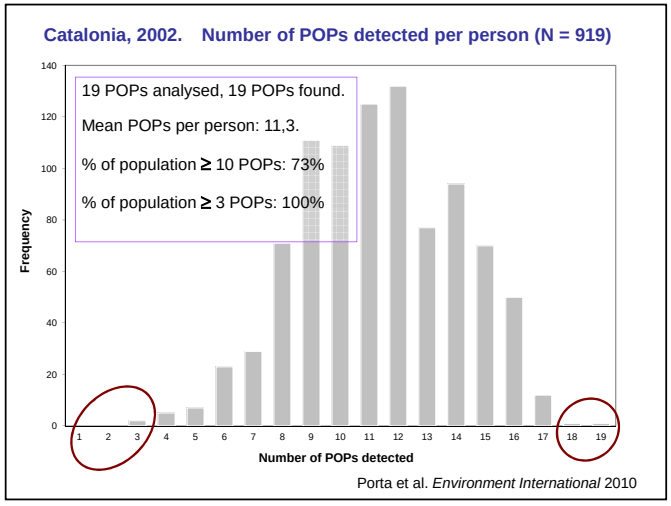
We know too little about
→ the etiopathogenesis of the most prevalent diseases.

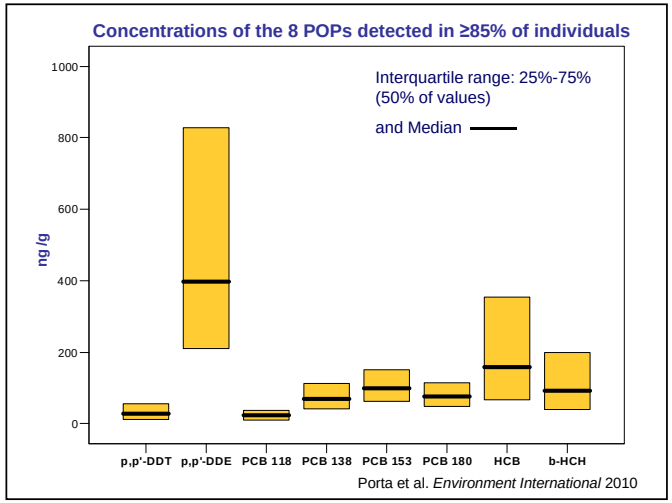
OR let's put it this way:
when you do not integrate biomarkers of internal dose of environmental factors in your research on the etiopathogenesis of human diseases of complex etiology,

- you are studying 'something' that hardly exists (uncontaminated human beings);
- your causal inferences are less likely to be relevant for human health; and
- you miss causes and mechanisms of the processes that interest you (e.g., causes of changes in gene expression, of accumulation of genetic defects).

i. Most individuals accumulate complex mixtures of persistent toxic substances throughout the life course, both at high and low concentrations;







Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

Concentrations of p,p'-DDT, p,p'-DDE, HCB and β-HCH in a representative sample of the general population of Catalonia
(N = 919)

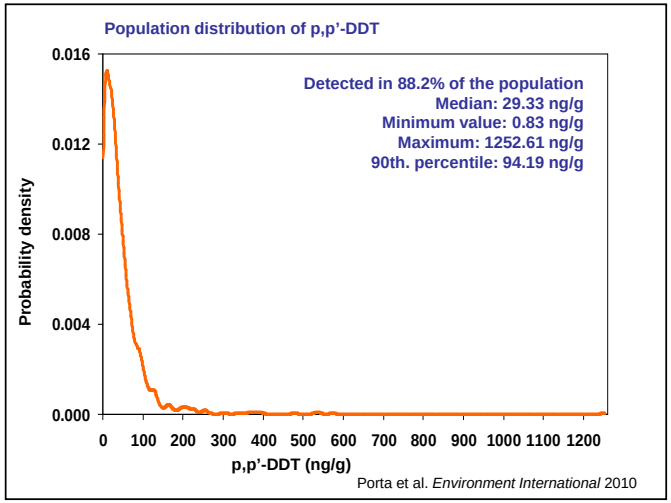
		(ng/g)
***p,p'*-DDT**	mean	46.59
	median	29.33
	min.	0.83
	max.	1252.61
***p,p'*-DDE**	mean	705.96
	median	399.33
	min.	1.17
	max.	9036.01

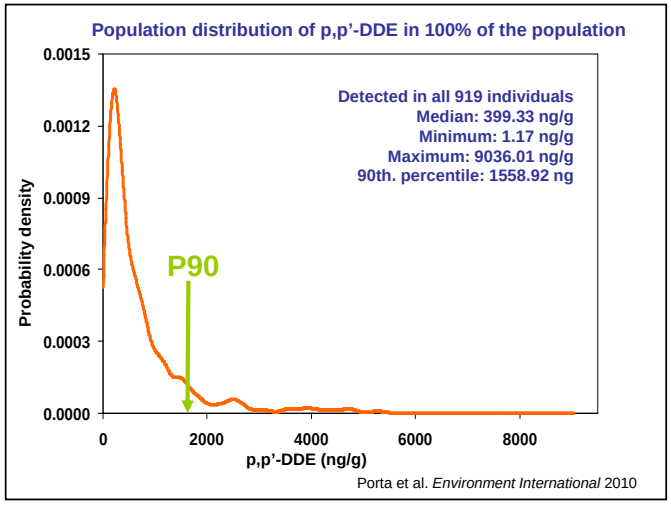
7,723 times higher

		(ng/g)
HCB	mean	270.79
	median	159.43
	min.	0.79
	max.	4798.57
β-HCH	mean	158.24
	median	91.93
	min.	1.35
	max.	2716.16

6,074 times higher

Porta et al. Environment International 2010





i. Most individuals accumulate complex mixtures of persistent toxic substances throughout the life course, both at high and low concentrations;

The **number of compounds detected per person** may be misleading: it does not account for the corresponding concentrations.

Analysis of the **concentration of each individual chemical**, does not address adequately the accumulation of / the contamination by multiple chemicals.

→ **Number of compounds detected at high concentrations**

as simple as that?

Combination effects may result from pollutants each of which produces small effects, if they are present in sufficiently large numbers. The existence of **mixture effects** (e.g., additive, synergistic, antagonistic) depends on the number of contaminants in the mixture, their respective concentrations, and the concentration-response curves. Two crucial factors for combination effects to occur are the **number of chemicals** and **their concentrations**.

Porta M et al. *Environment International* 2012

The **number of compounds detected per person** may be misleading:
it does not account for the corresponding concentrations.

Analysis of the **concentration of each individual chemical**,
does not address adequately
the accumulation of / the contamination by
multiple chemicals.

→ **Number of compounds detected at high concentrations**

Other factors:
- Number of compounds analysed (...19 ...100 ...>200 ...).
- Limits of detection, quantification, lab procedures.
- Percentage of detection of each compound.
- Number of compounds detected / person (distribution of).
- Definitions of exposure categories (P75, P90...).
- Lipid-corrected (e.g., ng/g of lipid) vs. crude (e.g., ng/mL) concentrations.
- Population distribution of the concentrations of each POP (density plots, 'G Rose curves').
- Definitions of 'high concentrations'.

Porta M et al. *Environment International* 2012

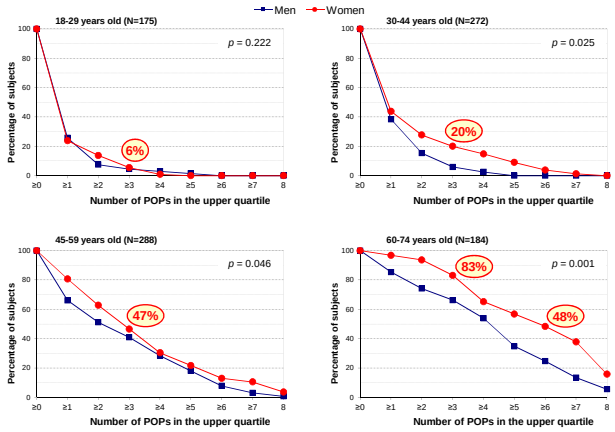
The **number of compounds detected per person** may be misleading:
it does not account for the corresponding concentrations.

Analysis of the **concentration of each individual chemical**,
does not address adequately
the accumulation of / the contamination by
multiple chemicals.

→ **Number of compounds detected at high concentrations**

Other factors:
- **Definitions of 'high concentrations':**
  - **Different cutoff point for each compound** ('internal' or population-specific cutoff points);
    e.g., P90 of each compound, different in each population.
  - **Same cutoff point for all compounds** ('external' or 'universal' cutoff points);
    e.g., 500 ng/g for each and all compounds.
  - **Different cutoff point for each compound** ('internal' or 'external');
    e.g., 500 ng/g for DDE, 100 ng/g for PCB 153, 50 ng/g for β-HCH.

Porta M et al. *Environment International* 2012



Porta M et al. *Environment International* 2012

Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

i. Most individuals accumulate complex mixtures of persistent toxic substances throughout the life course, both at high and low concentrations;

Table 2 Frequency of subjects with high concentrations of the eight most frequently detected POPs according to different definitions of 'high concentration'.

Cutoff point of 'high concentration'	Number of the most prevalent POPs at 'high concentrations'					
	0	≥1	≥2	1 to 5	6 to 8	
	N (%)	N (%)	N (%)	N (%)	N (%)	GM (95% CI)*
Different cutoff point for each compound						
≥Percentile 75 (top quartile)	381 (41.5)	538 (58.5)	402 (43.7)	433 (47.1)	105 (11.4)	2.7 (2.6 – 2.9)
≥Percentile 80 (top quintile)	439 (47.8)	480 (52.2)	327 (35.6)	404 (44.0)	76 (8.3)	2.4 (2.3 – 2.6)
≥Percentile 90 (top decile)	622 (67.7)	297 (32.3)	179 (19.5)	281 (30.6)	16 (1.7)	2.0 (1.9 – 2.2)
Same cutoff point for all compounds						
≥50 ng/g of lipid[1]	3 (0.3)	916 (99.7)	875 (95.2)	335 (36.5)	581 (63.2)	4.9 (4.8 – 5.1)
≥100 ng/g of lipid[2]	32 (3.5)	887 (96.5)	739 (80.4)	655 (71.3)	232 (25.2)	3.1 (3.0 – 3.3)
≥250 ng/g of lipid[3]	231 (25.1)	688 (74.9)	399 (43.4)	669 (72.8)	19 (2.1)	1.8 (1.8 – 1.9)
≥500 ng/g of lipid[4]	463 (50.4)	456 (49.6)	181 (19.7)	455 (49.5)	1 (0.1)	1.4 (1.4 – 1.5)
≥750 ng/g of lipid	608 (66.2)	311 (33.8)	92 (10.0)	311 (33.8)	0 (0.0)	1.3 (1.2 – 1.3)

* GM: Geometric Mean; calculated for subjects with ≥1 of the eight most prevalent POPs at 'high concentrations' according to each cutoff point for 'high concentration'.

[1] Percentile 95 of the serum concentration of β-HCH in the US Fourth National Report on Human Exposure to Environmental Chemicals was 56.5 ng/g (Patterson et al. 2009; DHHS 2009).

[2] Percentile 95 of the serum concentration of PCB 153 in the US Fourth National Report was 97.1 ng/g.

[3] Percentile 75 of the serum concentration of *p,p'*-DDE in the Report on Human Biomonitoring of Environmental Chemicals in Canada was 285 ng/g (Health Canada 2010).

[4] In the present study the median value of *p,p'*-DDE (the compound with highest concentrations) was 436.28 ng/g of lipid. Percentile 75 of the serum concentration of *p,p'*-DDE in the US Fourth National Report was 509 ng/g.

Porta M et al. *Environment International* 2012

How many chemicals do people accumulate during their lifetime?

– In 9 healthy volunteers from New York a **minimum of 77** chemical contaminants were found (out of 210 agents analysed) in the same individual; there were **up to 106 compounds in one person**.

– In a study comprising members of 13 families from 12 European countries, **between 18 and 39 chemicals were found in any one individual** (of 107 analysed); **half of the subjects had ≥28** compounds detected.

– In 155 volunteers from 13 locations in the United Kingdom, **up to 49 chemicals were found in any one person** (of 78 substances analysed); **the median number was 27**, and the minimum, 9.

In a US nationally representative assessment of 268 pregnant women's exposure to 163 chemicals, essentially **all women were exposed to at least 43 chemicals**.

Polychlorinated biphenyls, organochlorine pesticides, phenols, polybrominated diphenylethers, phthalates and polycyclic aromatic hydrocarbons were **detected in 99 to 100% of women**.

More than 300 industrial chemicals have been detected in umbilical-cord blood.

Summary of findings

Over 58% of the 919 participants had concentrations in the top quartile of ≥1 of the 8 most prevalent POPs, and 34% of ≥3 POPs.

Of women 60 to 74 years old
83% had concentrations of ≥3 POPs in the top quartile;
56% had *p,p'*-DDE, HCB and b-HCH all in their respective top quartiles;
48% had concentrations of ≥6 POPs in the top quartile.

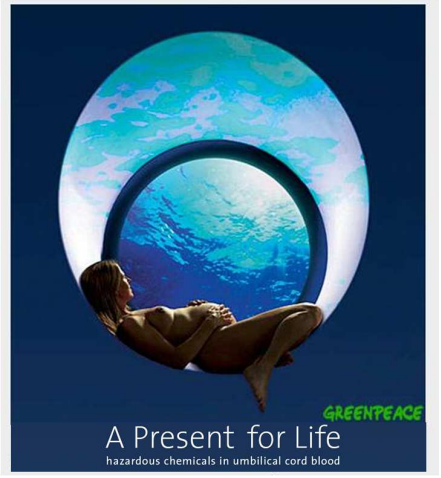
Over 30% of the 919 subjects had concentrations in the top decile of 1 to 5 of the 8 most prevalent POPs.

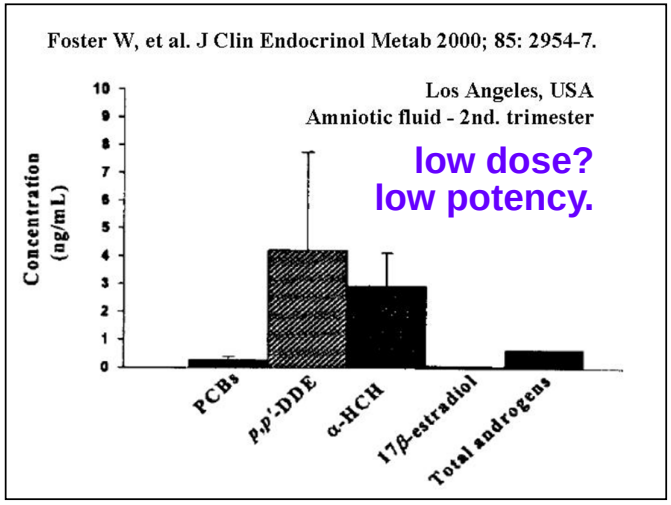
Half of the population had levels of 1 to 5 POPs >500 ng/g.

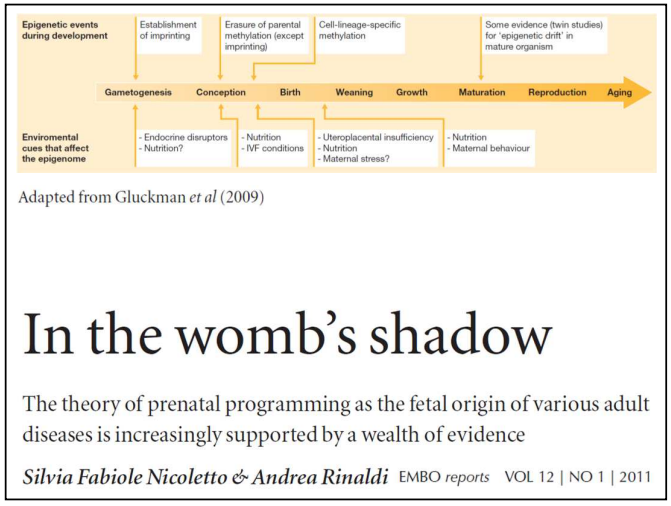
Less than 4% of the 919 subjects had all 8 POPs in the lowest quartile.

Porta M et al. *Environment International* 2012

Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012







Adapted from Gluckman *et al* (2009)

In the womb's shadow

The theory of prenatal programming as the fetal origin of various adult diseases is increasingly supported by a wealth of evidence

Silvia Fabiole Nicoletto & Andrea Rinaldi EMBO *reports* VOL 12 | NO 1 | 2011

This new idea about the influence of the environment during prenatal development on adult disease risk comes with a better understanding of epigenetic processes…

The Dutch Famine Birth Cohort Study […] found a strong link between malnutrition and under-nutrition *in utero* and cardiovascular disease and diabetes in later life…

Several environmental pollutants, nutritional components and pharmaceuticals have been suggested to have 'obesogenic' properties…

Early nutrition and chemical exposure could alter the metabolic set-point of an individual, making their subsequent fight against weight gain more difficult

Silvia Fabiole Nicoletto & Andrea Rinaldi EMBO *reports* VOL 12 | NO 1 | 2011

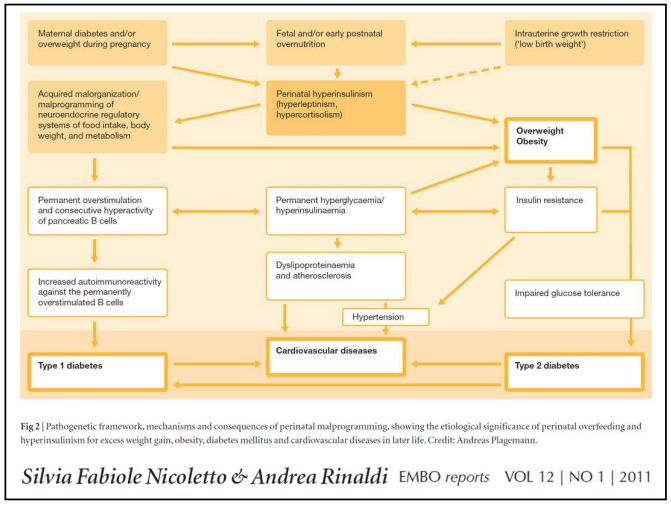


Fig 2 | Pathogenetic framework, mechanisms and consequences of perinatal malprogramming, showing the etiological significance of perinatal overfeeding and hyperinsulinism for excess weight gain, obesity, diabetes mellitus and cardiovascular diseases in later life. Credit: Andreas Plagemann.

Silvia Fabiole Nicoletto & Andrea Rinaldi EMBO *reports* VOL 12 | NO 1 | 2011

3 reasons / 3 suggestions for you to think about (if you wish):

There are strong scientific reasons to integrate biomarkers of internal dose of environmental factors in basic, clinical and epidemiological research on the etiopathogenesis of human diseases of complex etiology;

i. Most individuals accumulate complex mixtures of persistent toxic substances throughout the life course, both at high and low concentrations;

ii. Knowledge on **the joint effects of such 'cocktails'** (including alterations of metabolic functions and gene expression) ought to be assessed more often when **building causal scenarios that aim at being relevant for human health**; and

Many of such pollutants are known to alter a range of physiological functions, and known or reasonably suspected to contribute to cause severe clinical effects and a substantial burden of disease.

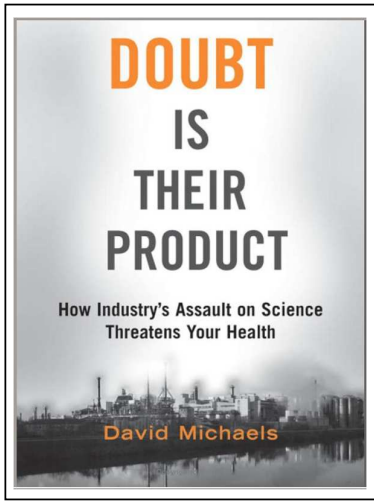
It is impossible to explain on pure scientific grounds why persistent organic pollutants and other environmental chemical agents are not integrated more deeply into basic, clinical and epidemiological studies.

www.sciencemag.org SCIENCE VOL 308 3 JUNE 2005

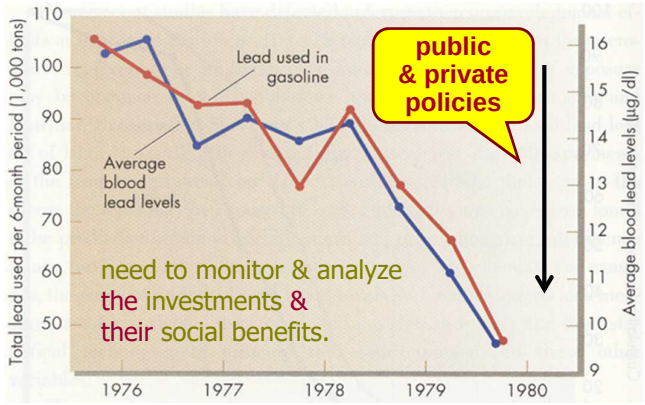
DEVELOPMENTAL BIOLOGY

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.



Contents



Stolley PD & Lasky T. ***Investigating disease patterns. The science of epidemiology.*** **New York: Scientific American Library, 1995.**

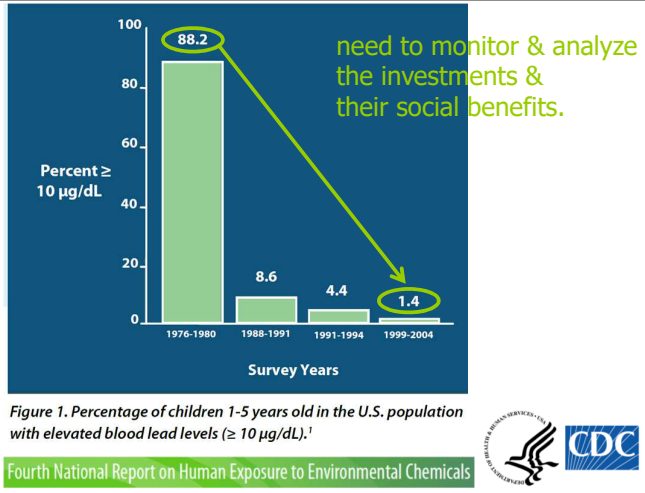


Figure 1. Percentage of children 1-5 years old in the U.S. population with elevated blood lead levels (≥ 10 µg/dL).[1]

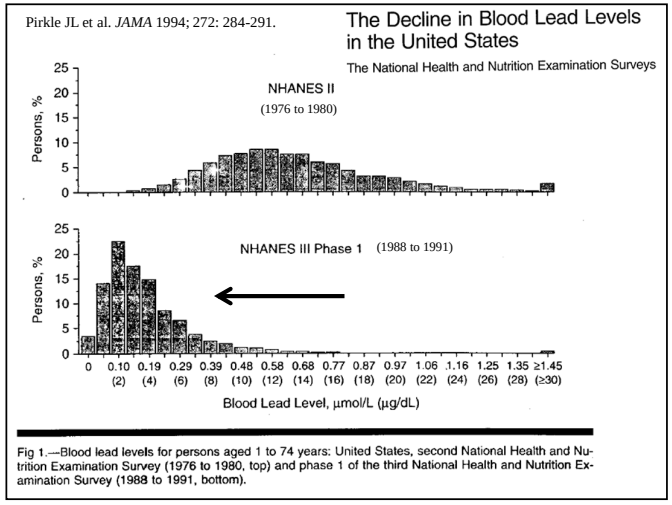
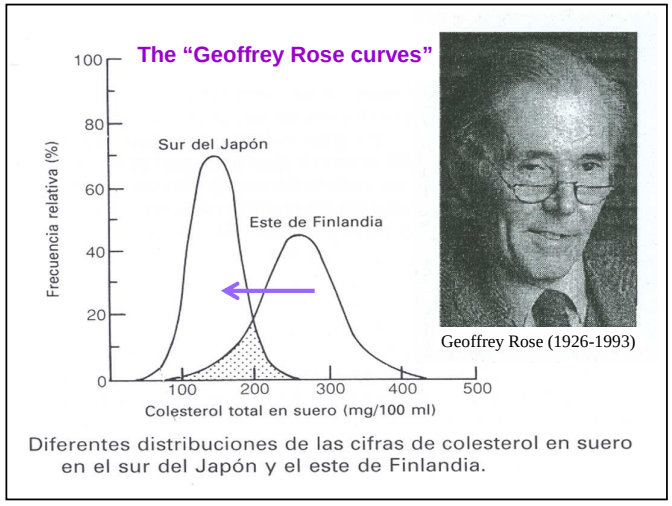


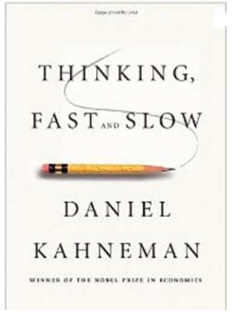
Fig 1.—Blood lead levels for persons aged 1 to 74 years: United States, second National Health and Nutrition Examination Survey (1976 to 1980, top) and phase 1 of the third National Health and Nutrition Examination Survey (1988 to 1991, bottom).

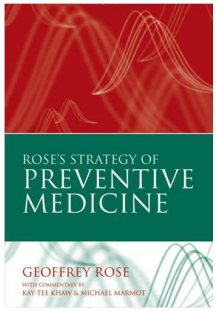


Diferentes distribuciones de las cifras de colesterol en suero en el sur del Japón y el este de Finlandia.

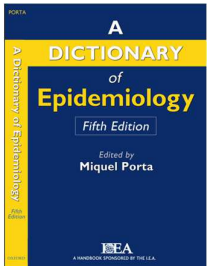
"the powerful notion of causal base rates..."

"the neglect of base-rate information is a cognitive flaw..."





GENETIZATION
The process by which issues traditionally considered to be medical, but not necessarily genetic, become defined as problems with a strong or a single genetic component, or as having a genetic cause and, sometimes, also a genetic treatment.



The expansion of genetics into the life & health sciences and professions (e.g., the genetization of prenatal medicine, oncology, primary care).

The attribution of physiological, pathological, behavioral or social conditions to genetic causes, often at the expense of clinical, environmental, cultural, economic or social explanations.

In genetization processes 'genetic' is often considered synonymous of 'inherited', and viceversa, thus neglecting somatic (acquired) genetic alterations and cultural inheritance.

International Journal of Epidemiology 2003;**32**:29–31

The genome sequence is a jazz score

Miquel Porta

It is not possible to do the work of science without using a language that is filled with metaphors.

In: The Triple Helix (2000) Richard C Lewontin

The main purpose of this paper is to suggest a metaphor—among many possibly valid and evocative—for the role of genes in complex chronic diseases. It is based on the inherent role of host-environmental interactions on the expression of low-penetrant genes. The relationship between an individual's genetic makeup and its phenotypic expression can be likened to the relationship between a jazz score and the performed music.

CLAVES
DE RAZÓN PRÁCTICA
Directores Javier Pradera / Fernando Savater
Diciembre 2005 Precio 8€ Nº 158

LA SECUENCIA DEL GENOMA ES UNA PARTITURA DE JAZZ

MIQUEL PORTA SERRA

"Más allá de esta metáfora algo importante está en juego: el papel de la cultura, de la salud pública y de las otras ciencias sociales, de la salud y de la vida en la construcción social de riesgos y metáforas relacionadas con la genética y la salud."

And why has the gene revolution failed so spectacularly to deliver anything tangible for patients? Because we have underestimated, even wilfully disregarded, the complexity of disease. Our indifference to physiology—to an understanding of systems in disease—has been a catastrophic loss to medicine.

The Lancet

Richard Horton Vol 378 November 12, 2011 1688

GENOMICS SCIENCE VOL 331 18 FEBRUARY 2011

Deflating the Genomic Bubble

James P. Evans,[1]* Eric M. Meslin,[2] Theresa M. Marteau,[3] Timothy Caulfield[4]

Unrealistic expectations and uncritical translation of genetic discoveries may undermine other promising approaches to preventing disease and improving health.

With global funding for genomics approaching $3 billion/year (*4*)

Impediments and Hyperbole

SCIENCE VOL 331 18 FEBRUARY 2011

Impediments and Hyperbole

The problem of clinical utility and relative risk. The numerous genetic variants that mediate disease risk typically confer woefully low relative risks (i.e., compared with the much more meaningful absolute risk) and are thus meager in their predictive power (*10*). Their applicability to patient care shows little promise; studies (*11*–*14*) demonstrate that even combining dozens of risk markers provides little clinically meaningful information. In the public health realm, the prospect of effectively stratifying populations as high or low risk, thereby guiding screening, is equally dismal. Given the multifactorial nature of common diseases and the weak predictive properties of genetic-risk alleles, the probability of misclassifying individuals as high or low risk is likely too great to make such an approach feasible in the general population

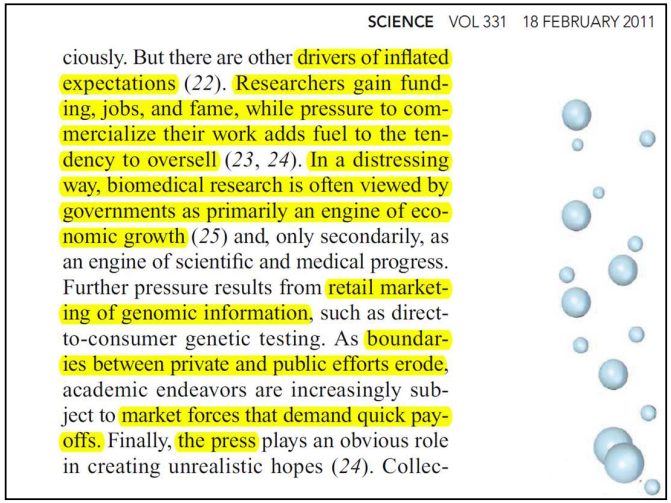
SCIENCE VOL 331 18 FEBRUARY 2011

Impediments and Hyperbole

The illusion of parsing risk. For common diseases, by definition, we are all at high levels of absolute risk. In this setting, defining precise relative risk on the basis of individuals' genetic information is less meaningful;

The difficulty of changing behaviors. The idea that genetic information will promote a healthy life-style has emerged as a dominant claim by those who promote genomic medicine (*16*, *17*). However, there is little evidence

Altering environments is increasingly recognized as a more effective way



SCIENCE VOL 331 18 FEBRUARY 2011

ciously. But there are other drivers of inflated expectations (*22*). Researchers gain funding, jobs, and fame, while pressure to commercialize their work adds fuel to the tendency to oversell (*23*, *24*). In a distressing way, biomedical research is often viewed by governments as primarily an engine of economic growth (*25*) and, only secondarily, as an engine of scientific and medical progress. Further pressure results from retail marketing of genomic information, such as direct-to-consumer genetic testing. As boundaries between private and public efforts erode, academic endeavors are increasingly subject to market forces that demand quick payoffs. Finally, the press plays an obvious role in creating unrealistic hopes (*24*). Collec-

CARLOS LÓPEZ BELTRÁN / Filósofo de la ciencia e historiador de biología

"A finales del siglo XX el gen se evaporó y la gente no se ha enterado"

ANTONIO CALVO ROY, **Madrid**

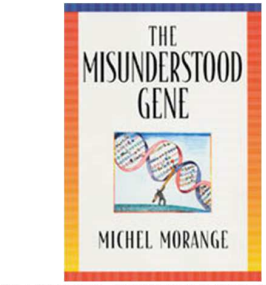
Carlos López Beltrán, (Minatitlán, Veracruz, México, 1957) trabaja en el Instituto de Investigaciones Filosóficas, en México, y es profesor de la Universidad Nacional Autónoma de ese país, donde se licenció en biología. Después hizo una maestría en historia y filosofía de la ciencia en Cambridge, Inglaterra, y se doctoró en la misma especialidad en el King's College, en Londres. Ha estado en España para dar varias conferencias. Su último libro es *El sexo hereditario* y es autor también de varios libros de poesía y coautor de *La generación del cordero*, una antología de poetas británicos contemporáneos.

Pregunta. ¿Cómo ha cambiado el concepto de la herencia en la historia?

Respuesta. La idea típica que uno encuentra en los libros de texto y de historia es que existe una etapa anterior a Mendel en donde la herencia es una región oscura llena de mitos y a partir del redescubrimiento de los experimentos de Mendel, a principios del siglo XX, entra en su

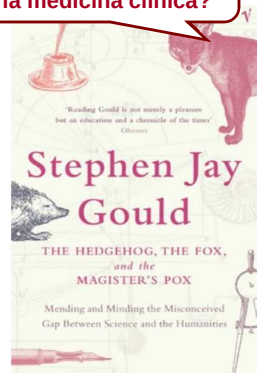
EL PAÍS, miércoles 28 de enero de 2004

Carlos López Beltrán, durante su reciente estancia en Madrid. / BERNARDO PÉREZ



HARVARD UNIVERSITY PRESS
2001

TU investigación ¿dialoga lo necesario con la medicina clínica?



The hedgehog, the fox and the magister's pox. Mending and minding the misconceived gap between science and the humanities.
London: Vintage, 2004.

3 reasons / 3 suggestions for you to think about (if you wish):

ii. Knowledge on **the joint effects of such 'cocktails'** (including alterations of metabolic functions and gene expression) ought to be assessed more often when **building causal scenarios that aim at being relevant for human health**; and

Many of such pollutants are known to **alter a range of physiological functions,** and known or reasonably suspected to **contribute to cause severe clinical effects** and **a substantial burden of disease.**

Physico-chemical characteristics, functional properties and clinical effects of many environmental agents are better known than those of many genetic loci.

GWAS cannot assume that genes function independently,
EWAS must cope with the fact that environmental exposures often interact.
Neither GWAS nor EWAS can feign that genes and environmental exposures act individually (in the 3 facets of the expression).

In the past few years ~100 studies indicated that **some contaminants may contribute to cause components of the metabolic syndrome, including type 2 diabetes**.
A few of such studies were prospective
and largely ruled out 'reverse causality bias' or 'disease progression bias'.

The effects of some POP mixtures (immunosuppressive, oxidative, inflammatory, neuroendocrine, non-genotoxic, epigenetic) may lie beneath –and partly explain– some intriguing disease-disease associations;
e.g., between some cancers and obesity, diabetes or autoimmune and inflammatory disorders.

Analyses centred on individual pollutants may miscalculate clinically or socially important adverse health effects, potentially leading to lack of physiological & clinical coherence and public health relevance.

Discussions on "low dose" effects –some of which are real (the effects)–, **and the "low dose hypothesis" should also consider the findings we presented.**

Mutation Research 682 (2009)

There is a variety of mechanisms

Receptor-mediated	Mitogen/tumor promoter	Hyper/hypomethylation
X (AhR)	Inhibition of GJICs	Immunosuppressor
X (ER)		
X (AhR)		
X (TR)		
X (ER + AR)		
X (PR + AR + MCR)	Cytotoxicity and regenerative hyperplasia	
X (PR + AR + MCR)		
X (PR + AR + MCR)		
X (TR)	Inflammation	↑ROS
X (TR)		

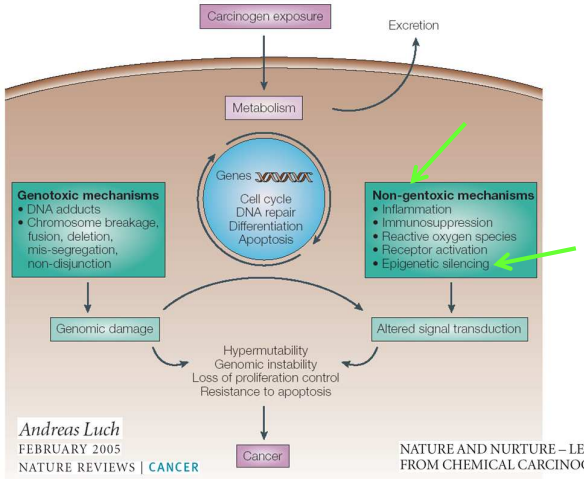
gap-junction intercellular communications

Review Mutation Research 682 (2009)

Mechanisms of non-genotoxic carcinogens and importance of a weight of evidence approach

Lya G. Hernández, Harry van Steeg, Mirjam Luijten, Jan van Benthem

IARC Group	Chemical
1	TCDD
1	17β-Estradiol
2A	'Dioxin-like' PCBs
2A	'Non-dioxin-like' PCBs
2B	DDT
2B	Progesterone
2B	Progestins
2B	Medroxyprogesterone acetate
2B	Hexachlorobenzene
2B	Polybrominated biphenyls
1	Dimethylarsinic acid
1	Monosodium methane arsenate
1	Berryllium
1	Gallium aresenide
1	Vanadium pentoxide
2A	Lead acetate
2B	1,4-Dioxane
2B	Hexachloroethane
2B	Mirex
2B	Pentachlorophenol
2B	Nitrobenzene
2B	1,4-Dichlorobenzene
2B	Catechol
2B	Nitrilotriacetic acid and its salts
2B	Phenytoin
2B	Lindane
1	Nickel compounds
2B	Chlordane
2B	Polybrominated biphenyls
2B	6-Propyl-2-thiouracil
2B	6-Mehtyl-2-thiouracil
1	Cyclosporine
2A	Perchloroethylene
2B	Butylated hydroxyanisole
2B	Acetamide
2B	Carbon tetrachloride



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

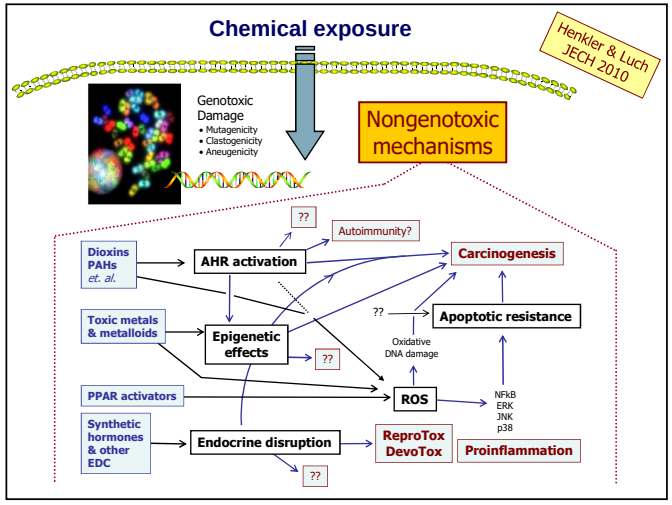
NATURE AND NURTURE – LESSONS
FROM CHEMICAL CARCINOGENESIS

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



Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

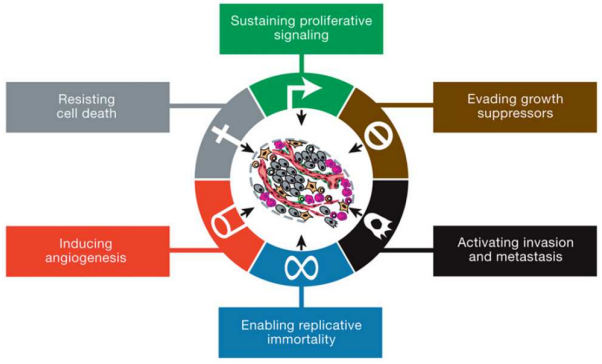
Cell *144*, March 4, 2011

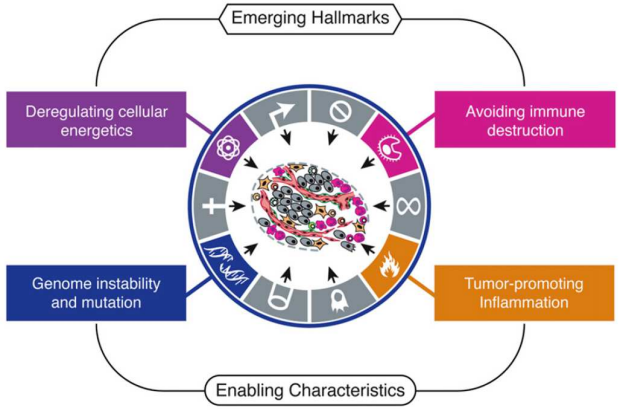
Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]

The hallmarks of cancer comprise six biological capabilities acquired during the multistep development of human tumors. The hallmarks constitute an organizing principle for rationalizing the complexities of neoplastic disease. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Underlying these hallmarks are genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation, which fosters multiple hallmark functions. Conceptual progress in the last decade has added two emerging hallmarks of potential generality to this list—reprogramming of energy metabolism and evading immune destruction. In addition to cancer cells, tumors exhibit another dimension of complexity: they contain a repertoire of recruited, ostensibly normal cells that contribute to the acquisition of hallmark traits by creating the "tumor microenvironment." Recognition of the widespread applicability of these concepts will increasingly affect the development of new means to treat human cancer.

Figure 1. The Hallmarks of Cancer
This illustration encompasses the six hallmark capabilities originally proposed in our 2000 perspective.





MOLECULAR BIOLOGY

More Chemicals Show Epigenetic Effects across Generations

Epigenetic changes occur when the function of a gene is altered by various mechanisms although its DNA sequence remains stable. Transgenerational effects result from a mother's exposure and are inherited through successive generations in the absence of direct exposure of the offspring.[2] Such environmentally induced effects have been demonstrated in people, rodents, birds, fish, insects, worms, plants, and microbes, in some cases lasting dozens of generations.[3]

February 2012 PLoS one

Transgenerational Actions of Environmental Compounds on Reproductive Disease and Identification of Epigenetic Biomarkers of Ancestral Exposures

Mohan Manikkam, Carlos Guerrero-Bosagna, Rebecca Tracey, Md. M. Haque, Michael K. Skinner*

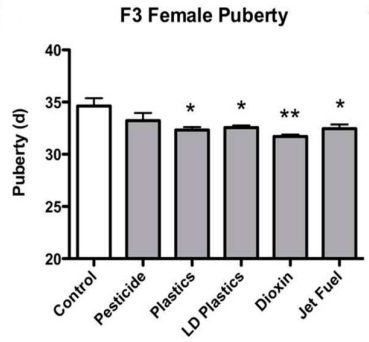
Center for Reproductive Biology, School of Biological Sciences, Washington State University, Pullman, Washington, United States of America

Environmental factors during fetal development can induce a permanent epigenetic change in the germ line (sperm) that then transmits epigenetic transgenerational inheritance of adult-onset disease in the absence of any subsequent exposure. The epigenetic transgenerational actions of various environmental compounds and relevant mixtures were investigated with the use of a pesticide mixture (permethrin and insect repellant DEET), a plastic mixture (bisphenol A and phthalates), dioxin (TCDD) and a hydrocarbon mixture (jet fuel, JP8). After transient exposure of F0 gestating female rats during the period of embryonic gonadal sex determination, the subsequent F1–F3 generations were obtained in the absence of any environmental exposure. The effects on the F1, F2 and F3 generations pubertal onset and gonadal function were assessed. The plastics, dioxin and jet fuel were found to promote early-onset female puberty transgenerationally (F3 generation). Spermatogenic cell apoptosis was affected transgenerationally. Ovarian primordial follicle pool size was significantly decreased with all treatments transgenerationally. Differential DNA methylation of the F3 generation sperm promoter epigenome was examined. Differential DNA methylation regions (DMR) were identified in the sperm of all exposure lineage males and found to be consistent within a specific exposure lineage, but different between the exposures. Several genomic features of the DMR, such as low density CpG content, were identified. Exposure-specific epigenetic biomarkers were identified that may allow for the assessment of ancestral environmental exposures associated with adult onset disease.

February 2012 PLoS one

Transgenerational Actions of Environmental Compounds on Reproductive Disease and Identification of Epigenetic Biomarkers of Ancestral Exposures

Mohan Manikkam Michael K. Skinner*



Interest of paying attention to "indirect effects" of environmental pollutants

- **Enzymatic induction: procarcinogen → carcinogen.**
- **Alterations in DNA repair.**
- **Alterations of apoptosis and other disruptions of cell-cycle checkpoints.**
- **Provision of a growth advantage to mutated cells.**
- **Immunological alterations.**
- **Epigenetic effects.**

Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

Attention to – mechanisms
– interactions
– "indirect effects"

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

NOT negligible: 1) mechanistic interest.
2) ↑↑↑ number of individuals exposed to environmental chemical agents.

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

FOCUS ON EPIGENETICS

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

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)

Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

Review *Trends in Endocrinology and Metabolism* Vol.21 No.4 Cell PRESS

Epigenetic transgenerational actions of environmental factors in disease etiology

Michael K. Skinner, Mohan Manikkam and Carlos Guerrero-Bosagna

Endocrine disruptor	Effect
DDT	Reproductive failure
Phytoestrogens (e.g. genistein)	Impaired fertility, reproductive effects, breast cancer protection
DES	Vaginal cancer in humans
	Developmental toxicity in hamsters
Dicofol	Abnormal ovarian follicles, high plasma estrogen levels
BPA	Prostate cancer
Aflatoxin	Liver cancer
Cadmium	Lung cancer, reproductive problems
Heterocyclic amines	Cancer of colon, stomach and breast
Arsenic	Liver cancer
Dioxins (TCDD)	Mammary tumor
Vinclozolin	Impaired male fertility
Methoxychlor	Impaired male fertility
Phthalates	Impairs male reproductive tract and testis

Review Trends in Endocrinology and Metabolism Vol.21 No.4

Epigenetic transgenerational event, environmental factor and generation	Reference
Paramutation in maize Modification of plant color (F1–F2)	[118]
Paramutation in *Arabidopsis* (F1–F4)	[91]
Epigenetic (paramutation) non-mendelian change in mouse (F1–F6)	[92,93]
Vinclozolin-induced epigenetic transgenerational adult-onset disease in rat (F1–F4)	[33,86]
BPA-induced transgenerational testicular abnormality (F1–F3)	[89]
Transgenerational promotion of long term potentiation (F1–F2) by altered environment	[95]
Stress-induced behavior alterations (F0–F2)	[96]
Nutrition-induced transgenerational obesity in mice (F1–F3)	[61]
Transgenerational response in longevity to nutrition (F0–F2)	[94]
Gender bias in multiple sclerosis following epigenetic changes in HLA class III risk haplotypes (F1–F2)	[98]
Tumor susceptibility in *Drosophila* (F1–F3)	[119]
Stem cell culture-induced adult-onset disease (F0–F4)	[99]

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

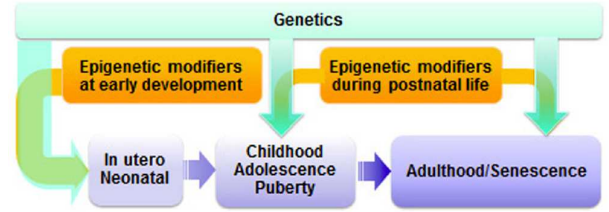


Figure 1 Periods of vulnerability to environmental influences. The most critical period is the perinatal period, during which epigenetic plasticity is high and can be influenced by a variety of environmental cues, including chemicals, nutrition, infection, etc.). Later in life, growth and the hormonally active puberty period is also a vulnerability period. In adults it is believed that elder persons are more vulnerable to a variety of insults.

Barouki et al. Environmental Health 2012, 11:42
http://www.ehjournal.net/content/11/1/42

ENVIRONMENTAL HEALTH

REVIEW Open Access

Developmental origins of non-communicable disease: Implications for research and public health

Robert Barouki[1*], Peter D Gluckman[2], Philippe Grandjean[3,4], Mark Hanson[5] and Jerrold J Heindel[6]

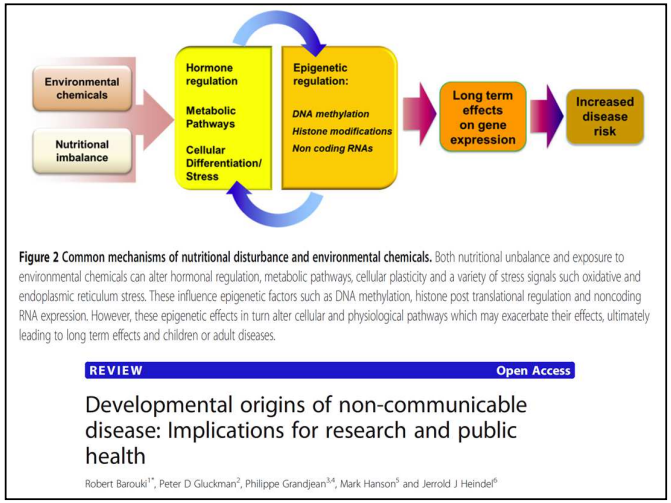


Figure 2 Common mechanisms of nutritional disturbance and environmental chemicals. Both nutritional unbalance and exposure to environmental chemicals can alter hormonal regulation, metabolic pathways, cellular plasticity and a variety of stress signals such oxidative and endoplasmic reticulum stress. These influence epigenetic factors such as DNA methylation, histone post translational regulation and noncoding RNA expression. However, these epigenetic effects in turn alter cellular and physiological pathways which may exacerbate their effects, ultimately leading to long term effects and children or adult diseases.

REVIEW Open Access

Developmental origins of non-communicable disease: Implications for research and public health

Robert Barouki[1*], Peter D Gluckman[2], Philippe Grandjean[3,4], Mark Hanson[5] and Jerrold J Heindel[6]

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]

Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

REVIEW Endocrine Reviews, June 2012

Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses

Laura N. Vandenberg, Theo Colborn, Tyrone B. Hayes, Jerrold J. Heindel, David R. Jacobs, Jr., Duk-Hee Lee, Toshi Shioda, Ana M. Soto, Frederick S. vom Saal, Wade V. Welshons, R. Thomas Zoeller, and John Peterson Myers

For decades, studies of endocrine-disrupting chemicals (EDCs) have challenged traditional concepts in toxicology, in particular the dogma of "the dose makes the poison," because EDCs can have effects at low doses that are not predicted by effects at higher doses. Here, we review two major concepts in EDC studies: low dose and nonmonotonicity. Low-dose effects were defined by the National Toxicology Program as those that occur in the range of human exposures or effects observed at doses below those used for traditional toxicological studies. We review the mechanistic data for low-dose effects and use a weight-of-evidence approach to analyze five examples from the EDC literature. Additionally, we explore nonmonotonic dose-response curves, defined as a nonlinear relationship between dose and effect where the slope of the curve changes sign somewhere within the range of doses examined. We provide a detailed discussion of the mechanisms responsible for generating these phenomena, plus hundreds of examples from the cell culture, animal, and epidemiology literature. We illustrate that nonmonotonic responses and low-dose effects are remarkably common in studies of natural hormones and EDCs. Whether low doses of EDCs influence certain human disorders is no longer conjecture, because epidemiological studies show that environmental exposures to EDCs are associated with human diseases and disabilities. We conclude that when nonmonotonic dose-response curves occur, the effects of low doses cannot be predicted by the effects observed at high doses. Thus, fundamental changes in chemical testing and safety determination are needed to protect human health. (*Endocrine Reviews* 33: 378–455, 2012)

2009 · Environmental Health Perspectives

A Clash of Old and New Scientific Concepts in Toxicity, Implications for Public Health

John Peterson Myers,[1] R. Thomas Zoeller,[2] and Frederick S. vom Saal[3]

BACKGROUND: A core assumption of current toxicologic procedures used to establish health standards for chemical exposures is that testing the safety of chemicals at high doses can be used to predict the effects of low-dose exposures, such as those common in the general population. This assumption is based on the precept that "the dose makes the poison": higher doses will cause greater effects.

OBJECTIVES: We challenge the validity of assuming that high-dose testing can be used to predict low-dose effects for contaminants that behave like hormones. We review data from endocrinology and toxicology that falsify this assumption and summarize current mechanistic understanding of how low doses can lead to effects unpredictable from high-dose experiments.

CONCLUSIONS: We recommend that procedures to establish acceptable exposure levels for endocrine-disrupting compounds incorporate the inability for high-dose tests to predict low-dose results. Setting acceptable levels of exposure must include testing for health consequences at prevalent levels of human exposure, not extrapolations from the effects observed in high-dose experiments.

Environmental chemical exposures and human epigenetics

International Journal of Epidemiology 2012

Lifang Hou,[1,2]* Xiao Zhang,[1] Dong Wang[1,3] and Andrea Baccarelli[4]

Rapidly growing evidence has linked environmental pollutants with epigenetic variations, including changes in DNA methylation, histone modifications and microRNAs.

All of these mechanisms are likely to play important roles in disease aetiology, and their modifications due to environmental pollutants might provide further understanding of disease aetiology, as well as biomarkers reflecting exposures to environmental pollutants and/or predicting the risk of future disease. We summarize the findings on epigenetic alterations related to environmental chemical exposures, and propose mechanisms of action by means of which the exposures may cause such epigenetic changes.

Future investigations are needed to solve methodological and practical challenges, including uncertainties about stability over time of epigenomic changes induced by the environment, tissue specificity of epigenetic alterations, validation of laboratory methods, and adaptation of bioinformatic and biostatistical methods to high-throughput epigenomics.

November 2008 · Environmental Health Perspectives

Global DNA Hypomethylation Is Associated with High Serum-Persistent Organic Pollutants in Greenlandic Inuit

Jennifer A. Rusiecki,[1] Andrea Baccarelli,[2] Valentina Bollati,[2] Letizia Tarantini,[2] Lee E. Moore,[3] and Eva C. Bonefeld-Jorgensen[4]

RESULTS: We found inverse correlations between percents methylcytosine and many of the POP concentrations measured. Linear regressions, adjusting for age and cigarette smoking, showed statistically significant inverse linear relationships mainly for the *Alu* assay for *p,p′*-DDT (1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; β = –0.26), *p,p′*-DDE [1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene; β = –0.38], β-hexachlorocyclohexane (β = –0.48), oxychlordane (β = –0.32), α-chlordane (β = -0.75), mirex (β = –0.27), sum of polychlorinated biphenyls (β = –0.56), and sum of all POPs (β = –0.48). Linear regressions for the LINE-1 assay showed β estimates of similar magnitudes to those using the *Alu* assay, however, none was statistically significant.

CONCLUSIONS: This is the first study to investigate environmental exposure to POPs and DNA methylation levels in a human population. Global methylation levels were inversely associated with blood plasma levels for several POPs and merit further investigation.

March 2010 · Environmental Health Perspectives

Association of Low-Dose Exposure to Persistent Organic Pollutants with Global DNA Hypomethylation in Healthy Koreans

Keon-Yeop Kim,[1] Dong-Sun Kim,[2]* Sung-Kook Lee,[1] In-Kyu Lee,[3] Jung-Ho Kang,[4] Yoon-Seok Chang,[4] David R. Jacobs, Jr.,[5,6] Michael Steffes,[7] and Duk-Hee Lee[1]*

RESULTS: Most OC pesticides were inversely and significantly associated with %5-mC in the *Alu* assay, with correlation coefficients in the range –0.2 to –0.3 after adjusting for age, sex, body mass index, smoking, and alcohol. The strongest OC pesticide associations with %5-mC in the *Alu* assay were observed with oxychlordane, *trans*-nonachlor, and *p,p′*-dichlorodiphenyldichloroethylene. The correlation coefficient of age with %5-mC in the *Alu* assay was –0.24, similar to correlations of OC pesticides with %5-mC in the *Alu* assay. Most PCBs and PBDEs showed nonsignificant inverse trends with %5-mC in the *Alu* assay, but for some PCBs the U-shaped association was significant. On the other hand, POPs were not associated with %5-mC in the LINE-1 assay.

CONCLUSIONS: We found that low-dose exposure to POPs, in particular OC pesticides, was associated with global DNA hypomethylation in apparently healthy Koreans.

In addition, inverse associations were observed mostly in the lower ranges of background exposure to POPs, rather than the higher ranges.

June 2012 · Environmental Health Perspectives

Low-Level Environmental Cadmium Exposure Is Associated with DNA Hypomethylation in Argentinean Women

Mohammad Bakhtiar Hossain,[1,2] Marie Vahter,[3] Gabriela Concha,[4] and Karin Broberg[1]

BACKGROUND: Cadmium, a common food pollutant, alters DNA methylation *in vitro*. Epigenetic effects might therefore partly explain cadmium's toxicity, including its carcinogenicity; however, human data on epigenetic effects are lacking.

OBJECTIVE: We evaluated the effects of dietary cadmium exposure on DNA methylation, considering other environmental exposures, genetic predisposition, and gene expression.

METHODS: Concentrations of cadmium, arsenic, selenium, and zinc in blood and urine of nonsmoking women (n = 202) from the northern Argentinean Andes were measured by inductively coupled mass spectrometry. Methylation in CpG islands of *LINE-1* (long interspersed nuclear element-1; a proxy for global DNA methylation) and promoter regions of *p16* [cyclin-dependent kinase inhibitor 2A (*CDKN2A*)] and *MLH1* (mutL homolog 1) in peripheral blood were measured by bisulfite polymerase chain reaction pyrosequencing. Genotyping (n = 172) for the DNA (cytosine-5-)-methyltransferase 1 gene (*DNMT1* rs10854076 and rs2228611) and DNA (cytosine-5-)-methyltransferase 3 beta gene (*DNMT3B* rs2424913 and rs2424932) was performed with Sequenom iPLEX GOLD SNP genotyping; and gene expression (n = 90), with DirectHyb HumanHT-12 (version 3.0).

RESULTS: Cadmium exposure was low: median concentrations in blood and urine were 0.36 and 0.23 μg/L, respectively. Urinary cadmium (natural log transformed) was inversely associated with *LINE-1* methylation (β = −0.50, p = 0.0070; β = −0.44, p = 0.026, adjusted for age and coca chewing) but not with *p16* or *MLH1* methylation. Both *DNMT1* rs10854076 and *DNMT1* rs2228611 polymorphisms modified associations between urinary cadmium and *LINE-1* (p-values for interaction in adjusted models were 0.045 and 0.064, respectively). The rare genotypes demonstrated stronger hypomethylation with increasing urinary cadmium concentrations. Cadmium was inversely associated with *DNMT3B* (r_S = −0.28, p = 0.0086) but not with *DNMT1* expression (r_S = −0.075, p = 0.48).

CONCLUSION: Environmental cadmium exposure was associated with DNA hypomethylation in peripheral blood, and *DNMT1* genotypes modified this association. The role of epigenetic modifications in cadmium-associated diseases needs clarification.

Increased Mitochondrial DNA Copy Number in Occupations Associated with Low-Dose Benzene Exposure

Michele Carugno,[1] Angela Cecilia Pesatori,[1,2] Laura Dioni,[1] Mirjam Hoxha,[1] Valentina Bollati,[1] Benedetta Albetti, Hyang-Min Byun,[3] Matteo Bonzini,[4] Silvia Fustinoni,[2] Pierluigi Cocco,[5] Giannina Satta,[5] Mariagrazia Zucca,[5] Domenico Franco Merlo,[6] Massimo Cipolla,[6] Pier Alberto Bertazzi,[1,2] and Andrea Baccarelli[3]

February 2012 · Environmental Health Perspectives

BACKGROUND: Benzene is an established leukemogen at high exposure levels. Although low-level benzene exposure is widespread and may induce oxidative damage, no mechanistic biomarkers are available to detect biological dysfunction at low doses.

OBJECTIVES: Our goals were to determine in a large multicenter cross-sectional study whether low-level benzene is associated with increased blood mitochondrial DNA copy number (mtDNAcn, a biological oxidative response to mitochondrial DNA damage and dysfunction) and to explore potential links between mtDNAcn and leukemia-related epigenetic markers.

METHODS: We measured blood relative mtDNAcn by real-time polymerase chain reaction in 341 individuals selected from various occupational groups with low-level benzene exposures (> 100 times lower than the Occupational Safety and Health Administration/European Union standards) and 178 referents from three Italian cities (Genoa, Milan, Cagliari).

RESULTS: In each city, benzene-exposed participants showed higher mtDNAcn than referents: mtDNAcn was 0.90 relative units in Genoa bus drivers and 0.75 in referents (p = 0.019); 0.90 in Milan gas station attendants, 1.10 in police officers, and 0.75 in referents (p-trend = 0.008); 1.63 in Cagliari petrochemical plant workers, 1.25 in referents close to the plant, and 0.90 in referents farther from the plant (p-trend = 0.046). Using covariate-adjusted regression models, we estimated that an interquartile range increase in personal airborne benzene was associated with percent increases in mtDNAcn equal to 10.5% in Genoa (p = 0.014), 8.2% (p = 0.008) in Milan, 7.5% in Cagliari (p = 0.22), and 10.3% in all cities combined (p < 0.001). Using methylation data available for the Milan participants, we found that mtDNAcn was associated with *LINE-1* hypomethylation (–2.41%; p = 0.007) and *p15* hypermethylation (+15.95%, p = 0.008).

CONCLUSIONS: Blood MtDNAcn was increased in persons exposed to low benzene levels, potentially reflecting mitochondrial DNA damage and dysfunction.

Research Article Cancer Res 2005

Persistent Organochlorine Chemicals in Plasma and Risk of Non-Hodgkin's Lymphoma

Anneclaire J. De Roos,[1] Patricia Hartge,[2] Jay H. Lubin,[2] Joanne S. Colt,[2] Scott Davis,[1] James R. Cerhan,[3,4] Richard K. Severson,[5] Wendy Cozen,[6] Donald G. Patterson, Jr.,[7] Larry L. Needham,[7] and Nathaniel Rothman[2]

Polychlorinated biphenyls (PCB) have been suspected as possible contributors to increasing non-Hodgkin's lymphoma incidence during the latter half of the 20th century based on their toxicologic properties and provocative epidemiologic reports. Certain PCB congeners were associated with increased risk Each of the furan congeners was associated with risk Our results add to existing literature, which suggests that exposure to organochlorines contributes to non-Hodgkin's lymphoma risk; these risks were most apparent for certain PCBs and furans.

Ana M. Soto and Carlos Sonnenschein NATURE REVIEWS | ENDOCRINOLOGY

Environmental causes of cancer: endocrine disruptors as carcinogens

Abstract | Environmental endocrine disrupting chemicals (EDCs), including pesticides and industrial chemicals, have been and are released into the environment producing deleterious effects on wildlife and humans. The effects observed in animal models after exposure during organogenesis correlate positively with an increased incidence of malformations of the male genital tract and of neoplasms and with the decreased sperm quality observed in European and US populations. Exposure to EDCs generates additional effects, such as alterations in male and female reproduction and changes in neuroendocrinology, behavior, metabolism and obesity, prostate cancer and thyroid and cardiovascular endocrinology. This Review highlights the carcinogenic properties of EDCs, with a special focus on bisphenol A. However, humans and wildlife are exposed to a mixture of EDCs that act contextually. To explain this mindboggling complexity will require the design of novel experimental approaches that integrate the effects of different doses of structurally different chemicals that act at different ages on different target tissues. The key to this complex problem lies in the adoption of mathematical modeling and computer simulations afforded by system biology approaches. Regardless, the data already amassed highlight the need for a public policy to reduce exposure to EDCs.

Ana M. Soto and Carlos Sonnenschein NATURE REVIEWS | ENDOCRINOLOGY

Key points

- The embryo is an open system and the environment is a co-determinant of phenotypes, such that the embryo 'reads' environmental cues as a forecast of the postnatal environment
- Hormones act as morphogens: extemporaneous exposure to even low doses of hormonally active chemicals increases the susceptibility to various diseases, including cancer
- Neoplasia is a tissue-based disease caused by various deleterious exposures that interfere with the reciprocal communication between cells and between cells and their surrounding extracellular matrix
- The effects of developmental exposure to diethylstilbestrol observed in humans have been reproduced in rodent models; thus, rodents are relevant models for assessing the human toxicity of environmental endocrine disruptors
- Endocrine disrupting chemicals act additively—their multiple and complex effects are dose-dependent and contextual; therefore, a systems biology approach should be adopted to tackle this complexity
- Sufficient supporting data have been gathered on the deleterious effects of endocrine disrupting chemicals to warrant immediate action to decrease human and wildlife exposure to these agents

Annual Review of Physiology 2011.

Endocrine Disruptors: From Endocrine to Metabolic Disruption

Cristina Casals-Casas and Béatrice Desvergne

Center for Integrative Genomics, Faculty of Biology and Medicine, University of Lausanne

Synthetic chemicals currently used in a variety of industrial and agricultural applications are leading to widespread contamination of the environment. Even though the intended uses of pesticides, plasticizers, antimicrobials, and flame retardants are beneficial, effects on human health are a global concern. These so-called endocrine-disrupting chemicals (EDCs) can disrupt hormonal balance and result in developmental and reproductive abnormalities. New in vitro, in vivo, and epidemiological studies link human EDC exposure with obesity, metabolic syndrome, and type 2 diabetes. Here we review the main chemical compounds that may contribute to metabolic disruption. We then present their demonstrated or suggested mechanisms of action with respect to nuclear receptor signaling. Finally, we discuss the difficulties of fairly assessing the risks linked to EDC exposure, including developmental exposure, problems of high- and low-dose exposure, and the complexity of current chemical environments.

Annual Review of Physiology 2011.

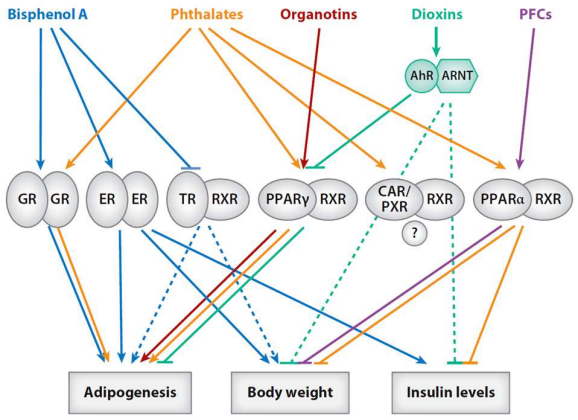
Endocrine Disruptors: From Endocrine to Metabolic Disruption

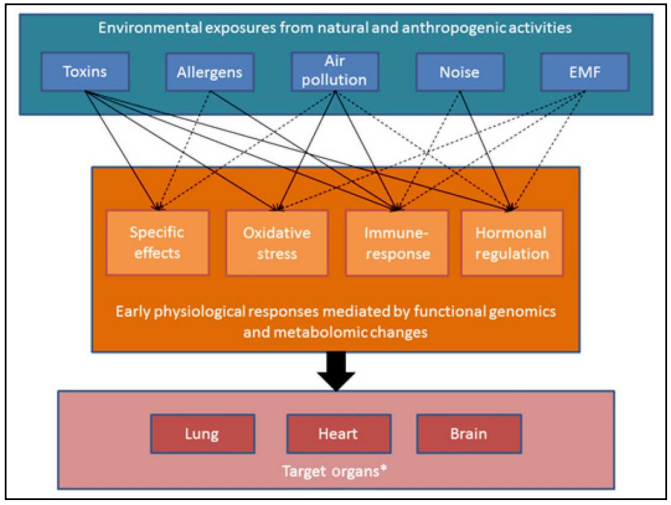
Cristina Casals-Casas and Béatrice Desvergne

because many EDCs are small lipophilic compounds, one privileged route is through their direct interaction with a given NR, which presumably perturbs or modulates downstream gene expression. For example, most EDC-associated reproductive and developmental defects are thought to result from EDCs interfering with the function of the estrogen receptor (ER) and/or androgen receptor (AR), thereby disrupting the normal activity of estrogens and androgens ligands.

Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

Annual Review of Physiology 2011.





Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

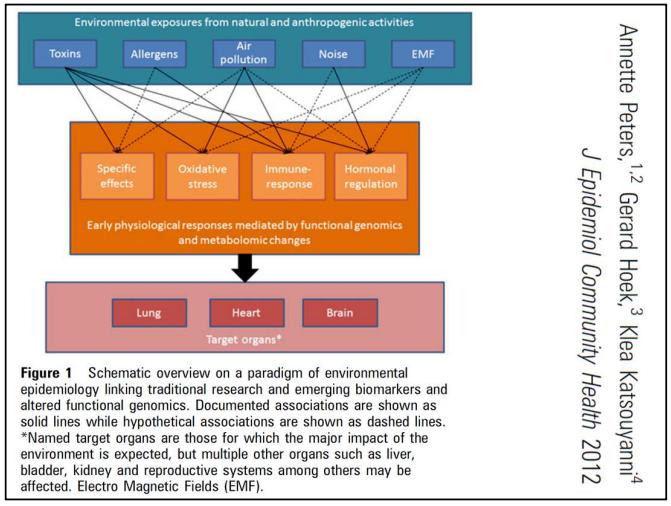


Figure 1 Schematic overview on a paradigm of environmental epidemiology linking traditional research and emerging biomarkers and altered functional genomics. Documented associations are shown as solid lines while hypothetical associations are shown as dashed lines. *Named target organs are those for which the major impact of the environment is expected, but multiple other organs such as liver, bladder, kidney and reproductive systems among others may be affected. Electro Magnetic Fields (EMF).

Annette Peters,[1,2] Gerard Hoek,[3] Klea Katsouyanni[4]
J Epidemiol Community Health 2012

NATURE REVIEWS | ENDOCRINOLOGY

Paloma Alonso-Magdalena, Ivan Quesada and Angel Nadal

Endocrine disruptors in the etiology of type 2 diabetes mellitus

Abstract | The etiology of type 2 diabetes mellitus involves the induction of insulin resistance along with the disruption of pancreatic β-cell function and the loss of β-cell mass. In addition to a genetic predisposition, lifestyle factors seem to have an important role. Epidemiological studies indicate that the increased presence of endocrine disrupting chemicals (EDCs) in the environment may also play an important part in the incidence of metabolic diseases. Widespread EDCs, such as dioxins, pesticides and bisphenol A, cause insulin resistance and alter β-cell function in animal models. These EDCs are present in human blood and can accumulate in and be released from adipocytes. After binding to cellular receptors and other targets, EDCs either imitate or block hormonal responses. Many of them act as estrogens in insulin-sensitive tissues and in β cells, generating a pregnancy-like metabolic state characterized by insulin resistance and hyperinsulinemia. Adult exposure in mice produces insulin resistance and other metabolic alterations; in addition, during pregnancy, EDCs alter glucose metabolism in female mice, as well as glucose homeostasis and endocrine pancreatic function in offspring. Although more experimental work is necessary, evidence already exists to consider exposure to EDCs as a risk factor in the etiology of type 2 diabetes mellitus and other diseases related to insulin resistance.

Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

NATURE REVIEWS | ENDOCRINOLOGY

Paloma Alonso-Magdalena, Ivan Quesada and Angel Nadal

Key points

- The etiology of T2DM is based on the induction of insulin resistance together with functional disruption of insulin producing β cells; genetic predisposition and environmental factors play key roles
- Some widespread endocrine disrupting chemicals (EDCs), at concentrations found in human plasma, induce insulin resistance and alter pancreatic β-cell function in cellular and adult animal models
- Epidemiological data indicate that exposure to EDCs is linked to an increased risk of diabetes mellitus in adults
- Data obtained from pregnant mice and offspring indicate that short exposure to the EDC bisphenol A during pregnancy disrupts glucose homeostasis in female mice and their adult male offspring
- Sufficient scientific evidence is available to consider the exposure to persistent organic pollutants, including bisphenol A, a risk factor for T2DM and other metabolic disorders

June 2012 · Environmental Health Perspectives

Role of Environmental Chemicals in Diabetes and Obesity: A National Toxicology Program Workshop Review

Kristina A. Thayer,[1] Jerrold J. Heindel,[2] John R. Bucher,[3] and Michael A. Gallo[4]

Overall, the existing literature was judged to provide plausibility, varying from suggestive to strong, that exposure to environmental chemicals may contribute to the epidemic of diabetes and/or obesity.

NIEHS Workshop January 11-13, 2011
very useful Tables of human studies. Available:
http://ntp.niehs.nih.gov/ntp/ohat/diabetesobesity/Wkshp/POPsAppendixEpiTableFormatted.pdf

June 2012 · Environmental Health Perspectives

Reference	Study description (*n*)	Chemical	Diagnostic	Relative risk adj OR (95% CI)	Exposure
Rylander et al. 2005	Sweden (national registry), CS fisherman's wives, ♀ (184)	PCB153	Self-report	1.06 (0.75, 1.5) per 100 ng/g ↑	230 (110–810) [med (5th–95th), cases] ng/g lipid (serum)
Jorgensen et al. 2008	Greenland (west coast) Inuit, CS ♂♀ (692)	PCBs, non-dioxin	OGTT, FBG	1.2 (0.4, 3.2)	Q4 vs. Q1 ng/g lipid (plasma)
Jorgensen et al. 2008	Greenland (west coast) Inuit, CS ♂♀ (692)	PCBs, dioxin-like	OGTT, FBG	1.2 (0.4, 3.6)	Q4 vs. Q1 ng/g lipid (plasma)
Rylander et al. 2005	Sweden (national registry), CS fishermen, ♂ (196)	PCB153	Self-report	1.20 (1.04, 1.39) per 100 ng/g ↑	560 (360–1,600) [med (5th–95th), cases] ng/g lipid (serum)
Ukropec et al. 2010	Slovakia (eastern, "polluted"), CS ≥ 21 year, ♂♀ (2,047)	PCBs	FBG	1.77 (1.05, 3.02)	1,341–2,330 (Q4) vs. 148–627 (Q1) ng/g lipid (serum)
Turyk et al. 2009b	USA (Great Lakes), CS fish eaters, ♂♀ (503)	PCBs	Self-report, HbA1c	1.9 (0.7, 5.2)	3.6–24.4 (Q4) vs. < 0.8 (Q1) ng/g (serum)
Turyk et al. 2009b	USA (Great Lakes), CS fish eaters, ♂♀ (503)	PCBs, dioxin-like	Self-report, HbA1c	2.1 (1.1, 4.2)	0.3–1.6 (T3) vs. < LOD (T1) ng/g (serum)
Codru et al. 2007	USA (Akwesasne) Mohawks, CS ♂♀ (352)	PCB153	FBG, medication	2.4 (1.0, 5.6)	104.1 (T3) vs. 59.8 (T1) ng/g lipid (serum)
Lee et al. 2006	USA (NHANES 1999–2002) ≥ 20 year, CS ♂♀ (2,106)	PCB153	FBG, self-report	2.5 (1.1, 6)	14.3 (< 25th) vs. ND ng/g lipid (serum)
Uemura et al. 2008	Japan (multisite), CS ♂♀ (1,374)	PCBs, dioxin-like	Self-report, HbA1c	3.07 (1.16, 8.81)	≥ 7.60 to < 13 vs. ≤ 7.60 pg TEQ/g lipid (serum)
Codru et al. 2007	USA (Akwesasne) Mohawks, CS ♂♀ (352)	PCBs	FBG, medication	3.2 (1.4, 7.5)	756.2 (T3) vs. 448.6 (T1) ng/g lipid (serum)
Lee et al. 2010	USA (multisite) CARDIA, nested CC ≥ 18 year, ♂♀ (180)	PCB153	FBG, medication	0.8 (0.2, 2.6)	> 466 (Q4) vs. ≤ 204 (Q1) pg/g (serum)
Rignell-Hydbom et al. 2009	Sweden (Lund) WHILA, nested CC ♀ (742)	PCB153	OGTT	1.6 (0.61, 4)	> 1,790 vs. ≤ 1,790 pg/ml (serum)
Wang et al. 2008	Taiwan (Yucheng), nested CC ≥ 30 year, ♂ (167)	PCBs	Self-report	1.7 (0.7, 4.6)	99.4 vs. 53.9 ppb (serum)
Wang et al. 2008	Taiwan (Yucheng), nested CC ≥ 30 year, ♀ (244)	PCBs	Self-report	5.5 (2.3, 13.4)	121.4 vs. 72.6 ppb (serum)
Vasiliu et al. 2006	USA (Michigan) PBB cohort, Pros ♂ (688)	PCBs	Self-report	1.74 (0.91, 3.34) IDR	> 10 vs. ≤ 5.0 ng/mL (serum)
Turyk et al. 2009a	USA (Great Lakes), Pros fish eaters, ♂♀ (471)	PCBs	Self-report	1.8 (0.6, 5) IRR	4.3–29.8 (T3) vs. < 1.6 (T1) ng/g ww (serum)
Vasiliu et al. 2006	USA (Michigan) PBB cohort, Pros ♀ (696)	PCBs	Self-report	2.04 (1.10, 3.78) IDR	5.1–7.0 vs. ≤ 5.0 ng/mL (serum)

NIEHS Workshop January 11-13, 2011
very useful Tables of human studies. Available:
http://ntp.niehs.nih.gov/ntp/ohat/diabetesobesity/Wkshp/POPsAppendixEpiTableFormatted.pdf

Organochlorine Exposure and Incidence of Diabetes in a Cohort of Great Lakes Sport Fish Consumers

Mary Turyk,[1] Henry Anderson,[2] Lynda Knobeloch,[2] Pamela Imm,[2] and Victoria Persky[1]

2009 · Environmental Health Perspectives

OBJECTIVES: This study was designed to determine whether POP body burdens are related to incidence of diabetes in a cohort of Great Lakes sport fish consumers.

METHODS: The cohort was established in the early 1990s and followed through 2005. We tested serum for DDE and PCB congeners and assessed diabetes diagnosis, demographics, and fish consumption. Associations of diabetes with exposures were examined prospectively in participants without diabetes in 1994–1995, followed through 2005. Annual percent changes in DDE and PCB-132/153 from 1994 to 2005 were examined by diabetes status.

RESULTS: DDE exposure was associated with incident diabetes. Incident diabetes was not associated with mono-*ortho* PCB-118, total PCBs, or years of sport fish consumption. Annual percent change in DDE and PCB-132/153 did not differ significantly by diabetes status.

CONCLUSIONS: This study demonstrates an association between DDE exposure and incident diabetes. The findings of an association of DDE with incident diabetes and the lack of effect of diabetes on annual percent change in POPs do not support the hypothesis that associations of POPs with diabetes are attributable to reverse causality. Additional studies should address the biological pathways by which DDE could affect glucose homeostasis.

Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

September 2010 · Environmental Health Perspectives

Low Dose of Some Persistent Organic Pollutants Predicts Type 2 Diabetes: A Nested Case–Control Study

Duk-Hee Lee,[1] Michael W. Steffes,[2] Andreas Sjödin,[3] Richard S. Jones,[3] Larry L. Needham,[3] and David R. Jacobs, Jr.

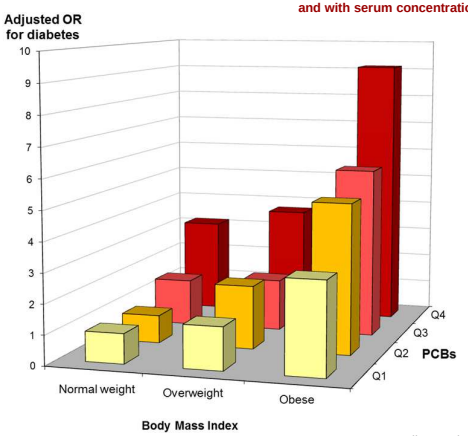
OBJECTIVES: We investigated whether several POPs prospectively predict type 2 diabetes within the Coronary Artery Risk Development in Young Adults (CARDIA) cohort.

METHODS: Participants in this nested case–control study were diabetes free in 1987–1988. By 2005–2006, the 90 controls remained free of diabetes, whereas the 90 cases developed diabetes. Using serum collected in 1987–1988, we measured 8 organochlorine pesticides, 22 polychlorinated biphenyl congeners (PCBs), and 1 polybrominated biphenyl (PBB). We compared POP concentrations from CARDIA and the National Health and Nutrition Examination Survey (NHANES) in 2003–2004. We computed odds ratios (ORs) for incident diabetes using logistic regression analysis.

RESULTS: Chlorinated POPs in CARDIA in 1987–1988 were much higher than corresponding NHANES 2003-2004 concentrations. POPs showed nonlinear associations with diabetes risk. The highest risk was observed in the second quartiles of *trans*-nonachlor, oxychlordane, mirex, highly chlorinated PCBs, and PBB153—a finding that suggests low-dose effects. We concentrated risk by summing these POPs and isolated very low concentrations of multiple POPs in the lowest sextile of the sum. The adjusted OR in the second sextile vs. the lowest sextile was 5.3 overall and 20.1 for body mass index ≥ 30 kg/m^2.

CONCLUSIONS: Several POPs at low doses similar to current exposure levels may increase diabetes risk, possibly through endocrine disruption. Certain POPs may a play a role in the current epidemic of diabetes, which has been attributed to obesity.

Catalonia 2002. The prevalence of diabetes increases with Body Mass Index and with serum concentrations of PCBs (N = 684).

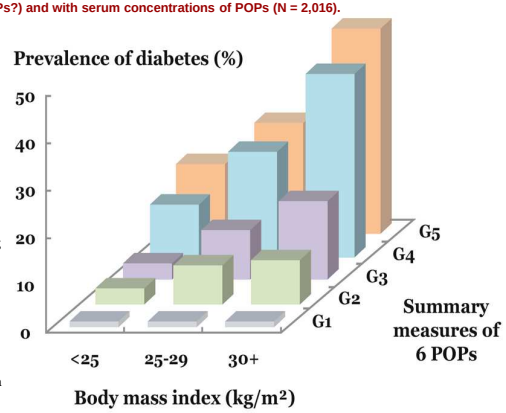


PCBs: Sum of orders of PCBs 118, 138, 153, 180.

All odds ratios (OR) are computed with Q1 and normal weight as the reference category, with models adjusted by age, sex, total cholesterol and triglycerides.

Gasull M et al. *Environ Sci Technol* 2012

USA 1999-2002. The prevalence of diabetes increases with BMI (only if contaminated by POPs?) and with serum concentrations of POPs (N = 2,016).



Among people with lower concentrations of the summary POPs (G1 row), the frequency of diabetes did not increase with increasing BMI, and diabetes was very rare (even among people with BMI ≥30kg/m²). Furthermore, the frequency of diabetes increased with rising concentrations of POPs, even among people with low BMI (<25).

Lee DH et al. *Diabetes Care* 2006

A Strong Dose-Response Relation Between Serum Concentrations of Persistent Organic Pollutants and Diabetes

Results from the National Health and Examination Survey 1999–2002

Diabetes Care 29:1638–1644, 2006

DUK-HEE LEE, MD, PHD[1]
DAVID R. JACOBS, JR., PHD[2,3]

OBJECTIVE — Low-level exposure to some persistent organic pollutants (POPs) has recently become a focus because of their possible link with the risk of diabetes.

RESULTS — Compared with subjects with serum concentrations below the limit of detection, after adjustment for age, sex, race and ethnicity, poverty income ratio, BMI, and waist circumference, diabetes prevalence was strongly positively associated with lipid-adjusted serum concentrations of all six POPs. When the participants were classified according to the sum of category numbers of the six POPs, adjusted odds ratios were 1.0, 14.0, 14.7, 38.3, and 37.7 (P for trend < 0.001). The association was consistent in stratified analyses and stronger in younger participants, Mexican Americans, and obese individuals.

Response to Porta DIABETES CARE, NOVEMBER 2006

Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

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

Diabetologia (2007)

Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999–2002

D.-H. Lee · I.-K. Lee · M. Porta · M. Steffes
D. R. Jacobs Jr

Results Among five POPs subclasses, organochlorine (OC) pesticides were most strongly and consistently associated with metabolic syndrome: adjusted odds ratios (ORs) of 1.0, 1.5, 2.3 and 5.3 across OC pesticide quartiles (p for trend <0.01). Dioxin-like polychlorinated biphenyls (PCBs) were also positively associated with adjusted ORs of 1.0, 1.1, 2.2 and 2.1 (p for trend=0.01).

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).

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

Persistent organic pollutants and the burden of diabetes

Studies from the USA[1,2] have drawn attention to the possibility that persistent organic pollutants might contribute to cause diabetes.[3-6]

Because they contaminate virtually all people, even if they confer only a low individual risk of diabetes, these pollutants might have a substantial overall population effect.

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

W Karmaus,[1] J R Osuch,[2] I Eneli,[3] L M Mudd,[2] J Zhang,[1] D Mikucki,[2] P Haan,[2] S Davis[2]

Occup Environ Med March 2009

Editorial

Transgenerational inheritance of environmental

Miquel Porta,[1] Duk-Hee

- third, the vast majority of humans acquire persistent organic pollutants (POPs) from their mothers during pregnancy and lactation, and subsequently from fatty foods, following culturally-inherited familial dietary patterns,[15]
- second, heritable environmentally induced epigenetic modifications are a plausible link between non-mutagenic environmental exposures early in development and reversible transgenerational alterations in gene expression that lead to adult disease phenotypes,[14 15]

Occup Environ Med March 2009

Editorial

- fourth, in many populations there is a positive association between POP levels and BMI,[1 16] and
- fifth, strong associations—although mostly cross-sectional—have been reported between POP level and diabetes.[6 16]

- third, the vast majority of humans acquire persistent organic pollutants (POPs) from their mothers during pregnancy and lactation, and subsequently from fatty foods, following culturally-inherited familial dietary patterns,[15]
- second, heritable environmentally induced epigenetic modifications are a plausible link between non-mutagenic environmental exposures early in development and reversible transgenerational alterations in gene expression that lead to adult disease phenotypes,[14 15]

Occup Environ Med March 2009

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.

Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

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.

PNAS 2007

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

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

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.

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
David Melzer, MB, 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.

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; $P = .002$).

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.

DDE in Mothers' Blood During Pregnancy and Lower Respiratory Tract Infections in Their Infants

Jordi Sunyer,[a,b,c,d] Raquel Garcia-Esteban,[a,b,c] Mar Alvarez,[a,b,c] Mònica Guxens,[a,b,c] Fernando Goñi, Mikel Basterrechea,[c,f] Martine Vrijheid,[a,b,c] Stefano Guerra,[a,b,c] and Josep M. Antó, [a,b,c,d]

DDE was the only organochlorine that showed an association with recurrent lower respiratory tract infection (at levels >83 ng/g, the first tertile, relative risk = 2.40 [95% confidence interval = 1.19–4.83]), lower respiratory tract infection at 6 months (1.68 [1.06–2.66]), and lower respiratory tract infection at 14 months (1.52 [1.05–2.21]). Adjusting for PCBs, hexachlorobenzene or β-hexachlorocyclohexane did not confound the association.

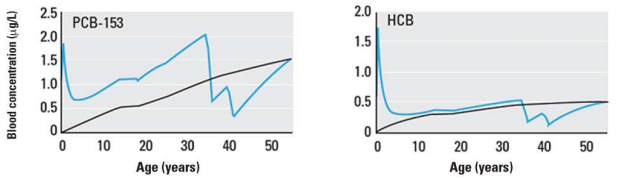
Conclusions: Immunologic suppression by DDE as observed in experimental studies could explain the relation between DDE and lower respiratory tract infection, independently of PCBs. Exposure to DDE during prenatal life could be critical for the development of the immune and respiratory systems. *Epidemiology* 2010;21

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).

March 2009 • Environmental Health Perspectives

A Physiologically Based Pharmacokinetic Model for the Assessment of Infant Exposure to Persistent Organic Pollutants in Epidemiologic Studies

Marc-André Verner,

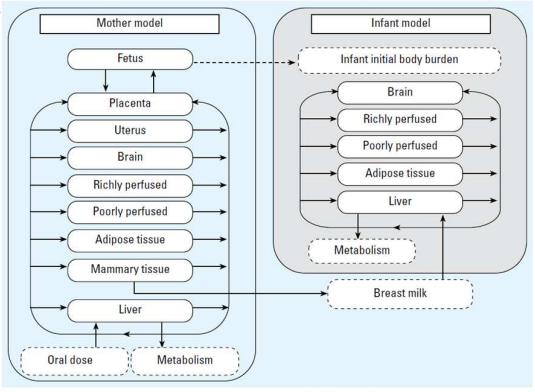
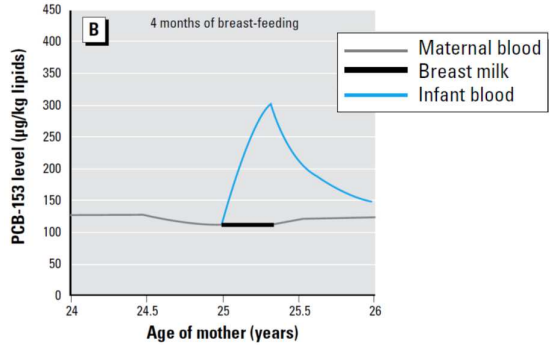


Figure 1. Conceptual representation of the mother–infant PBPK model.

March 2009 • Environmental Health Perspectives

A Physiologically Based Pharmacokinetic Model for the Assessment of Infant Exposure to Persistent Organic Pollutants in Epidemiologic Studies

Marc-André Verner,[1] Pierre Ayotte,[2] Gina Muckle,[2] Michel Charbonneau,[3] and Sami Haddad[1]



toxicokinetic profiles for PCB-153 in maternal blood, breast milk, and infant blood

We know quite a lot about
→ generalized human contamination
→ toxic effects of environmental pollutants

i. Most individuals accumulate complex mixtures of persistent toxic substances throughout the life course, both at high and low concentrations;

ii. Knowledge on **the joint effects of such 'cocktails'** (including alterations of metabolic functions and gene expression) ought to be assessed more often when **building causal scenarios that aim at being relevant for human health**; and

iii. It may be scientifically unfounded to study mechanisms of diseases of complex etiology without considering environmental mixtures and the hypothesis that **key causal processes involve contamination by toxic pollutants and the ensuing accumulation of genetic and epigenetic alterations.**

We know too little about
→ the etiopathogenesis of the most prevalent diseases.

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)

nature **scienceupdate**

molecular biology ↔ molecular epidemiology

news

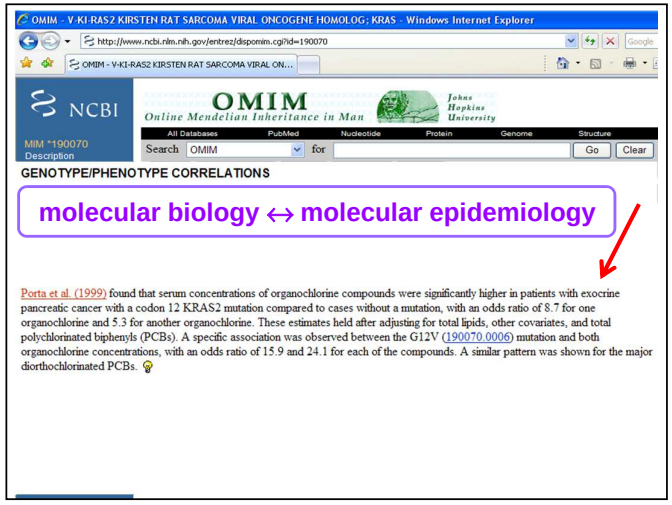
• home
content

Mocha and mutations

morenews
• Suffocating cells

15 December 1999

Following recent conflicting but intriguing results thrown up by rodent and cell culture research, about the effects of caffeine and coffee, Miquel Porta of the Universitat Autonoma de Barcelona, Spain, and colleagues, carried out this new work in five Spanish hospitals. They showed for the first time that, in people suffering from pancreatic cancer, those who also had mutations in K-*ras* drank around 14 and a half cups of coffee a week-significantly more coffee than those without K-*ras* mutations, who tended to consume nearer 9 cups. Nine of the 121 patients studied drank more than 21 cups of coffee a week, and all of them had mutated tumours.



Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

THE LANCET

EARLY REPORT

2125 **Serum concentrations of organochlorine compounds and K-*ras* mutations in exocrine pancreatic cancer**

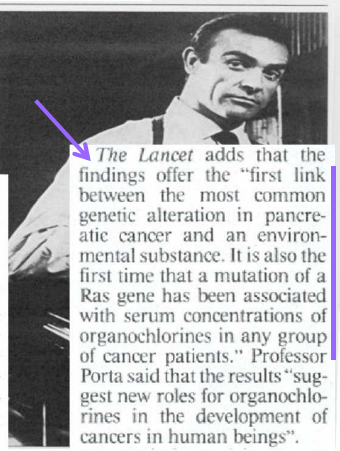
M Porta and others, for the PANKRAS II Study Group

Volume 354, Number 9196 · Founded 1823 · Published weekly · Saturday 18/25 December 1999

Several organochlorine compounds can act as carcinogens and tumour promoters.[3–8] Some modulate the expression of oncogenes, including *ras* genes.[9,10] DDT and some PBCs have endocrine effects.[1,2,11,12] Although presumably weak, such effects may be enhanced by environmental biodegradation, the long half-lives of the compounds (about 10 years for DDE, 30 years or more for some PCBs), and their concentrations in target tissues (100-fold to 350-fold higher in adipose tissue than in blood).[1,5,6]

THE TIMES FRIDAY DECEMBER 17 1999

Pesticide pollution is linked to cancer



The cancer link has been made by Professor Miguel Porta and colleagues at the Municipal Institute of Medical Research and Autonomous University in Barcelona. They have been studying compounds known as organochlorines, including the pesticide DDT, and polychlorinated biphenyls or PCBs, used historically for insulating and cooling electrical equipment.

The Lancet adds that the findings offer the "first link between the most common genetic alteration in pancreatic cancer and an environmental substance. It is also the first time that a mutation of a Ras gene has been associated with serum concentrations of organochlorines in any group of cancer patients." Professor Porta said that the results "suggest new roles for organochlorines in the development of cancers in human beings".

PATTERNS

Trace Elements and Pancreatic Cancer Risk

A new study has found that high bodily levels of the trace elements nickel and selenium may be associated with reduced risk for pancreatic cancer, and that high levels of arsenic, cadmium and lead may increase the risk.

The study, published online Dec. 19 in the journal Gut, included 118 pancreatic cancer patients and 399 patients with other diagnoses at several hospitals in Spain. Researchers analyzed toenail samples with plasma mass spectrometry, a highly sensitive technique for detecting trace elements.

After controlling for age, sex, smoking, diabetes and other factors, the scientists found that the subjects with the highest levels of arsenic were at twice the risk for pancreatic cancer, compared with those with the lowest concentrations. Those with high levels of cadmium were at three times the risk for pancreatic cancer, while those with the highest levels of lead were at six times the risk.

Those with the highest levels of nickel and selenium, on the other hand, were at significantly lower risk for pancreatic cancer.

Dr. Núria Malats, an epidemiologist at the Spanish National Cancer Research Center and the senior author of the new study, said that it was the first to provide these kinds of results with trace elements, and that it did not mean that people should take dietary supplements.

the shape of the spike, making the virus more transmissible. Dr. Sasisekharan's study did not involve A(H5N1) bird flu. Instead, the researchers started with a type of duck flu and spliced in genes from the highly contagious 1918 Spanish flu.

To invade cells, viruses need to latch onto structures on the surface called receptors. In people and ferrets, cells in the nose mostly carry receptors called alpha 2,6, whereas birds have alpha 2,3 receptors in their guts. Normally the A(H5N1) virus prefers the bird receptors, but the HA mutation changes the shape of the spike.

The rare people who have caught bird flu

taminated
nostril or an e
The rare c
man transm
long, close co
sick daughte
have coughe
droplets drift
But there l
cases, includi
who apparen
blood puddin
cocks who w
and mucus o
Experts dis

Protocol for Treatir

From First Science Page

an for the Academy of Nutrition and Dietetics. "These adolescents are so young they can't process the information, and here they've gained five pounds in a week and their biggest fear is happening: They're getting fat. Which we know isn't true, but that's

"All the News That's Fit to Print"

The New York Times

VOL. CLXI . . No. 55,639 © 2012 The New York Times NEW YORK, TUESDAY, JANUARY 3, 2012

MOLECULAR CARCINOGENESIS 36:45–52 (2003)

WORKING HYPOTHESIS

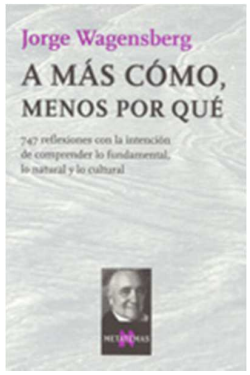
Exploring Environmental Causes of Altered *ras* Effects: Fragmentation Plus Integration?

Miquel Porta,[1,2]* Daniel Ayude,[1,2] Juan Alguacil,[1,3] and Manuel Jariod[1]

Organochlorine compounds, organic solvents, and coffee compounds may play an indirect role in causing Ki-*ras* mutations, rather than as direct inducers of the mutations.

Although for some organochlorine compounds the induction of point mutations in *ras* oncogenes cannot be excluded, it seems more likely that the effects of these compounds are mediated through nongenomic or indirectly genotoxic mechanisms of action. Organic solvents also may act via enzymatic induction of *ras* mutagens or by providing a proliferation advantage to *ras*-mutated cell clones. In exocrine pancreatic cancer, caffeine, other coffee compounds, or other factors with which coffee drinking is associated could modulate Ki-*ras* activation by interfering with DNA repair, cell-cycle checkpoints, and apoptosis.

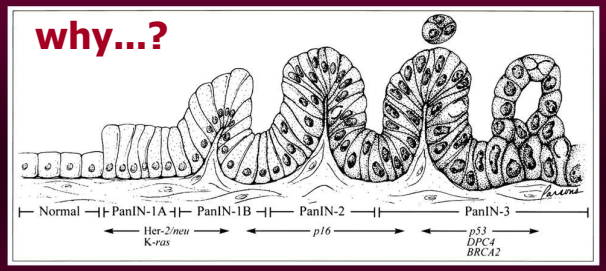
repair, cell-cycle checkpoints, and apoptosis. Asbestos, cigarette smoking, and some dietary factors also may be involved in the initiation or the promotion of Ki-*ras* mutations in lung and colon cancers. Further development of the mechanistic scenarios proposed here could contribute to a meaningful integration of biological, clinical, and environmental knowledge on the causes of altered *ras* effects.



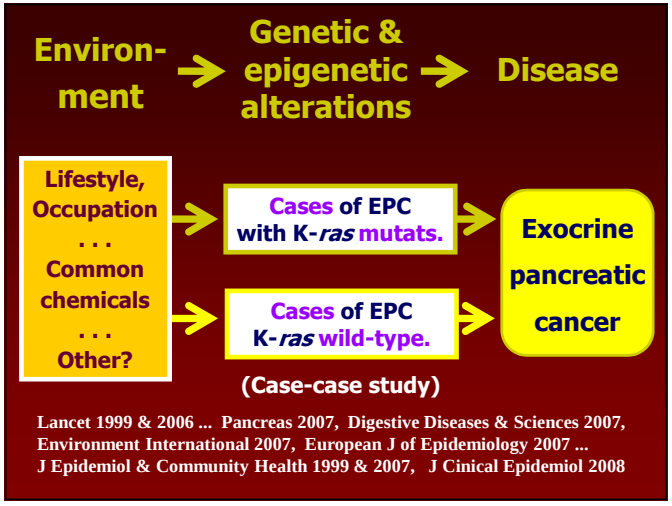
TUSQUETS EDITORES

Jorge Wagensberg (Barcelona, 1948)

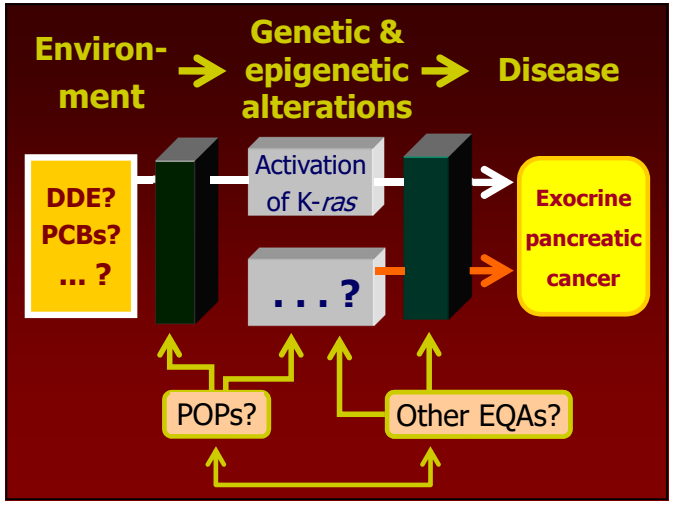
a progression model (i.e., hypothesis) for EPC:

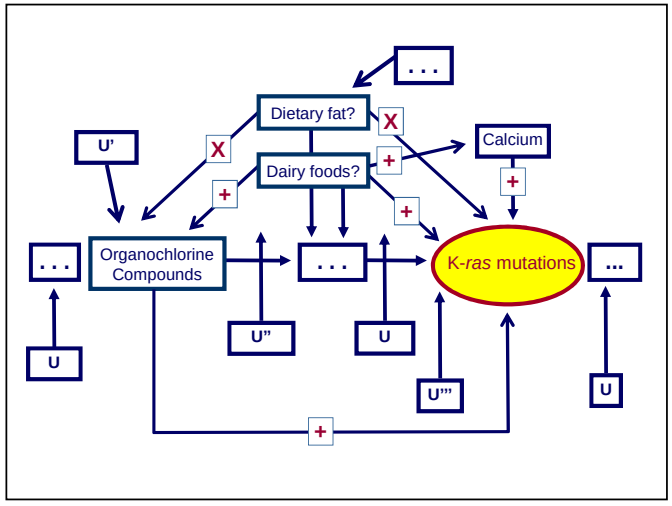


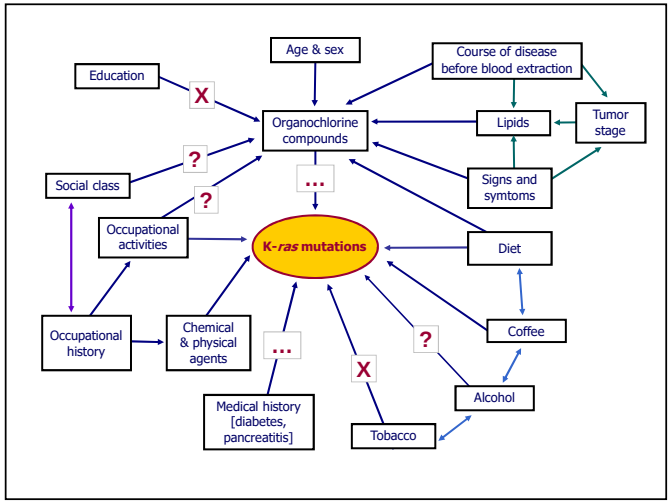
Hruban RH, Goggins M, Parsons J, Kern SE.
Progression model for pancreatic cancer.
Clin Cancer Res 2000.



Lancet 1999 & 2006 ... Pancreas 2007, Digestive Diseases & Sciences 2007, Environment International 2007, European J of Epidemiology 2007 ... J Epidemiol & Community Health 1999 & 2007, J Cinical Epidemiol 2008







Mutagenesis vol. 24 no. 6 pp. 513–521, 2009

In pancreatic ductal adenocarcinoma blood concentrations of some organochlorine compounds and coffee intake are independently associated with *KRAS* mutations

Cases whose tumours harboured a *KRAS* mutation had higher concentrations of *p,p′*-dichlorodiphenyltrichloroethane (DDT), *p,p′*-dichlorodiphenyldichloroethene (DDE) and polychlorinated biphenyls (PCBs) 138, 153 and 180 than cases with wild-type *KRAS*.

The association between coffee intake and *KRAS* mutations remained significant (*P*-trend < 0.015) when most OCs where accounted for. When *p,p′*-DDT, PCB 153, coffee and alcohol intake were included in the same model, all were associated with *KRAS*.

Mutagenesis vol. 24 no. 6 pp. 513–521, 2009

In pancreatic ductal adenocarcinoma blood concentrations of some organochlorine compounds and coffee intake are independently associated with *KRAS* mutations

OCs and coffee may have independent roles in the aetiopathogenesis of PDA through modulation of *KRAS* activation, acquisition or persistence, plausibly through non-genotoxic or epigenetic mechanisms. Given that *KRAS* mutations are the most frequent abnormality of oncogenes in human cancers, and the lifelong accumulation of OCs in humans, refutation or replication of the findings is required before any implications are assessed.

Mutagenesis vol. 24 no. 6 pp. 513–521, 2009

In pancreatic ductal adenocarcinoma blood concentrations of some organochlorine compounds and coffee intake are independently associated with *KRAS* mutations

In recent years, higher concentrations of several common OCs—including DDT, DDE and PCBs—have been associated with an increased prevalence of health disorders as diabetes, obesity and several other components of the metabolic syndrome (36,48,77–80); remarkably, all such disorders are also under scrutiny as risk factors for pancreatic cancer (42,43,81). Similarly, higher concentrations of persistent organic pollutants (POPs), especially OC pesticides, have been found positively associated with periodontal disease (82). Independently, periodontal diseases have also been associated with the risk of pancreatic and other cancers (83). Thus, our findings suggest that POPs might explain observed associations between some disorders (diabetes, obesity, metabolic syndrome and periodontal diseases) and pancreatic cancer risk.

NEWS OF THE WEEK 18 SEPTEMBER 2009 VOL 325 SCIENCE

BIOTECHNOLOGY

Researcher, Two Universities Sued Over Validity of Prostate Cancer Test

A Johns Hopkins University (JHU) researcher whose reports of a potential new blood test for diagnosing prostate cancer generated excitement—but also skepticism—is now being sued by his industry sponsor for scientific fraud. The company, Onconome Inc., says it poured millions of dollars over 5 years into the laboratory of Robert Getzenberg and alleges that he presented the company with misleading data. The lawsuits say that the biomarker test, which Getzenberg claimed could distinguish between cancerous and normal tissue, was "essentially as reliable as flipping a coin." Onconome in Redmond, Washington, is suing Getzenberg, JHU, and the University of Pittsburgh (Pitt), his previous institution, for unspecified damages.

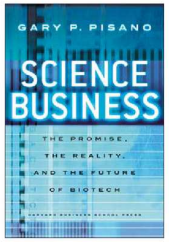
in blood and offered an alternative to the prostate specific antigen test, which has well-known limitations. Onconome was

cancers that he described as "amazing": sensitivities and specificities approaching 100%,

were unable to replicate Getzenberg's

The suit alleges that he exaggerated statistical associations, "cherry-picked the data" to report favorable results, that his technician broke the blind on samples, and that he

Pisano argues that "monetization of IP" has been a powerful shaping force in biotech. The idea behind monetization of IP is that you do not need to actually develop a product; you can just develop a piece of IP, and then capture financial returns through licensing or other market arrangements. This has worked wonderfully in semiconductors and software; but monetization of IP only works there because of some very specific conditions. You need to have a very modular knowledge base; that is, you need to be able to break up a "big puzzle" into its relatively independent pieces so that a particular piece can be valued independently. So, we have been breaking up the pieces of the puzzle into independent pieces when what matters is the way we integrate the pieces. Integration matters a lot.



[1] Excerpts of an interview by Sean Silverthorne, editor of the Harvard Business School newsletter "Working knowledge," to Gary Pisano, author of *Science Business: The Promise, the Reality, and the Future of Biotech* (Harvard Business School Press, 2006). Published 13 November 2006 [12].

Journal of Clinical Epidemiology 60 (2007)

- According to Arthur D. Levinson, Chief Executive Officer of Genentech, "Since 1976, when our company was founded, the biotech industry has lost $90 billion in aggregate. I think it's the biggest money-losing industry of all time. It is hemorrhaging. There are some exceptions: We are doing well, and Amgen is doing well, But for most of the 1,300 to 1,400 companies -300 or 400 of them public- this is a money-losing enterprise."[2]

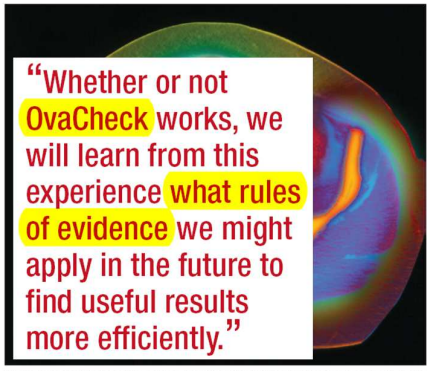
[2] Chase M. How Genentech wins at blockbuster drugs. CEO to critics of prices: "Give me a break". The Wall Street Journal; 5 June 2007: page B1

Journal of Clinical Epidemiology 60 (2007)

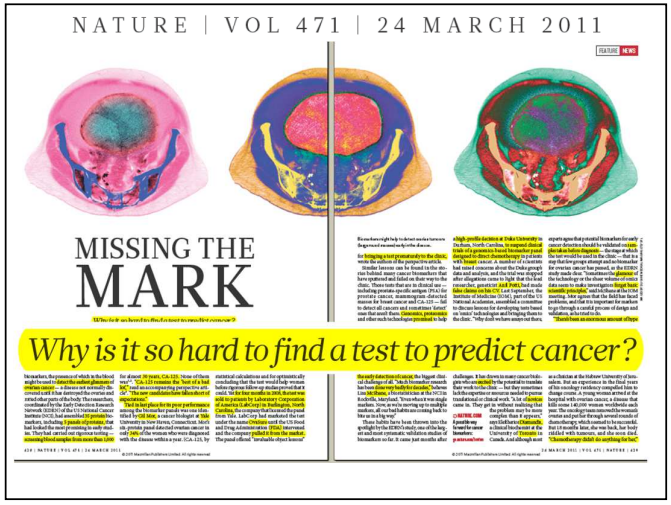
news feature NATURE | VOL 429 | 3 JUNE 2004

Running before we can walk?

Two years ago, a new proteomic test was heralded as the future of cancer diagnostics. But since then, doubts about its effectiveness have begun to grow. Erika Check reports.



On target: can proteins in the blood reveal ovarian tumours (pink/yellow) before they reach this stage?



NATURE | VOL 471 | 24 MARCH 2011

FEATURE NEWS

MISSING THE MARK

Why is it so hard to find a test to predict cancer?

OPEN ACCESS Freely available online PLoS Medicine | www.plosmedicine.org October 2011 PLOS MEDICINE

Guidelines and Guidance

STrengthening the Reporting of OBservational studies in Epidemiology – Molecular Epidemiology (STROBE-ME): An Extension of the STROBE Statement

Valentina Gallo[1,2*], Matthias Egger[3], Valerie McCormack[4], Peter B. Farmer[5], John P. A. Ioannidis[6,7], Micheline Kirsch-Volders[8], Giuseppe Matullo[9,10], David H. Phillips[11], Bernadette Schoket[12], Ulf Stromberg[13], Roel Vermeulen[14], Christopher Wild[4], Miquel Porta[15], Paolo Vineis[9,16]

- Specific additions relate to the collection, handling and storage of biological samples; laboratory methods, validity and reliability of biomarkers; specificities of study design; and ethical considerations.
- A checklist to help authors in reporting biomarker studies is published as supporting information (Table S1).

Clinical Chemistry 55:4
786–794 (2009)

exaggeration

Overinterpretation of Clinical Applicability in Molecular Diagnostic Research

Blanca Lumbreras,[1] Lucy A. Parker,[1*] Miquel Porta,[2] Marina Pollán,[3] John P.A. Ioannidis,[4] and Ildefonso Hernández-Aguado[1]

RESULTS: Of 108 articles included in the study, 104 articles (96%) made definitely favorable or promising statements regarding clinical applicability, and 61 (56%) of the articles apparently overinterpreted the clinical applicability of their findings. Articles published in journals with higher impact factors were more likely to overinterpret their results than those with lower impact factors (adjusted odds ratio, 1.71 per impact factor quartile; 95% CI, 1.09–2.69; $P = 0.020$). Overinterpretation was more common when authors were based in laboratories than in clinical settings (adjusted odds ratio, 18.7; 95% CI, 1.41–249; $P = 0.036$).

3 reasons / 3 suggestions for you to think about (if you wish):

We know quite a lot about
1.→ generalized human contamination
2.→ toxic effects of environmental pollutants

i. Most individuals accumulate complex mixtures of persistent toxic substances throughout the life course, both at high and low concentrations;

ii. Knowledge on **the joint effects of such 'cocktails'** (including alterations of metabolic functions and gene expression) ought to be assessed more often when **building causal scenarios that aim at being relevant for human health**; and

iii. It may be scientifically unfounded to study mechanisms of diseases of complex etiology without considering environmental mixtures and the hypothesis that **key causal processes involve contamination by toxic pollutants and the ensuing accumulation of genetic and epigenetic alterations.**

3.→ If we neglect 1 & 2 less
we will improve understanding of the etiopathogenesis (mechanisms)
control (primary prevention)
of the most prevalent diseases.

www.imim.es

Home > Research programmes > Epidemiology and public health >

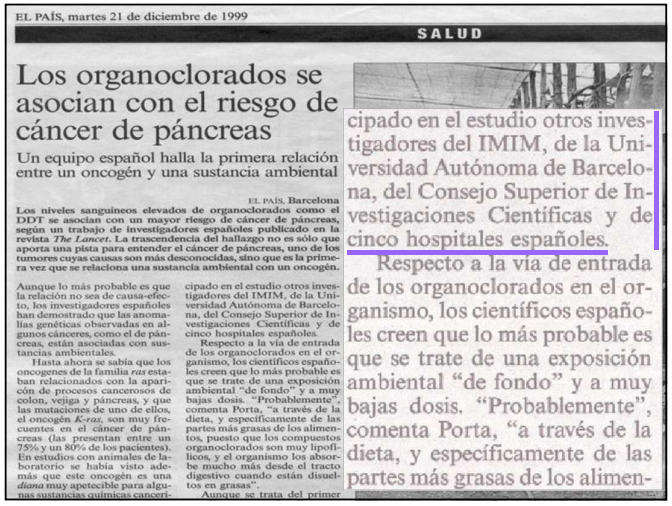
Clinical and Molecular Epidemiology of Cancer

Scientific documents

THANK YOU FOR YOUR ATTENTION

facebook Miquel Porta Video YouTube Miquel Porta (miquelporta) on Twitter

IMIM Institut de Recerca Hospital del Mar · Parc de Salut MAR Barcelona · prbb Parc Recerca Biomèdica Barcelona · ciberesp Centro de Investigación Biomédica en red Epidemiología y Salud Pública · UAB Universitat Autònoma de Barcelona Facultat de Medicina



EL PAÍS, martes 21 de diciembre de 1999

SALUD

Los organoclorados se asocian con el riesgo de cáncer de páncreas

Un equipo español halla la primera relación entre un oncogén y una sustancia ambiental

EL PAÍS, Barcelona

Los niveles sanguíneos elevados de organoclorados como el DDT se asocian con un mayor riesgo de cáncer de páncreas, según un trabajo de investigadores españoles publicado en la revista *The Lancet*. La trascendencia del hallazgo no es sólo que aporta una pista para entender el cáncer de páncreas, uno de los tumores cuyas causas son más desconocidas, sino que es la primera vez que se relaciona una sustancia ambiental con un oncogén.

Aunque lo más probable es que la relación no sea de causa-efecto, los investigadores españoles han demostrado que las anomalías genéticas observadas en algunos cánceres, como el de páncreas, están asociadas con sustancias ambientales.

Hasta ahora se sabía que los oncogenes de la familia *ras* estaban relacionados con la aparición de procesos cancerosos de colon, vejiga y páncreas, y que las mutaciones de uno de ellos, el oncogén *K-ras*, son muy frecuentes en el cáncer de páncreas (las presentan entre un 75% y un 80% de los pacientes). En estudios con animales de laboratorio se había visto además que este oncogén es una *diana* muy apetecible para algunas sustancias químicas cancerígenas.

cipado en el estudio otros investigadores del IMIM, de la Universidad Autónoma de Barcelona, del Consejo Superior de Investigaciones Científicas y de cinco hospitales españoles.

Respecto a la vía de entrada de los organoclorados en el organismo, los científicos españoles creen que lo más probable es que se trate de una exposición ambiental "de fondo" y a muy bajas dosis. "Probablemente", comenta Porta, "a través de la dieta, y específicamente de las partes más grasas de los alimentos, puesto que los compuestos organoclorados son muy lipofílicos, y el organismo los absorbe mucho más desde el tracto digestivo cuando están disueltos en grasas".

Aunque se trata del primer

EL PAÍS, martes 21 de diciembre de 1999

SALUD

Los organoclorados se asocian con el riesgo de cáncer de páncreas

Un equipo español halla la primera relación entre un oncogén y una sustancia ambiental

EL PAÍS, Barcelona

Los niveles sanguíneos elevados de organoclorados como el DDT se asocian con un mayor riesgo de cáncer de páncreas, según un trabajo de investigadores españoles publicado en la revista *The Lancet*. La trascendencia del hallazgo no es sólo que aporta una pista para entender el cáncer de páncreas, uno de los tumores cuyas causas son más desconocidas, sino que es la primera vez que se relaciona una sustancia ambiental con un oncogén.

Aunque lo más probable es que la relación no sea de causa-efecto, los investigadores españoles han demostrado que las anomalías genéticas observadas en algunos cánceres, como el de páncreas, están asociadas con sustancias ambientales.

Hasta ahora se sabía que los oncogenes de la familia *ras* estaban relacionados con la aparición de procesos cancerosos de colon, vejiga y páncreas, y que las mutaciones de uno de ellos, el oncogén *K-ras*, son muy frecuentes en el cáncer de páncreas (las presentan entre un 75% y un 80% de los pacientes). En estudios con animales de laboratorio se había visto además que este oncogén es una *diana* muy apetecible para algunas sustancias químicas cancerígenas.

cipado en el estudio otros investigadores del IMIM, de la Universidad Autónoma de Barcelona, del Consejo Superior de Investigaciones Científicas y de cinco hospitales españoles.

Respecto a la vía de entrada de los organoclorados en el organismo, los científicos españoles creen que lo más probable es que se trate de una exposición ambiental "de fondo" y a muy bajas dosis. "Probablemente", comenta Porta, "a través de la dieta, y específicamente de las partes más grasas de los alimentos, puesto que los compuestos organoclorados son muy lipofílicos, y el organismo los absorbe mucho más desde el tracto digestivo cuando están disueltos en grasas".

Aunque se trata del primer

Miquel Porta (IMIM Hospital del Mar PRBB UAB)
prbb Group Leader Seminar · 13-06-2012

CIENCIA

La Vanguardia 18.12.1999: 36.

Médicos españoles descubren la relación entre tóxicos de los alimentos y cáncer de páncreas

JOSEP CORBELLA

BARCELONA. – Las sustancias organocloradas que se acumulan en la grasa de los alimentos aumentan el riesgo de una mutación genética frecuente en el cáncer de páncreas y de colon. Es el resultado de una investigación realizada por científicos españoles a lo largo de diez años cuyos resultados se presentan hoy en la revista médica "The Lancet".

Los investigadores han observado que, cuanto mayor es el nivel de organoclorados en la sangre de una persona, mayor es el riesgo de sufrir una mutación en el gen K-ras.

El K-ras es uno de los oncogenes (o genes de cáncer) más importantes. "Está mutado en más del 75% de las cánceres de páncreas y en aproximadamente la mitad de los de colon", informa Miquel Porta, miembro del Institut Municipal d'Investigació Mèdica (IMIM) de Barcelona y director del estudio.

Los investigadores han estudiado varios tipos de organoclorados: el DDT, utilizado como pesticida en España hasta los años 80; el DDE, un residuo del DDT que tiene una vida media superior a diez años (es decir, que por cada 2 microgramos de DDE que una persona tenga en 1999, en el año 2009 le quedará todavía 1); y los PCB, sustancias ubicuas que se utilizan, por ejemplo, en electrodomésticos, pinturas y plásticos.

"Cualquier persona nacida después de 1940 ha estado expuesta a estas sustancias durante la mayor parte de su vida", señala Porta. Dos recientes estudios de la Universidad de Zaragoza han revelado que más del 70% de las muestras de carne analizadas contienen residuos de DDT y que la mitad de las muestras de pescado contienen los PCB asociados con la mutación del gen K-ras.

FATRICIO SIMÓN

Miquel Porta

La ignorancia consiste en no saber. Es posible no saber porque se carece de información pero también es posible no saber teniendo información pero ignorando cuál es su significado, su relevancia o su pertinencia, qué hacer con ella...

La información es un insumo del conocimiento, no su definición.

datos ≠ datos sesgados ≠ datos con validez ≠ datos válidos y relevantes **≠ información ≠ conocimiento ≠ acciones clínicas y políticas públicas** relevantes, útiles…

La idea de que todas las tecnologías son neutrales es un error.

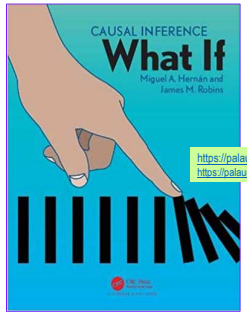
Algunas de las nuevas tecnologías y sus usos cambian nuestros intereses: SOBRE QUÉ pensamos y actuamos.

Alteran nuestros símbolos y herramientas: CÓMO y CON QUÉ pensamos.

Y alteran el ESPACIO personal, profesional y social EN EL QUE pensamos, conversamos, priorizamos, decidimos, promovemos valores, normas y conductas...

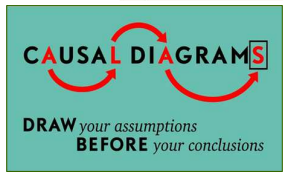
https://www.intramed.net/contenidover.asp?contenidoid=106526
https://www.intramed.net/contenidover.asp?contenidoid=105473
https://www.intramed.net/contenidover.asp?contenidoid=106739

Dr. Daniel Flichtentrei IntraMed



https://palaumacaya.fundacionlacaixa.org/es/p/-funciona-lo-que-hacemos-en-salud-
https://palaumacaya.fundacionlacaixa.org/es/p/los-datos-de-130-millones-de-brasilenos-mejoran-la-salud

a great course: **90,032** learners enrolled

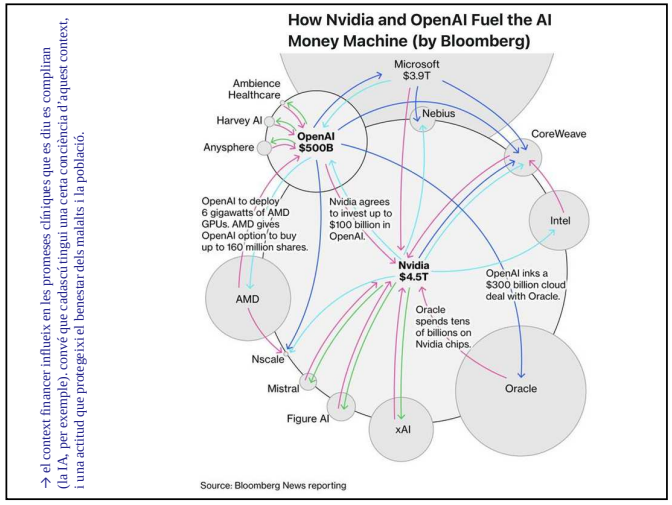


https://hsph.harvard.edu/research/causalab/

https://miguelhernan.org/

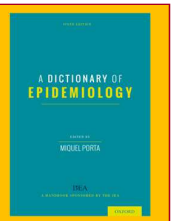
https://miguelhernan.org/whatifbook

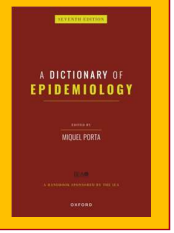
https://www.imim.cat/media/upload//arxius/porta/2025-10-06%20jda%20episap%20new%20methods%205.pdf
https://www.youtube.com/watch?v=x9ROEARdxMo



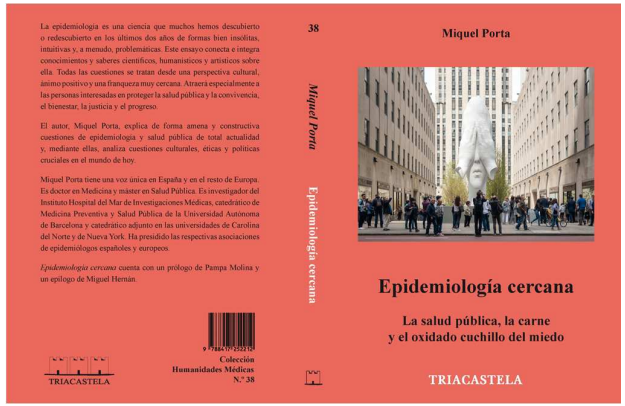
→ el context financer influeix en les promeses clíniques que es diu es compliran (la IA, per exemple), convé que cadascú tingui una certa consciència d'aquest context, i una actitud que protegeixi el benestar dels malalts i la població.

SCREENING.
EARLY CLINICAL DETECTION.
NATURAL HISTORY OF DISEASE.
INCUBATION PERIOD.
INDUCTION PERIOD.
LATENCY PERIOD.
PREVENTION.
RISK FACTOR.
STRATEGY, "HIGH-RISK."
STRATEGY, "POPULATION."
PREVENTION PARADOX.
SIGNIFICANCE, CLINICAL.
SIGNIFICANCE, PUBLIC HEALTH
DETERMINANT, DISTAL (DISTANT).
DETERMINANT, PROXIMAL (PROXIMATE).
CASE FINDING.





prova'l→ http://www.oxfordreference.com/view/10.1093/acref/9780199976720.001.0001/acref-9780199976720



https://www.lacentral.com/porta-miquel/epidemiologia-cercana/9788417252212
https://www.laie.es/es/libro/epidemiologia-cercana/2023352/9788417252212
https://www.amazon.es/Epidemiología-cercana-pública-oxidado-cuchillo/dp/8417252215/

https://www.imim.cat/media/upload//arxius/porta/2025-10-06%20jda%20episap%20new%20methods%205.pdf
https://www.youtube.com/watch?v=x9ROEARdxMo ←recording of this talk on YouTube
https://www.imim.cat/programesrecerca/epidemiologia/es_documentsgrecm.html
https://linktr.ee/mporta

https://palaumacaya.fundacionlacaixa.org/es/p/-funciona-lo-que-hacemos-en-salud-

https://www.lacentral.com/porta-miquel/epidemiologia-cercana/9788417252212
https://www.laie.es/es/libro/epidemiologia-cercana/2023352/9788417252212
https://www.amazon.es/Epidemiología-cercana-pública-oxidado-cuchillo/dp/8417252215/