

**RISCHI PER LA SALUTE
NELLA CATENA ALIMENTARE E DA INQUINANTI
AMBIENTALI (RE 27-9-2014)**

**INTERFERENTI ENDOCRINI E PATOLOGIE
PEDIATRICHE**

S.BERNASCONI

CLINICA PEDIATRICA

UNIVERSITA' DI PARMA



Endocrine News April 2014

Fast FACTS About EDCs

A 2000 report documented 2,300 pesticide exposures in American schools from 1993 to 1996.



In 2004, levels of polybrominated diphenyl ethers (PBDEs) were about 40 times higher in North American women than in Swedish women, based on samples of breast milk.

96%
+ bisphenol-A (BPA)

A 2011 study showed that 96% of the pregnant women surveyed tested positive for bisphenol-A (BPA).

1,000

As of October 2013, there are nearly 1,000 endocrine-disrupting chemicals on The Endocrine Disruption Exchange's (TEDX) list.

Most of the 2,000 chemicals that come on the market each year don't go through even simple tests to determine toxicity.

-3 to -5 points

Lead can lessen a child's I.Q. by 3 to 5 points.

A 2008 study showed that 19 out of 20 children tested had PBDE levels an average of 3.2 times higher than their mothers.

PBDE Levels

Sources: The Endocrine Disruption Exchange, Natural Resources Defense Council, *Environmental Health Perspectives* – University of California San Francisco, *Environmental Science & Technology* – Indiana University, Environmental Working Group, General Accounting Office; California State University, *The New York Times* – Mount Sinai Medical Center



Aspetti fondamentali

- 1) Definizione
- 2) Controversie sull'impatto sulla salute
- 3) Patologie più studiate
- 4) Alcune considerazioni pratiche



Aspetti fondamentali

- 1) Definizione



DEFINIZIONE

Sostanza o materiale esogeno che possa alterare una o più funzioni del sistema endocrino e conseguentemente causare effetti avversi sulla salute di un organismo sano e della sua progenie

European Commission

Qualsiasi sostanza esogena in grado di interferire con la sintesi, la secrezione, il trasporto, il metabolismo, il legame recettoriale o l'escrezione di una sostanza endogena con azione ormonale normalmente in grado di garantire l'omeostasi, il normale sviluppo e la funzione riproduttiva di un individuo

U. S. Environmental Protection Agency



Dove si trovano gli ftalati?



Aspetti fondamentali

- 1) Definizione
- **2) Controversie sull'impatto sulla salute**
- 3) Patologie più studiate
- 4) Alcune considerazioni pratiche



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

Scientifically unfounded precaution drives European Commission's recommendations on EDC regulation, while defying common sense, well-established science and risk assessment principles

Daniel R. Dietrich, Editor-in-Chief, Chemico Biological Interactions

Sonja von Aulock, Editor-in-Chief, ALTEX

Hans Marquardt, Editor-in-Chief, Toxicology

Bas Blaauboer, Editor-Europe, Toxicology in Vitro

Wolfgang Dekant, Editor-in-Chief, Toxicology Letters

James Kehrer, Editor-in-Chief, Toxicology Letters

Jan Hengstler, Editor-in-Chief, Archives of Toxicology

Abby Collier, Section Editor, Chemico Biological Interactions

Gio Batta Gori, Editor-in-Chief, Regulatory Pharmacology and Toxicology

Olavi Pelkonen, Editor-in-Chief, Frontiers in Predictive Toxicology

Florian Lang, Editor-in-Chief, Toxins

Frank A. Barile, Editor-in-Chief, Toxicology in Vitro

Frans P. Nijkamp, Editor-in-Chief, European Journal of Pharmacology

Kerstin Stemmer, Assoc. Editor, Toxicology in Vitro

Albert Li, Section Editor, Chemico Biological Interactions

Kai Savolainen, Editor for Europe and rest of the World, Human and Experimental Toxicology

A. Wallace Hayes, Editor for the Americas, Human and Experimental Toxicology and Editor-in-Chief, Food and Chemical Toxicology

Nigel Gooderham, Editor-in-Chief, Toxicology Research

Alan Harvey, Editor-in-Chief, Toxicon

Chemico-Biological Interactions 205 (2013) A1-A5



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

Endocrine disruption: Fact or urban legend?

Gerhard J. Nohynek^{a,*}, Christopher J. Borgert^b, Daniel Dietrich^c, Karl K. Rozman^d

Toxicology Letters 223 (2013) 295–305

SUBSTANCE	POTENCY / POWER	EXAMPLE
Ethinyl estradiol (oral contraceptive)	1.000.000	
Coumestrol (clover)	10.000	
Genistein (soy beans)	37	
Butylparaben (preservative)	0.5	
Benzylparaben (preservative)	0.1	

Fig. 1. Assuming that one oestrogen potency unit (see Table 1) corresponds to one horse power, the power/potency of some of the substances in Table 1 may be ranked as follows.



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

Bergman et al. *Environmental Health* 2013, **12**:69
<http://www.ehjournal.net/content/12/1/69>



ENVIRONMENTAL HEALTH

COMMENTARY

Open Access

Science and policy on endocrine disrupters must not be mixed: a reply to a “common sense” intervention by toxicology journal editors

Åke Bergman^{1*}, Anna-Maria Andersson², Georg Becher³, Martin van den Berg⁴, Bruce Blumberg⁵, Poul Bjerregaard⁶, Carl-Gustaf Bornehag⁷, Riana Bornman⁸, Ingvar Brandt⁹, Jayne V Brian¹⁰, Stephanie C Casey⁵, Paul A Fowler¹¹, Heloise Frouin¹², Linda C Giudice¹³, Taisen Iguchi¹⁴, Ulla Hass¹⁵, Susan Jobling¹⁰, Anders Juul², Karen A Kidd¹⁶, Andreas Kortenkamp¹⁰, Monica Lind⁹, Olwenn V Martin¹⁰, Derek Muir¹⁷, Roseline Ochieng¹⁸, Nicolas Olea¹⁹, Leif Norrgren²⁰, Erik Ropstad²¹, Peter S Ross¹², Christina Rudén²², Martin Scheringer²³, Niels Erik Skakkebaek², Olle Söder²⁴, Carlos Sonnenschein²⁵, Ana Soto²⁵, Shanna Swan²⁶, Jorma Toppari²⁷, Charles R Tyler²⁸, Laura N Vandenberg²⁹, Anne Marie Vinggaard¹⁵, Karin Wiberg²⁰ and R Thomas Zoeller³⁰

“Common sense is the collection of prejudices acquired by age eighteen”

- Albert Einstein



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

Early homeostatic disturbances of human growth and maturation by endocrine disruptors

Jean-Pierre Bourguignon and Anne-Simone Parent

Current Opinion in Pediatrics 2010, 22:470–477

Table 3 Relevant issues accounting for limits in identification of endocrine disrupting compound (EDC) involvement in health disorders

Issues	Implication
Low-dose mixtures	Ineffective low doses of single EDCs become effective when associated with other EDCs. Mixture effects (more likely reflecting human exposure in the real world than single EDCs) are not simply additive, but studies are complex
Latency	At the time of adult expression of disorders determined by fetal or postnatal exposure to EDCs, the demonstration of exposure is no longer possible
Agonist/antagonist of one or several hormones	A single EDC can be agonist at some subtypes of receptors to a steroid and antagonist at others. It can interact with several hormonal systems that can each play different roles depending on sex and stage of development
Nonconventional dose–response relationship	Some EDCs exhibit U-shaped or inverted-U curves of dose–response, meaning that low doses are more effective than higher doses, with resulting importance of assessment of the level of exposure
Several mechanisms of action possibly coexisting	Classical endocrine receptors as well as nonclassical endocrine or nonendocrine receptors can be involved in addition to alterations in the rates of degradation of endogenous hormones and EDCs



STATEMENTS

Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society

R. Thomas Zoeller, T. R. Brown, L. L. Doan, A. C. Gore, N. E. Skakkebaek, A. M. Soto, T. J. Woodruff, and F. S. Vom Saal

Endocrinology, September 2012,

TABLE 2. Endocrine Principles Applied to EDC Research

Recommendations for the future



ENDOCRINE-DISRUPTING CHEMICALS
JUNE 2009

- Policy should be developed and revised under the direction of a collaborative group comprising endocrinologists, toxicologists, epidemiologists, and policymakers. The same group should identify knowledge gaps and recommend research directions to fill those gaps.
- **Until such time as conclusive scientific evidence exists to either prove or disprove harmful effects of substances, a precautionary approach should be taken in the formulation of EDC policy.**
- The federal government should develop a public awareness campaign to inform the public of the risks and potential risks related to the presence of EDCs in the environment and in the food supply.





State of the Science of
**Endocrine
Disrupting
Chemicals - 2012**

Edited by
Ake Bergman, Jerrold J. Heindel, Susan Jobling,
Karen A. Kidd and R. Thomas Zoeller

IOHC
INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among PAO, ILO, UNEP, UNEP, UNIDO, UNISTAR, WHO, World Bank and OECD



**World Health
Organization**



UNEP
United Nations
Environment Programme

Periodi critici per l'esposizione

- 
- Periodo fetale
 - Periodo neonatale
 - Infanzia
 - Pubertà



L'esposizione agli EDCs di un soggetto in una fase attiva e vivace dello sviluppo determina una peculiare modulazione dell'espressione genica con la possibilità di sviluppo di una condizione patologica anche dopo anni dall'esposizione.

*The developmental basis of adult disease
Barker, European Journal of epidemiology, 2003*



Aspetti fondamentali

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EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

Reproduction	Review
2.1.1. Fertility.....	Bisphenol A and human health: A review of the literature
2.1.2. Male sexual function	Johanna R. Rochester*
2.1.3. Reduced sperm quality	Reproductive Toxicology 42 (2013) 132–155
2.1.4. Sex hormone concentrations.....	
2.1.5. Polycystic ovary syndrome	
2.1.6. Endometrial disorders	
2.1.7. Breast cancer.....	
2.1.8. Miscarriage	
2.1.9. Premature deliveries	
Development	
2.2.1. Birth weight.....	
2.2.2. Male genital abnormalities	
2.2.3. Childhood behavior/neurodevelopment	
2.2.4. Childhood asthma/wheeze	
Metabolic disease.....	
2.3.1. Type-2 diabetes	
2.3.2. Cardiovascular disease, hypertension, and cholesterol levels	
2.3.3. Liver function	
2.3.4. Obesity	
Other health effects	
2.4.1. Thyroid function.....	
2.4.2. Immune function	
2.4.3. Albuminuria	
2.4.4. Oxidative stress and inflammation.....	
2.4.5. Epigenetics, gene expression, and sister chromatid exchange	

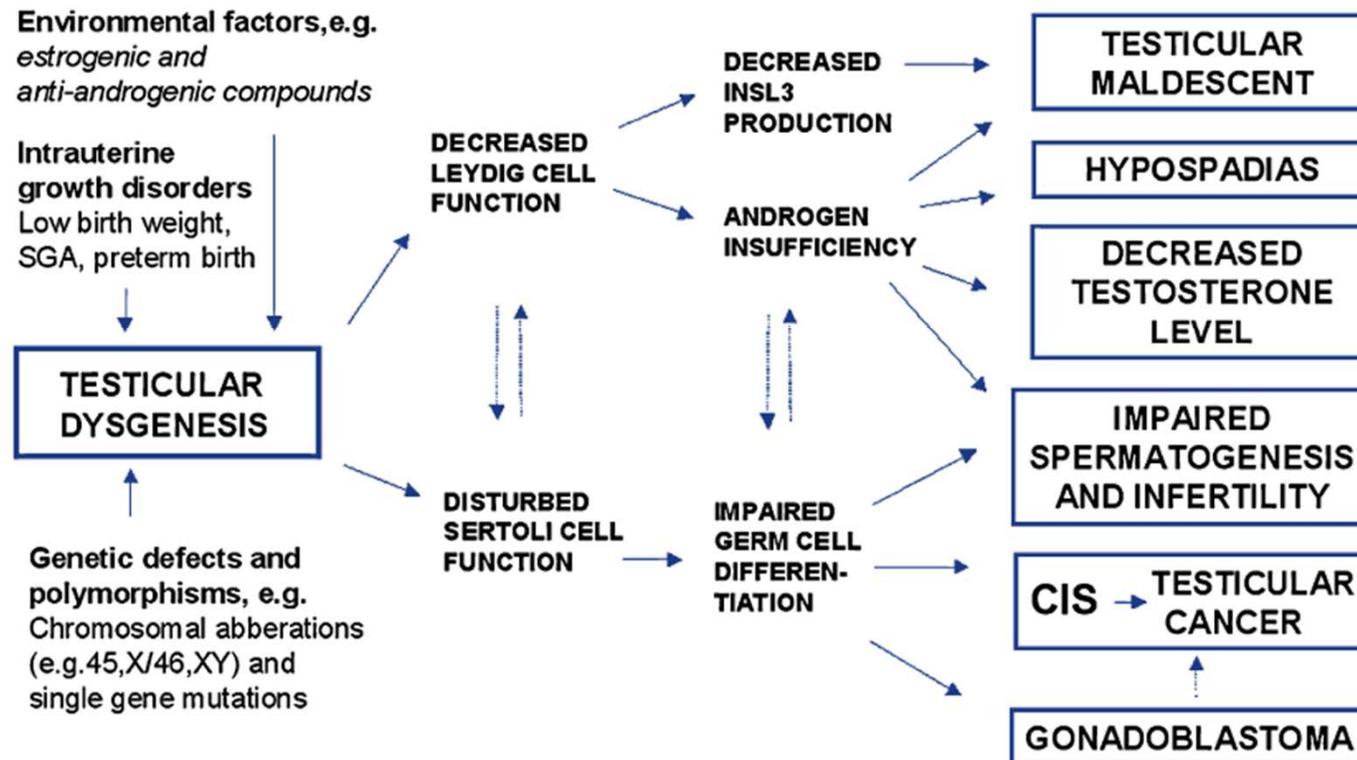


EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

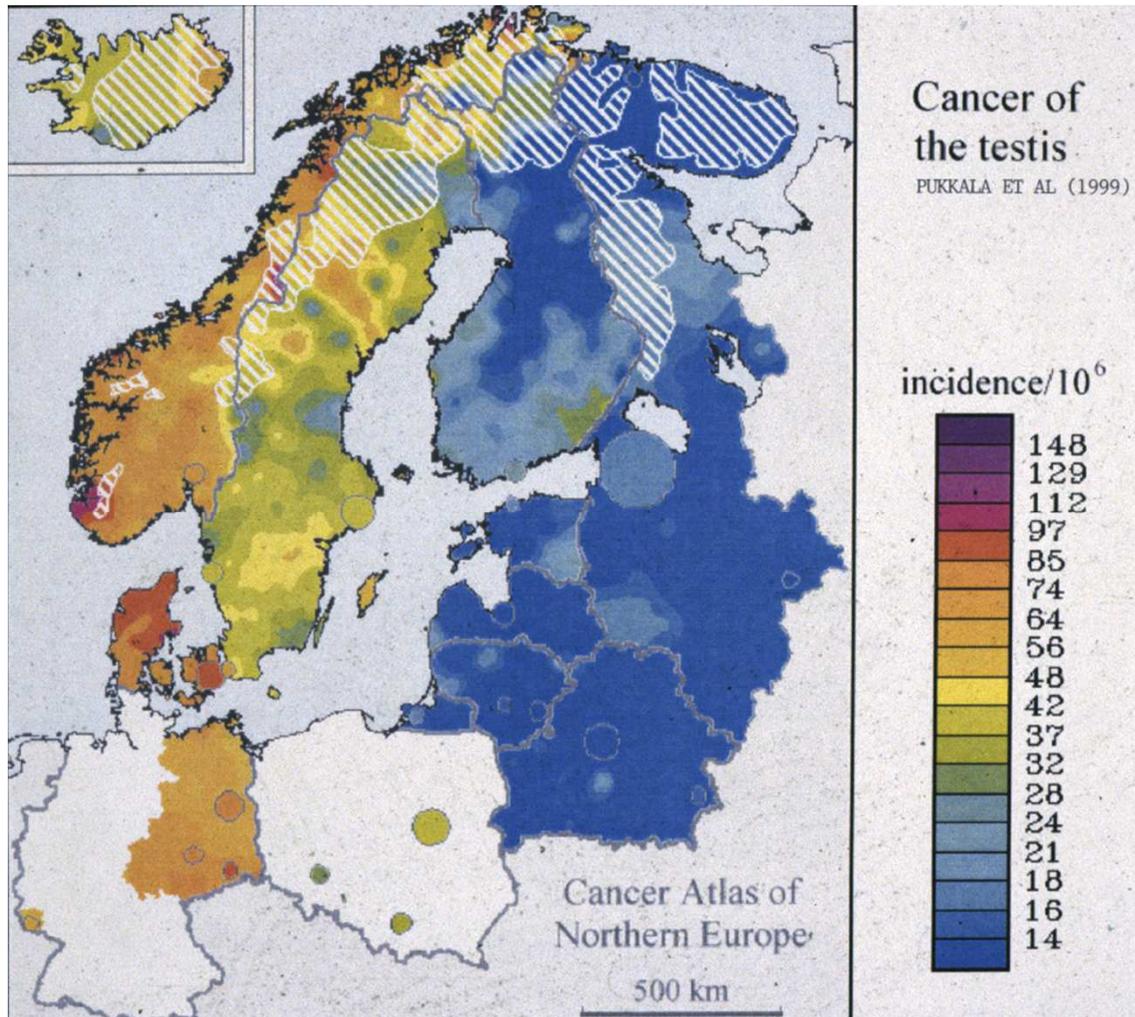
Environment, testicular dysgenesis and carcinoma in situ testis

Best Practice & Research Clinical Endocrinology & Metabolism
Vol. 21, No. 3, pp. 462–478, 2007

Testicular Dysgenesis Syndrome



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

Evidence for Epigenetic Abnormalities of the Androgen Receptor Gene in Foreskin from Children with Hypospadias

J Clin Endocrinol Metab, December 2011, 96(12):E1953–E1962

A. Vottero, R. Minari, I. Viani, F. Tassi, F. Bonatti, T. M. Neri, L. Bertolini, S. Bernasconi, and L. Ghizzoni

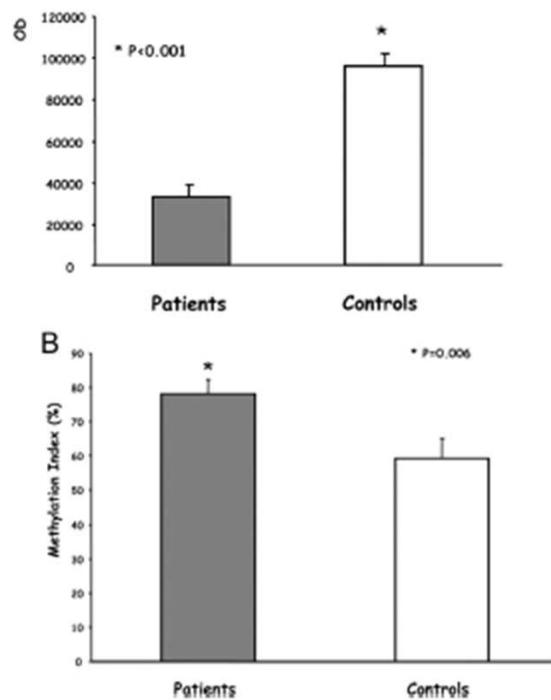


FIG. 2. A, AR gene expression (molecular mass 110 kDa) analyzed by Western blotting in foreskin tissue from patients with hypospadias and normal children (mean \pm se, $P < 0.001$). B, AR gene methylation in foreskin tissue from patients with hypospadias and normal children (methylation index, mean \pm se, $P < 0.006$).

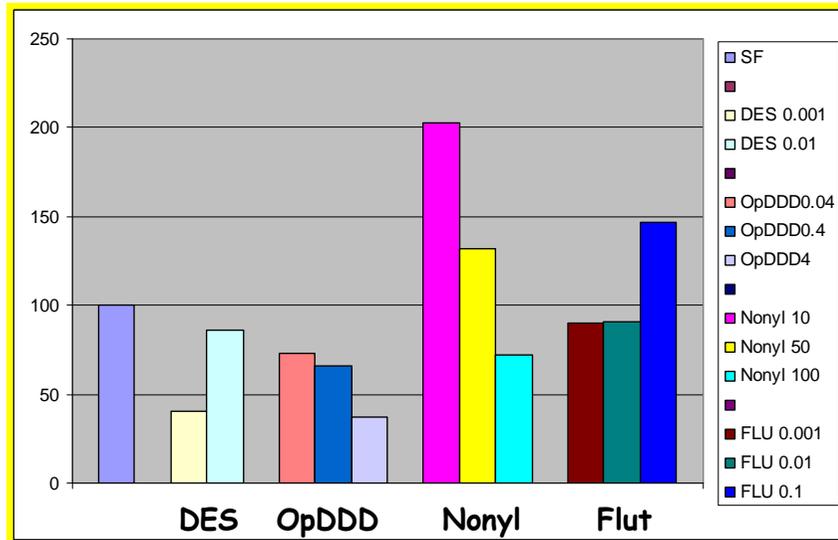
AR gene in foreskin tissue of hypospadiac patients is more methylated, and thus less active, than in normal children of the same age

Hypospadiac patients present a reduced expression of AR in comparison to controls

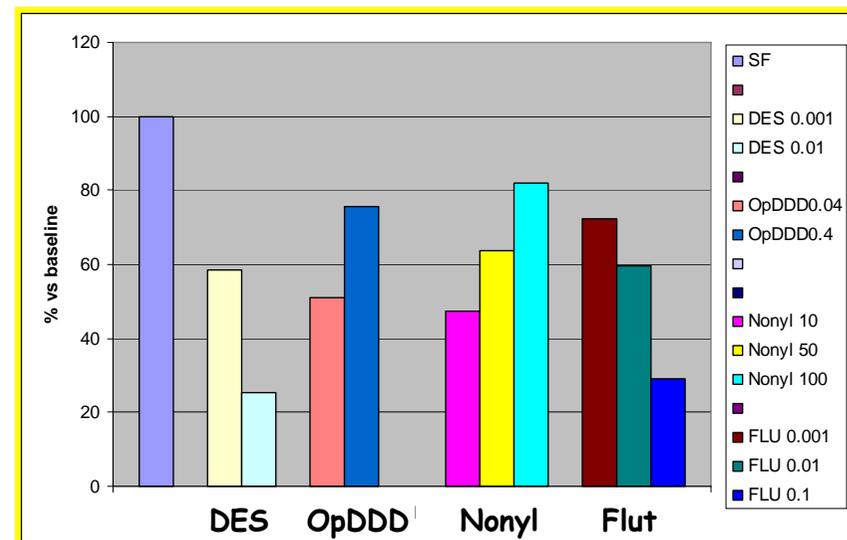


EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

Androgen receptor gene methylation



Androgen receptor gene expression



DES: Diethylstilbesterol
 OpDDD: o,p'-Diclorodiphenyldichloroethane
 Nonyl: Nonylphenol
 Flut: Flutamide

DES and Flutamide: AR gene methylation

AR gene expression



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™



Pediatrics 2008

Environmental Factors and Puberty Timing: Expert Panel Research Needs

Germaine M. Buck Louis, PhD^a, L. Earl Gray, Jr, PhD^b, Michele Marcus, PhD, MPH^c, Sergio R. Ojeda, DVM^d, Ora H. Pescovitz, MD^e, Selma Feldman Witchel, MD^f, Wolfgang Sippell, MD, PhD^g, David H. Abbott, PhD^h, Ana Soto, MDⁱ, Rochelle W. Tyl, PhD^j, Jean-Pierre Bourguignon, MD, PhD^k, Niels E. Skakkebaek, MD, DMSc^l, Shanna H. Swan, PhD^m, Mari S. Golub, PhDⁿ, Martin Wabitsch, MD, PhD^o, Jorma Toppari, MD, PhD^p, Susan Y. Euling, PhD^q

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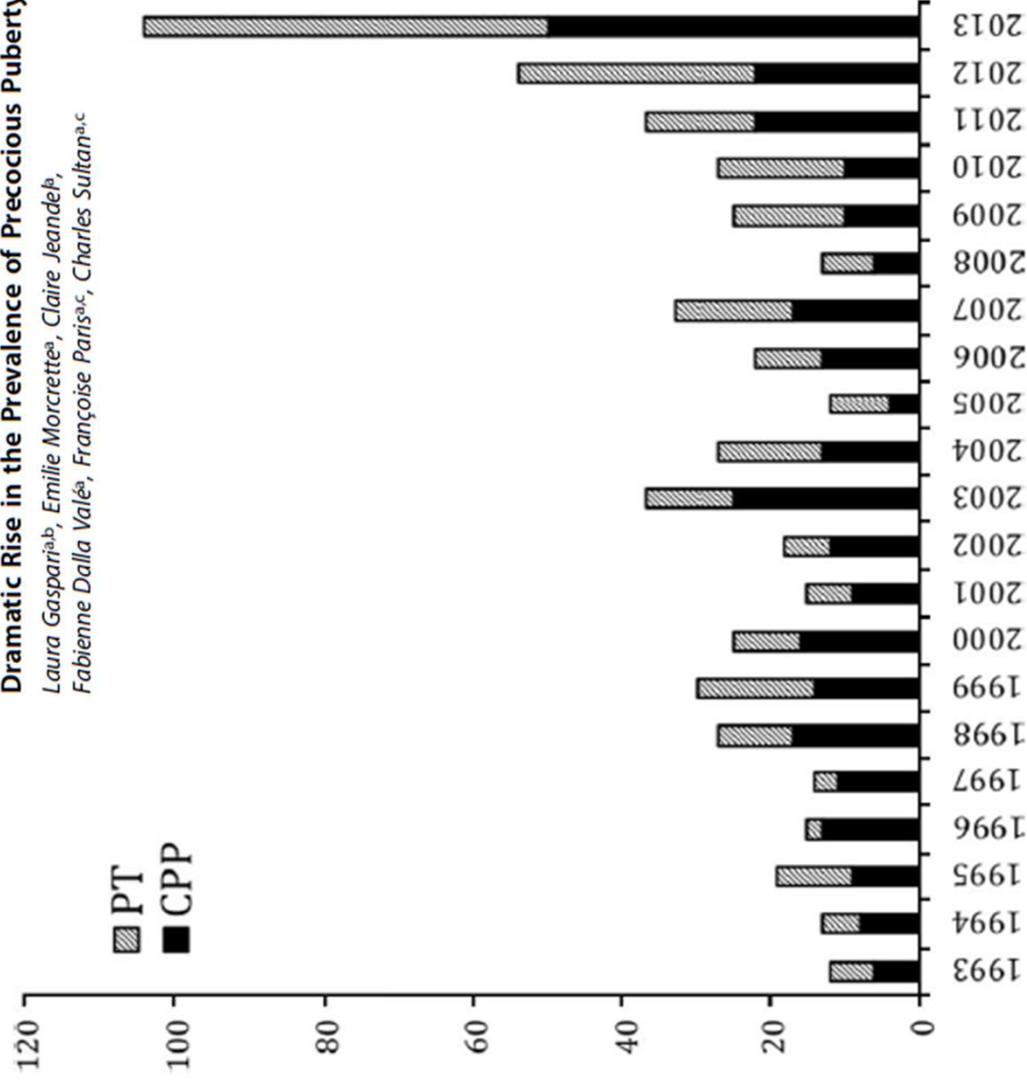


European Society for Paediatric Endocrinology (ESPE)

Dublin, Ireland, September 18–20, 2014

Dramatic Rise in the Prevalence of Precocious Puberty in Girls Over the Past 20 Years in the South of France

Laura Gaspari^{a,b}, Emilie Morcrette^a, Claire Jeandel^b,
Fabienne Dalla Valé^a, Françoise Paris^{a,c}, Charles Sultan^{a,c}



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

Recent data on pubertal milestones in United States children: the secular trend toward earlier development

Marcia E. Herman-Giddens

Department of Maternal and Child Health, University of North Carolina School of Public Health, Chapel Hill, NC, USA

international journal of andrology 29 (2006) 241–246.

Table 7 Earlier puberty: theories and speculations

- Genetic differences among racial/ethnic groups
 - Overweight and obesity, decreased physical activity
 - Pre- and postnatal exposure to endocrine disrupter chemicals ←
 - Infant soy-based formulas
 - Girls born small for gestational age
 - Stress, absent fathers, unrelated males in the household
 - Effects of different types of diet
 - Exogenous hormones
 - Hypersexualization of culture
-



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

Identification of Phthalate Esters in the Serum of Young Puerto Rican Girls with Premature Breast Development

Ivelisse Colón,¹ Doris Caro,¹ Carlos J. Bourdony,^{2,3} and Osvaldo Rosario¹

Environ Health Perspect 2000



Figure 1. Twenty-three-month-old Puerto Rican girl with premature breast development (thelarche).

Phthalate esters were consistently detected at significant concentration levels (ranging from tens of parts per billion to units of parts per million) in 28 of 41 (68%) serum samples obtained from the thelarche patients.



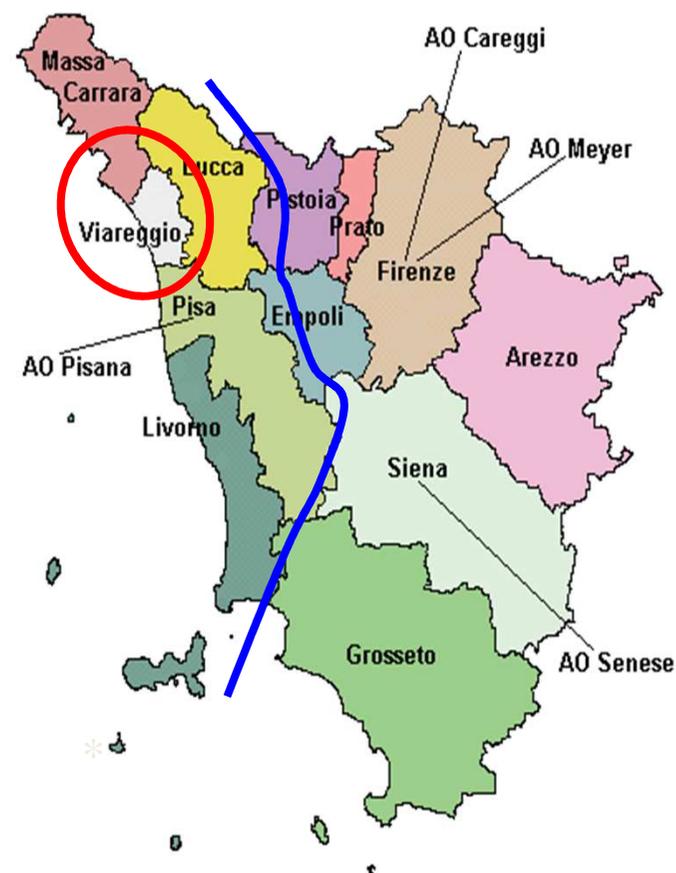
EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

a bounded area of northwest Tuscany

CPP prevalence in the five major health service areas (Livorno, Lucca, Massa, Pisa and Viareggio cities) of northwest Tuscany

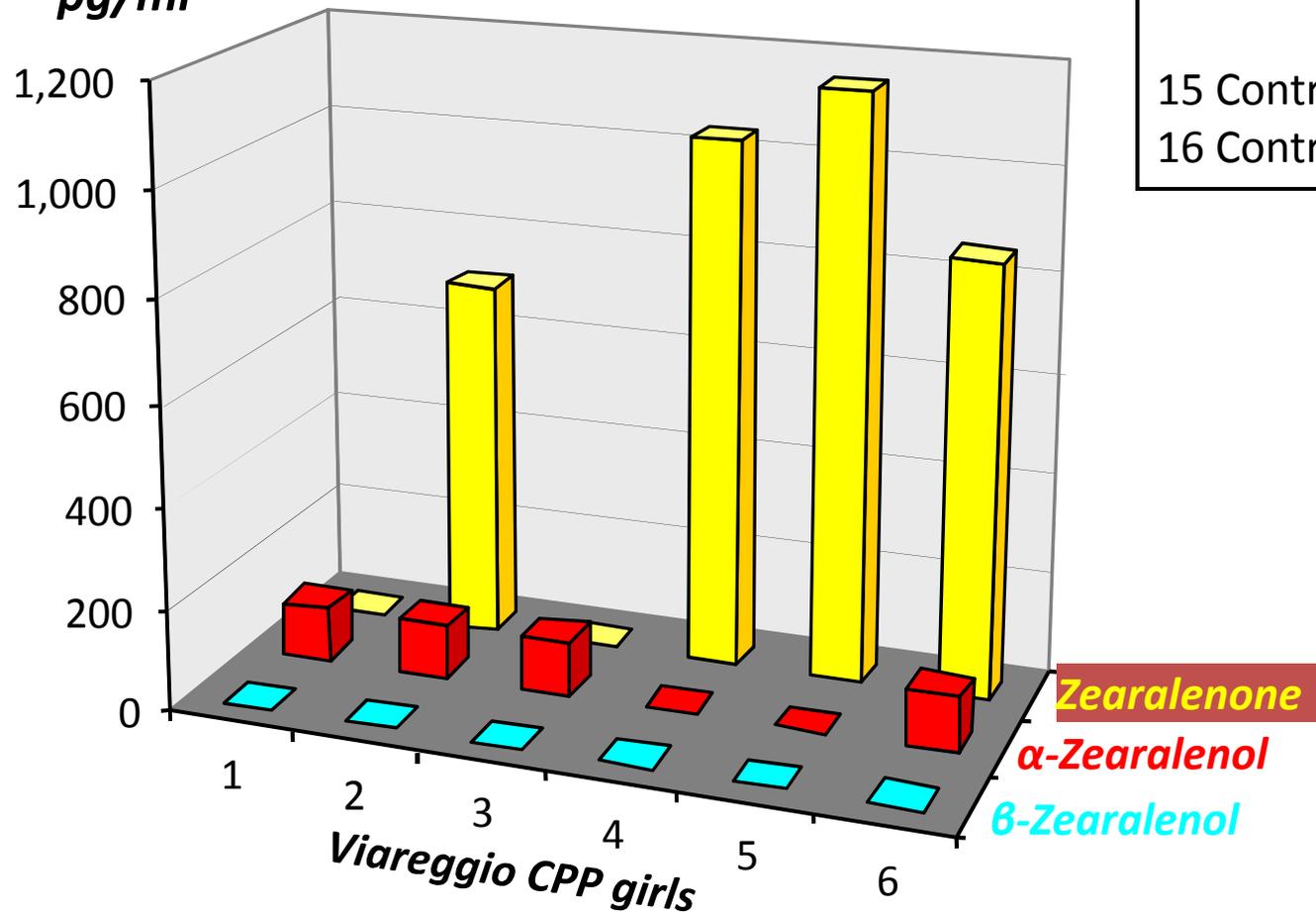
City area	Total number of 0-14 yr-old children	CPP cases	♀/♂ ratio	CPPs per 10000 children
Livorno	37332	7	12:1	18.7
Lucca	24630	5	10:1	20.3
Pisa	36420	9	7:2	24.7
Massa	22370	13	12:1	58.1*
Viareggio	19219	31	26:5	161.3*

*significant difference, $P < 0.05$



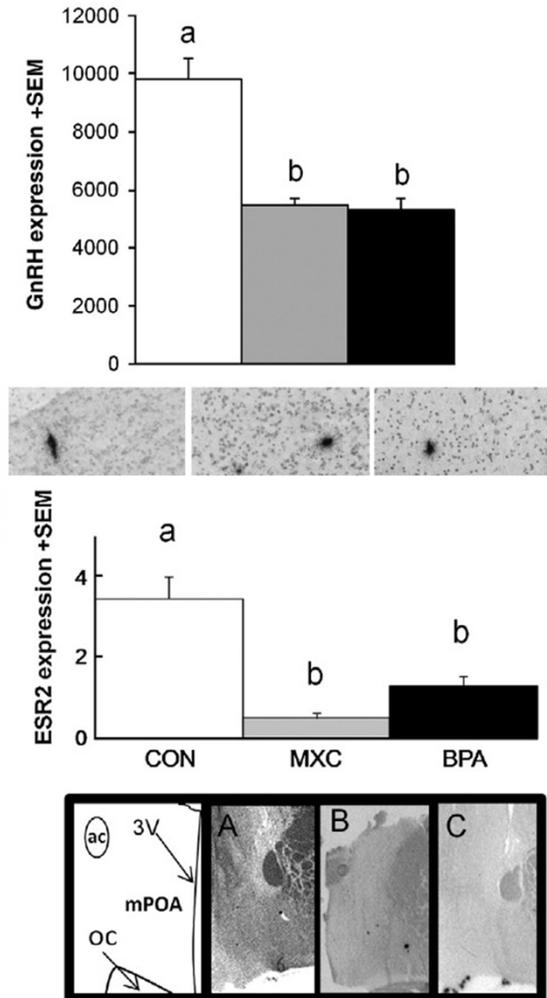
EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

Serum levels at CPP diagnosis
pg/ml



17 CPP from Viareggio area
15 CPP not from Viareggio
vs.
15 Controls from Viareggio
16 Controls not from Viareggio

EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?



Mahoney et al:

Esposizione di pecore gravide a BPA e MXC e studio della funzione dell'asse ipotalamo ipofisi gonadi nella prole in epoca puberale:



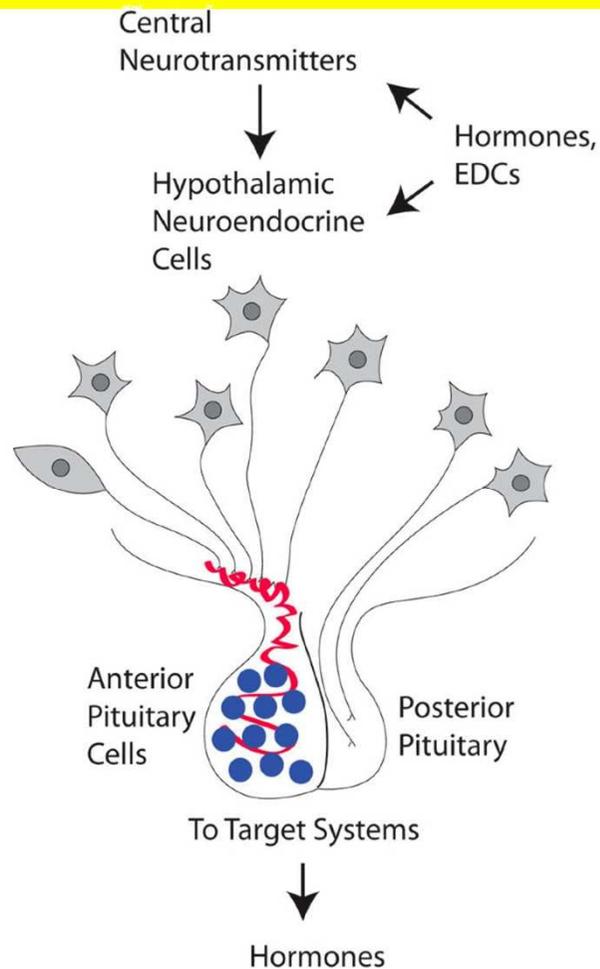
Riduzione dell'espressione del GnRH mRNA e del ER2 mRNA con conseguente

- 1. Riduzione dell'ampiezza del picco pre-ovulatorio dell'LH**
- 2. Alterazione del timing del picco pre-ovulatorio dell'LH**

Mahoney et al, Toxicol Appl Pharmacol 2010



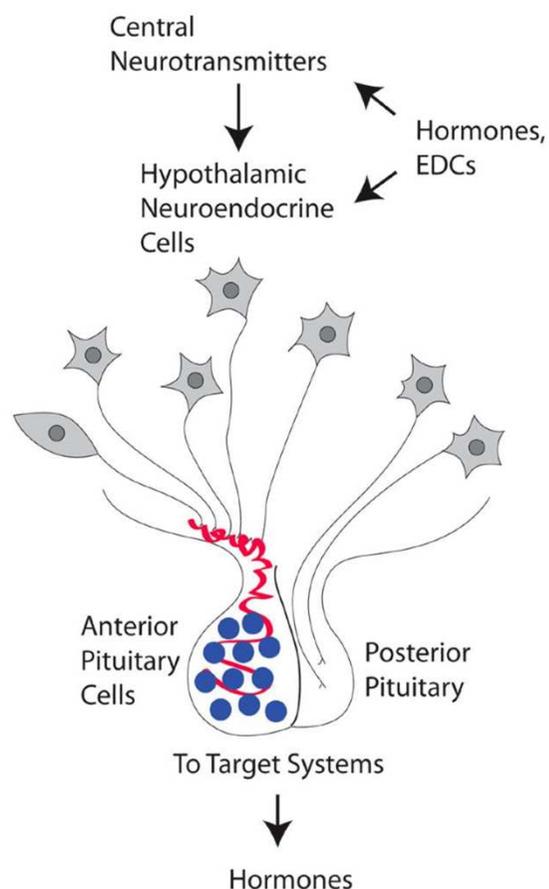
EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?



- ✓ Gene kiss I codifica per i peptidi kisspeptine, recentemente identificati come fattori chiave nell'attività del GnRH pulse ipotalamico
 - ✓ Studi nel topo hanno dimostrato come l'esposizione precoce a xenoestrogeni come il BPA determina una riduzione dei livelli di Kiss I mRNA e della densità delle fibre kisspetinergiche dell'ipotalamo
- ↓
- ✓ Alterazione della funzione del GnRH pulse ipotalamico e del conseguente sviluppo puberale



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?



Il pattern di espressione genere-specifico di aromatasi e 5 α -reduttasi, responsabile del corretto rapporto di estradiolo e testosterone, è essenziale per lo sviluppo differenziale del SNC di maschi e femmine

Colciago et al.

Esposizione a una miscela di PCBs di femmine gravide di ratto; scopi dello studio:

1. Valutare l'espressione ipotalamica di aromatasi e 5 α -reduttasi nella prole a differenti epoche dello sviluppo (feto, infanzia, divezzamento, giovane adulto)

2. Correlare tali parametri con:

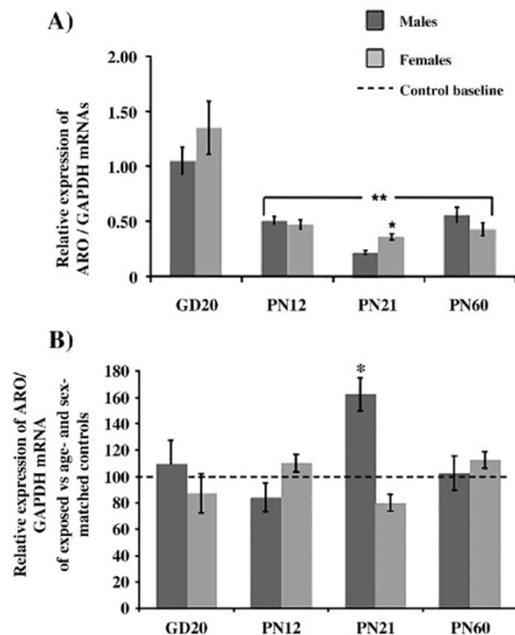
- Timing della discesa del testicolo
- Timing dello sviluppo puberale
- Regolarità mestruale
- Comportamento sessuale

3. Valutare la presenza di eventuali alterazioni di parametri non riproduttivi (es. apprendimento, memoria, motricità, umore)

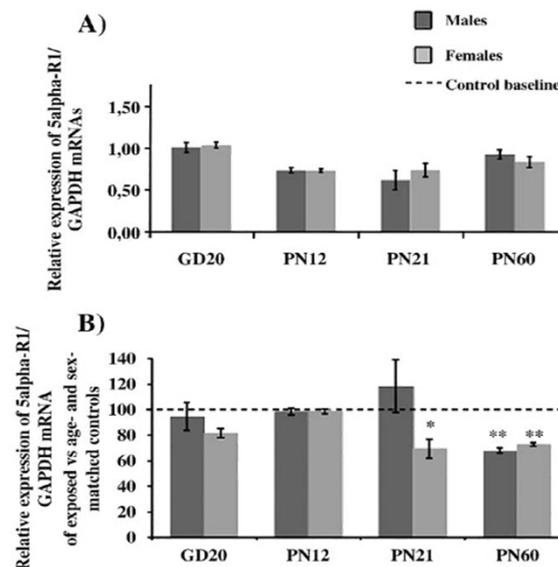


Gli “Endocrine Disrupters” : possibili danni nell’età evolutiva

Fig. I **Aromatasi**



5 α -reduttasi



Legenda:
 GD20 Feto
 PN12 Infanzia
 PN21 Divezzamento
 PN60 Giovane adulto

Risultati:

I. Modificazione del pattern dimorfico di espressione di aromatasi e 5 α -reduttasi che si mantiene fino all’età adulta (Fig. I)

Colciago et al, *Toxicol Appl Pharmacol*, 2009



Gli “Endocrine Disrupters” : possibili danni nell’età evolutiva

Female sexual maturation and reproduction after prepubertal exposure to estrogens and endocrine disrupting chemicals:
A review of rodent and human data

Molecular and Cellular Endocrinology 2006

G. Rasier^a, J. Toppari^b, A.-S. Parent^a, J.-P. Bourguignon^{a,*}

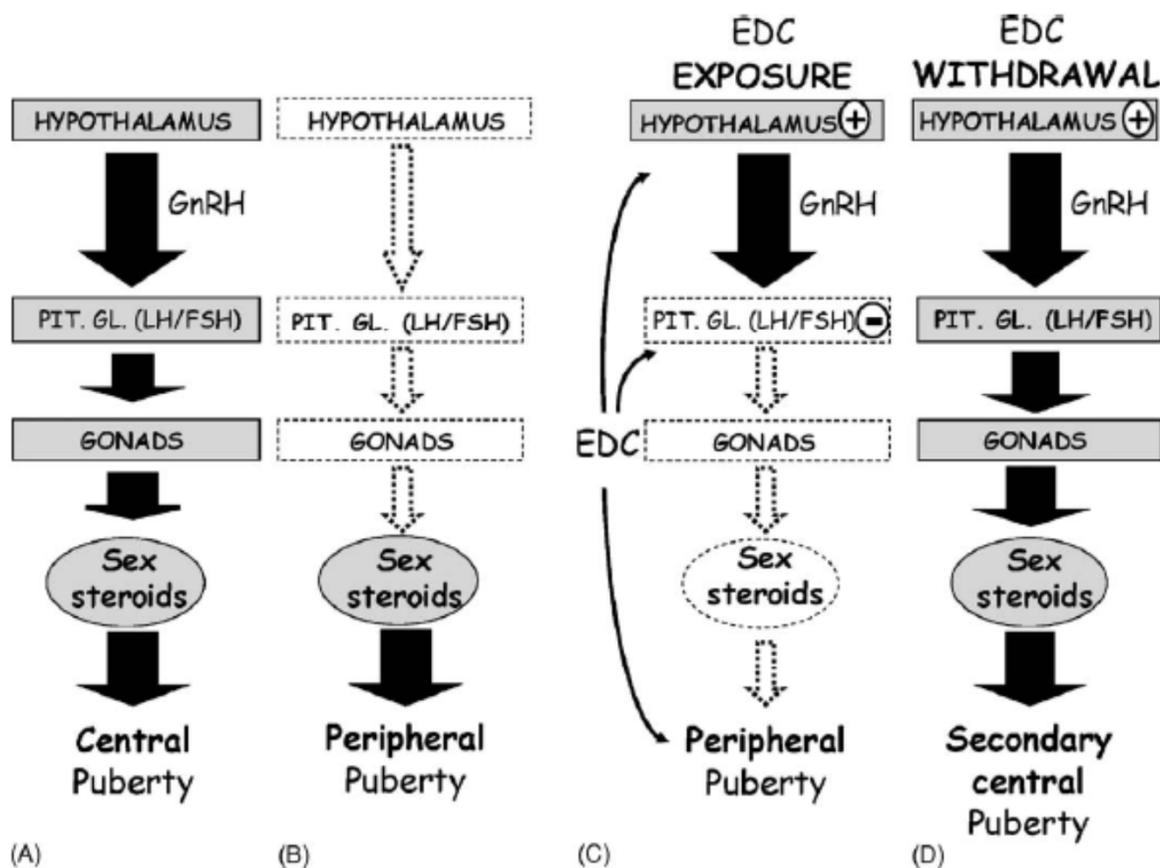


Fig. 2. Schematic illustration of the hypothalamic–pituitary–gonadal (HPG) axis function in different conditions: stimulation in physiological or precocious central puberty (A), inhibition in peripheral puberty due to steroids of extra-gonadal origin (B), hypothalamic stimulation and PG inhibition in the presence of an estrogenic EDC (C) and HPG stimulation after withdrawal from the EDC (D).



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

Association Between Urinary Bisphenol A Concentration and **Obesity Prevalence** in Children and Adolescents

JAMA, September 19, 2012—Vol 308, No. 11

Table 3. Association of Urinary Bisphenol A Concentration and Body Mass Outcomes From Full Multivariable Models^a

	Body Mass Outcome				
	Increment in BMI z Score (95% CI)	Overweight		Obesity	
		OR (95% CI)	Prevalence (95% CI), %	OR (95% CI)	Prevalence (95% CI), %
Urinary bisphenol A concentration quartile					
1	1 [Reference]	1 [Reference]	31.1 (25.4 to 36.8)	1 [Reference]	10.3 (7.5 to 13.1)
2	0.12 (-0.02 to 0.27)	1.26 (0.96 to 1.64)	36.0 (30.8 to 41.2)	2.24 (1.54 to 3.24) ^b	20.1 (14.5 to 25.6)
3	0.16 (0.01 to 0.30) ^c	1.28 (0.98 to 1.66)	36.4 (29.9 to 42.8)	2.08 (1.46 to 2.96) ^b	19.0 (13.7 to 24.2)
4	0.22 (0.06 to 0.39) ^d	1.26 (0.86 to 1.82)	35.9 (29.7 to 42.2)	2.57 (1.72 to 3.83) ^b	22.3 (16.6 to 27.9)
Log-transformed bisphenol A concentration, ng/mL	0.06 (0.001 to 0.11) ^c	1.04 (0.92 to 1.18)		1.24 (1.08 to 1.44) ^d	

^aFor all models, n=2814. All models control for sex, caloric intake, television watching, poverty to income ratio, parental education, serum cotinine level, urinary creatinine level, age, and race/ethnicity categories.

^bp<.001.

^cp<.05.

^dp<.01.



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?



Desvergne et al, Mol Cell Endocrinol 2009

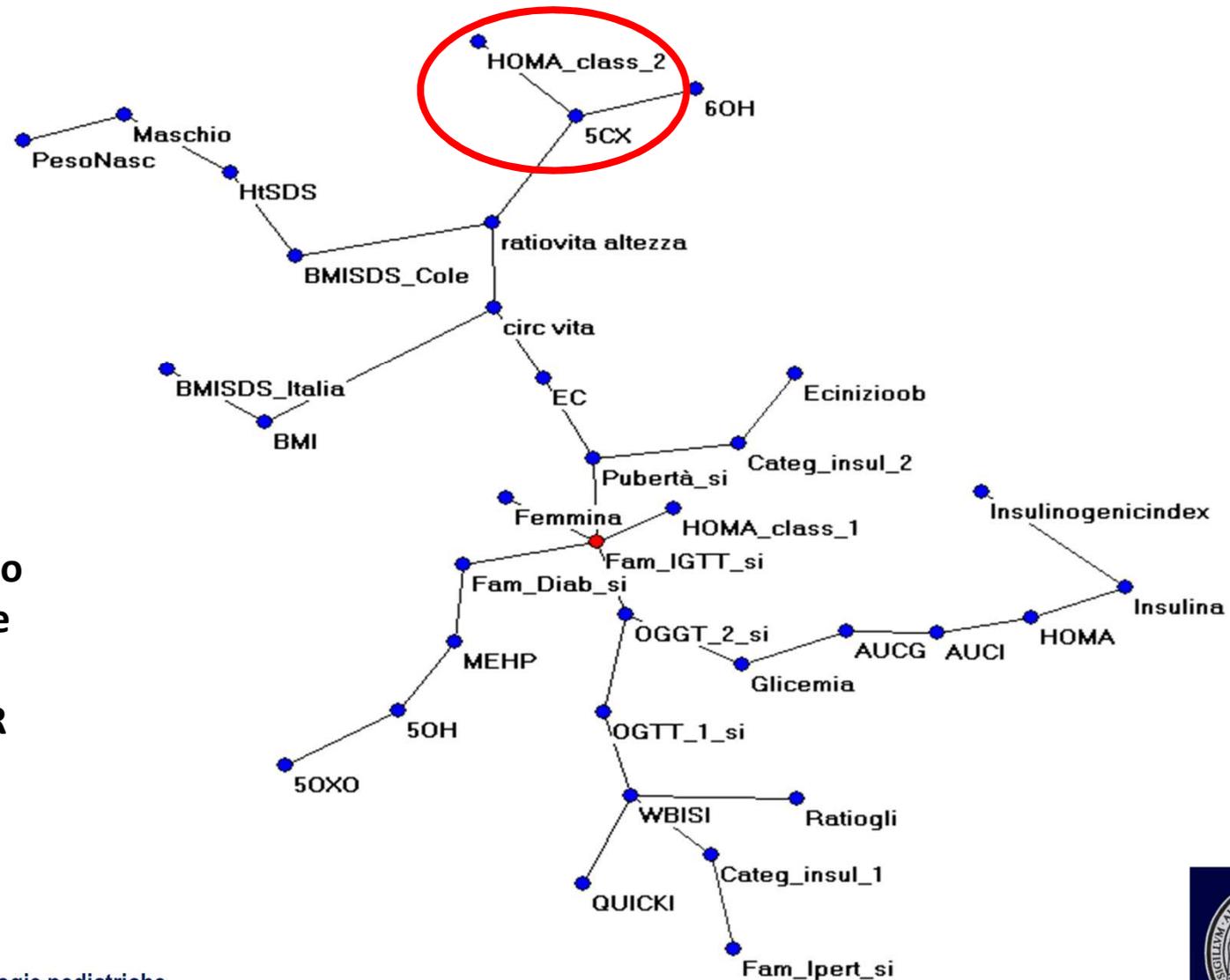
Feige et al, Envir Health Perspect 2010

Casals-Casas et al, Int J Obes, 2008

Latini et al, Environment International 2009



Dati personali



**Rapporto diretto
tra 5-cx-MEHP e
circonferenza
vita/altezza e IR**



EFFETTI NEGATIVI SULLA SALUTE DEL BAMBINO ?

Urinary Phthalates and Increased Insulin Resistance in Adolescents

Leonardo Trasande, Adam J. Spanier, Sheela Sathyanarayana, Teresa M. Attina and Jan Blustein

Pediatrics 2013;132:e646; originally published online August 19, 2013;
DOI: 10.1542/peds.2012-4022

TABLE 5 Associations of Individual Urinary Phthalate Metabolites With Insulin Resistance Outcomes in Linear and Logistic Regression Analyses

Increment/OR	Increment, HOMA-IR, <i>n</i> = 760	OR, Insulin Resistance, <i>n</i> = 758 ^a
LMW phthalates		
Log-transformed mono-ethyl phthalate	-0.07 (-0.16, +0.05)	0.89 (0.71, 1.11)
Log-transformed MBP	+0.13 (+0.01, +0.26) ^b	1.55 (1.11, 2.16) ^b
Log-transformed mono-isobutyl phthalate	+0.15 (+0.04, +0.26) ^c	1.57 (1.18, 2.09) ^c
HMW metabolites (non-DEHP)		
Log-transformed monobenzylphthalate	+0.02 (-0.08, +0.13)	1.26 (0.97, 1.63)
Log-transformed MCPP	+0.20 (+0.08, +0.32) ^c	1.47 (1.10, 1.95) ^c
HMW metabolites of DEHP		
Log-transformed MEHP	+0.11 (+0.04, +0.20) ^c	1.13 (0.91, 1.40)
Log-transformed MEHHP	+0.20 (+0.12, +0.29) ^d	1.51 (1.21, 1.88) ^d
Log-transformed MEOHP	+0.20 (+0.11, +0.29) ^d	1.49 (1.19, 1.87) ^c
Log-transformed MECPP	+0.16 (+0.07, +0.25) ^d	1.36 (1.08, 1.73) ^b

Increases are per log unit in urinary LMW/HMW/DEHP metabolite concentration. See methods for calculation.

All models control for continuous urinary creatinine, age (measured continuously), and caloric intake as well as gender, PIR, parental education, serum cotinine, BMI, and race/ethnicity categories. Results using unweighted modeling are presented.

^a No participants with missing poverty-income cotinine data were insulin resistant, and these were excluded from logistic models to permit convergence.

^b *P* < .05.

^c *P* < .01.

^d *P* < .001.

Interferenti endocrini e patologie pediatriche
S. Bernasconi



Aspetti fondamentali

- 1) Definizione
- 2) Controversie sull'impatto sulla salute
- 3) Patologie più studiate
- **4) Alcune considerazioni pratiche**





Bisphenol A (BPA)

What is BPA?

Bisphenol A, more commonly known as BPA, is a chemical widely used to make polycarbonate plastics and epoxy resins.

Where is BPA found?

Polycarbonate plastics have many applications including use in some food and drink packaging such as water and baby bottles, compact discs, impact-resistant safety equipment, and medical devices including those used in hospital settings.¹ Epoxy resins are used to coat metal products such as food cans, bottle tops, and water supply pipes. BPA can also be found in certain thermal paper products, including some cash register and ATM receipts. Some dental sealants and composites may also contribute to BPA exposure.

How does BPA get into the body?

BPA can leach into food from the epoxy resin lining of cans and from consumer products such as polycarbonate tableware, food storage containers, water bottles, and baby bottles. Additional traces of BPA can leach out of these products when they are heated at high temperatures. Recent studies also suggest that the public may be exposed to BPA by handling cash register receipts.² More research is needed to determine how much BPA from a receipt's coating enters the body and how it gets there. The National Institute of Environmental Health Sciences expects to support more research to determine if BPA in receipts poses a risk to human health.



Why are people concerned about BPA?

One reason people may be concerned about BPA is because human exposure to BPA is widespread. The 2003-2004 National Health and Nutrition Examination Survey (NHANES), conducted by the Centers for Disease Control and Prevention (CDC), found detectable levels of BPA in 93% of Americans six years and older. Another reason for concern, especially for parents, may be because some laboratory animal studies report subtle developmental effects in fetuses and newborns exposed to low doses of BPA.

Why did the National Toxicology Program (NTP) evaluate BPA?

The NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) conducted the BPA evaluation. BPA was selected for evaluation because of the following factors:

- Widespread human exposure from use and occurrence in the environment
- Growing public concern
- Amount of BPA produced
- Extensive database of animal studies on reproductive and developmental effects

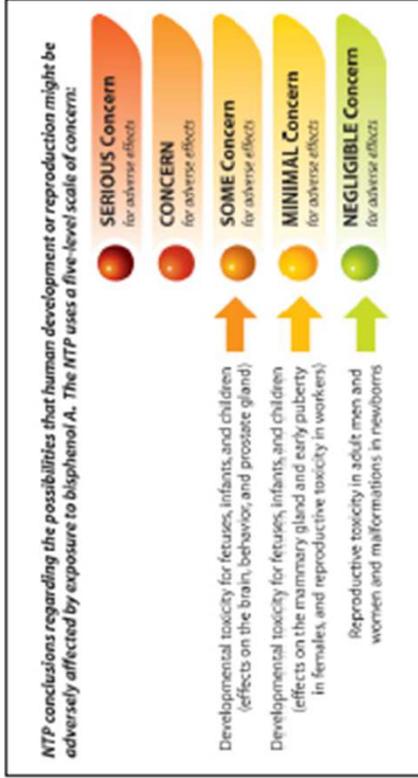
What did the NTP conclude about BPA?

The NTP has "some concern" for BPA's effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current exposure levels.

The NTP has "minimal concern" for effects on the mammary gland and an earlier age for puberty in females, fetuses, infants, and children at current exposure levels.

The NTP has "negligible concern" that exposure of pregnant women to BPA will result in fetal or neonatal mortality, birth defects, or reduced birth weight and growth in their offspring.

The NTP has "negligible concern" that exposure to BPA will cause reproductive effects in non-occupationally exposed adults and "minimal concern" for workers exposed to higher levels in occupational settings.



WHAT SHOULD I DO AS A PARENT?

- Talk to your pediatrician if you are concerned that your child has been in a “highly exposed” environment, such as a hobby shop or workplace that uses chemicals.
- Take steps to reduce exposure to chemical toxins. There are now many products that are labeled “phthalate-free” or “BPA-free.” Microwave foods in glass rather than plastic containers.
- Consider buying organic produce to reduce exposure to pesticides.
- If you live near polluted waters, be aware of and follow fishing advisories.
- Reduce indoor dust exposure by cleaning carpets and dusty surfaces regularly using a vacuum cleaner with a high-efficiency particulate air filter.

Children’s Environmental Health

Keeping children healthy includes understanding how the environment around a child’s home and community affects health. Environmental effects on health are particularly important for children:

- Children’s tissues and organs are growing and developing, so they are at greater risk of harm if they are exposed to a toxin in the environment.
- Children can have a higher exposure to a toxic chemical after touching it because they frequently put their hands, or other objects, in their mouths.

Chemicals (one of the many types of environmental toxins) are used to make things that we use every day. There are now more than 84,000 different chemicals used in making products such as food, clothes, and toys. Many of these chemicals have been created to help us store and use food, such as plastics. Others were developed to improve safety, such as flame retardants. Others were developed to improve quality of life, such as pesticides.

Despite the improvements that these chemicals can bring to our daily lives, there are concerns about children being exposed to harmful chemicals in multiple ways, such as through food, drinking water, air, soil, and even house dust. Some pediatricians work on researching possible environmental causes of children’s illnesses and disorders. A recent article in the *Archives* described several common chemicals and the current research about whether they could cause harm to children. Common environmental toxins discussed in that article include the following:

- Phthalates are a type of industrial chemical that is widely used in many ways. One example is to help make plastics more flexible. Some research that has been done found that high levels of phthalates have been related to decreased hormone levels and possibly breast cancer in adults.
- Bisphenol A, also called BPA, is a chemical used to make certain plastics, such as water bottles. Some research has found that high levels of BPA can negatively affect hormones and the cardiovascular system.
- Pesticides are used to keep insects off of fruits and vegetables so they can grow. Some research has shown that pesticides within homes, such as on the vegetables you get from the store, can persist for a long time. Pesticides have many negative health effects, especially on the brain.



What can I do to prevent exposure to BPA?

If you are concerned, you can make personal choices to reduce exposure:

- Don’t microwave polycarbonate plastic food containers. Polycarbonate is strong and durable, but over time it may break down from repeated use at high temperatures.
- Avoid plastic containers with the #7 on the bottom (http://www.recyclenow.org/r_plastics.html).
- Don’t wash polycarbonate plastic containers in the dishwasher with harsh detergents.
- Reduce your use of canned foods. Eat fresh or frozen foods.
- When possible, opt for glass, porcelain, or stainless steel containers, particularly for hot food or liquids.
- Use infant formula bottles that are BPA free and look for toys that are labeled BPA free.



9. Dealing with current uncertainty about the risks posed by environmental chemicals

Under normal lifestyle and dietary conditions, the level of exposure of most women to individual environmental chemicals will probably pose minimal risk to the developing fetus/baby. However, women who are pregnant are exposed to hundreds of chemicals at a low level. Potentially, this exposure could operate additively or interactively and raises the possibility of 'mixtures' effects. On present evidence, it is impossible to assess the risk, if any, of such exposures. Obtaining more definitive guidance is likely to take many years; there is considerable uncertainty about the risks of chemical exposure. The following steps would however reduce overall chemical exposure:

- use fresh food rather than processed foods whenever possible
- reduce use of foods/beverages in cans/plastic containers, including their use for food storage
- minimise the use of personal care products such as moisturisers, cosmetics, shower gels and fragrances
- minimise the purchase of newly produced household furniture, fabrics, non-stick frying pans and cars whilst pregnant/nursing
- avoid the use of garden/household/pet pesticides or fungicides (such as fly sprays or strips, rose sprays, flea powders)
- avoid paint fumes
- only take over-the-counter analgesics or painkillers when necessary
- do not assume safety of products based on the absence of 'harmful' chemicals in their ingredients list, or the tag 'natural' (herbal or otherwise).

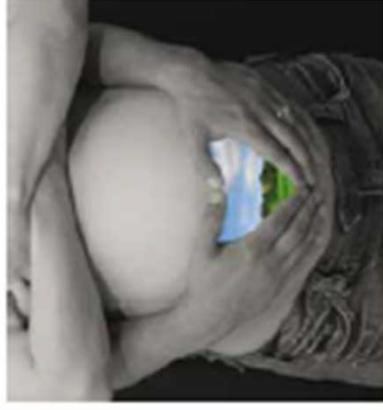
It is unlikely that any of these exposures are truly harmful for most babies, but in view of current uncertainty about risks, especially those relating to 'mixtures', these steps will reduce environmental chemical exposures.





MINISTERSTWO ZDROWIA
REPUBLICA POLSKA

CONOSCI, RIDUCI, PREVIENI GLI INTERFERENTI ENDOCRINI



UN DECALOGO PER IL CITTADINO



LIMITA O EVITA	PRIVILEGIA O SOSTITUISCI
1. Evita il ristagno di aria e polvere negli ambienti chiusi dove i bambini piccoli gattonano o giocano in terra	Garantisci il ricambio di aria negli ambienti chiusi ed effettua una adeguata e periodica pulizia; assicura una corretta manutenzione degli aspirapolveri (pulizia filtri e camera di raccolta, sostituzione sacchi ove presenti)
2. Se hai pavimenti in PVC contenenti DEHP su cui giocano bambini, utilizza un tappeto in fibra non trattata	
3. Limita l'uso di capi di abbigliamento per l'infanzia con trattamenti opzionali idrorepellenti o antimacchia	Privilegia capi di abbigliamento di origine e composizione ben identificabili
4. Evita materassi per lettini con rivestimento o telo impermeabile non conforme alle norme vigenti e comunque evita rivestimenti per materassi in PVC morbido contenente DEHP	
5. Utilizza fodere in fibre non trattate se hai fasciatoi e/o passeggini rivestiti in PVC morbido contenente DEHP; in generale, evita che i bambini entrino in contatto con la bocca con oggetti in PVC	
6. Per scaldare latte, bevande e pappe utilizza contenitori integri e solo secondo le indicazioni del produttore	
7. Lascia che i liquidi caldi si raffreddino prima di travasarli in contenitori di plastica non destinati all'uso ad elevate temperature	
8. Lava accuratamente biberon e altri contenitori dopo la sterilizzazione; non utilizzare biberon in policarbonato (non più consentiti)	
9. Abituata il bambino a consumare alimenti freschi e di stagione; risciacqua frutta e verdura in scatola prima del consumo	
10. Evita il consumo di alimenti con parti carbonizzate o bruciate	Per la cottura dei cibi destinati ai bambini, privilegia metodi che preservino il contenuto di vitamine idrosolubili (ad es. cottura a vapore)



Usa il vetro



Informare anche i colleghi!!!!

Potential Sources of Bisphenol A in the Neonatal Intensive Care Unit
 Susan M. Duty, Kaitlin Mendonca, Russ Hauser, Antonia M. Calafat, Xiaoyun Ye,
 John D. Meeker, Robin Ackerman, Judi Cullinane, Josephine Faller and Steven
 Ringer
Pediatrics 2013;131:483; originally published online February 18, 2013;
 DOI: 10.1542/peds.2012-1380

TABLE 3 Difference in Median (25th, 75th) Total BPA Urinary Concentrations ($\mu\text{g/L}$) and Calculated Daily Exposure Estimates by Type and Number of Medical Devices Used in the Past 3 Days^a

Medical Device	Used ^b			Not Used			<i>P</i> ^c
	Median	25th	75th	Median	25th	75th	
Nasal cannula							
Total urinary BPA concentration, $\mu\text{g/L}$	40	17	48	26	17	22	.024
Estimated exposure, $\mu\text{g/kg}$ per day	1.76	0.75	2.11	1.14	0.75	0.97	
CPAP							
Total urinary BPA concentration, $\mu\text{g/L}$	38	18	45	13	9	17	.034
Estimated exposure, $\mu\text{g/kg}$ per day	1.67	0.79	1.98	0.57	0.40	0.75	
Ventilator							
Total urinary BPA concentration, $\mu\text{g/L}$	17	15	32	31	13	49	.5
Estimated exposure, $\mu\text{g/kg}$ per day	0.75	0.66	1.41	1.36	0.57	2.16	
Peripheral IV							
Total urinary BPA concentration, $\mu\text{g/L}$	18	13	43	12	9	25	.55
Estimated exposure, $\mu\text{g/kg}$ per day	0.79	0.57	1.89	0.53	0.40	1.10	
Central IV							
Total urinary BPA concentration, $\mu\text{g/L}$	17	13	37	39	13	47	.54
Estimated exposure, $\mu\text{g/kg}$ per day	0.75	0.57	1.63	1.72	0.57	2.07	
Nasogastric tube							
Total urinary BPA concentration, $\mu\text{g/L}$	23	13	47	9	4	12	.003
Estimated exposure, $\mu\text{g/kg}$ per day	1.01	0.57	2.07	0.40	0.18	0.53	
Use of 4 or more medical devices^d							
Total urinary BPA concentration, $\mu\text{g/L}$	36.6	17.2	47.3	13.9	9.2	35.1	.02
Estimated exposure, $\mu\text{g/kg}$ per day	1.61	0.76	2.08	0.61	0.40	1.54	

CPAP, continuous positive airway pressure; IV, intravenous.

^a Used average of 2 unadjusted urine samples to obtain values. Exposure calculation based on a urine daily volume of 38 mL/kg.²¹

^b Used in past 3 days.

^c Mann-Whitney *U* Test *P* value.

^d Compared with 0 to 3 devices.



Ladenf, Schwartz Fe, Dockery Du, **Reduction in fine particulate air pollution and mortality. Extended follow-up of the Harvard six cities study**, AMJ Respir Crit Care **2006**; 173:667-672

una recente ri-analisi su sei città americane ha dimostrato come una **diminuzione dell'inquinamento urbano da particolato fine** comporta, **dopo soli 3 anni**, una **diminuzione anche del rischio di carcinoma polmonare**.

Hardell L. **Pesticides, soft tissue sarcoma and non Hodgkin lymphoma – historical aspects on the precaution principle in cancer prevention** Acta Oncologica ,47:347-354, **2008**

In Svezia, anche grazie a Lennart Hardell, **negli anni '70 furono messi al bando alcuni pesticidi**: ora, **a distanza di trenta anni**, in quel paese si sta registrando **una diminuzione nell'incidenza dei linfomi**.



Grazie per l'attenzione



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