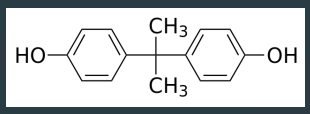


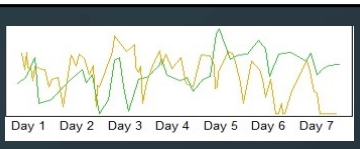


# Contemporary endocrine disruptors: assessing the health effects of non-persistent compounds

## *Perturbateurs endocriniens (2) : Caractériser l'effet des substances non persistantes dans l'organisme*

**Rémy Slama**

Collège de France & Inserm

The relations between human health and the environment in the Anthropocene

Lecture #6 – 18 May 2022

COLLÈGE DE FRANCE 1530

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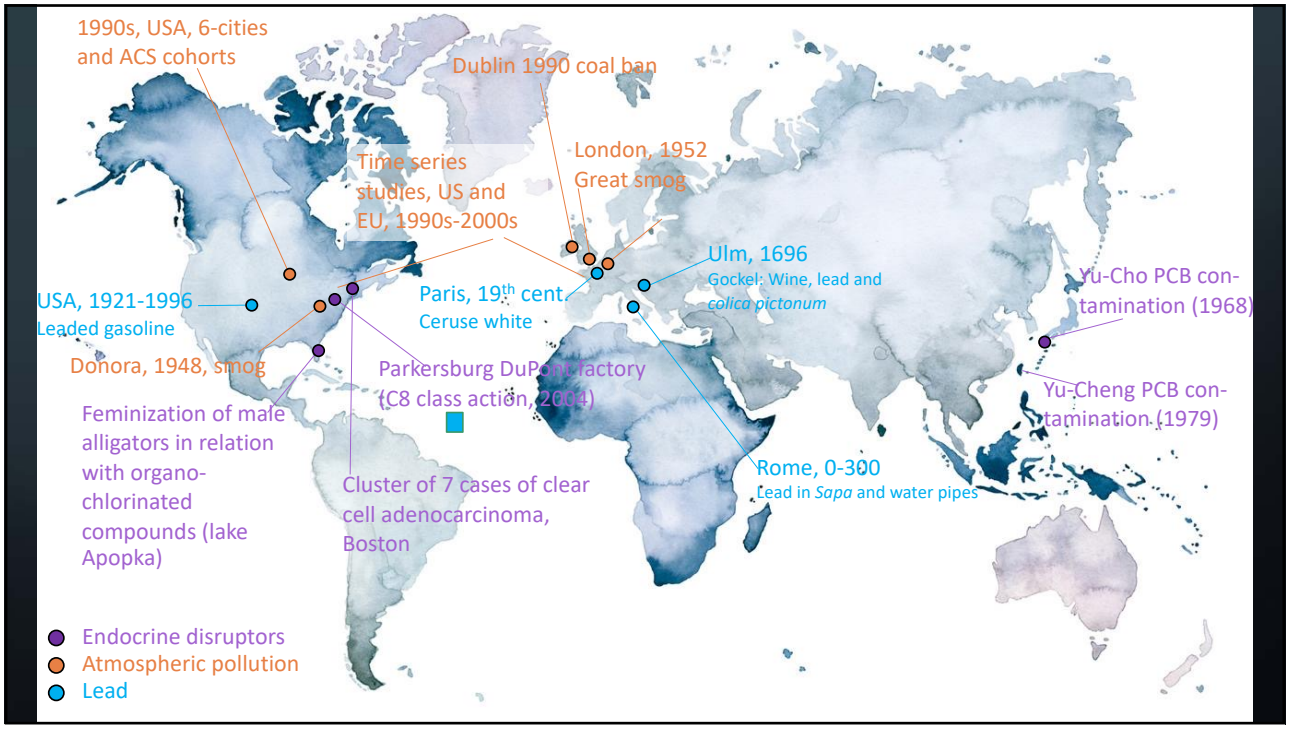


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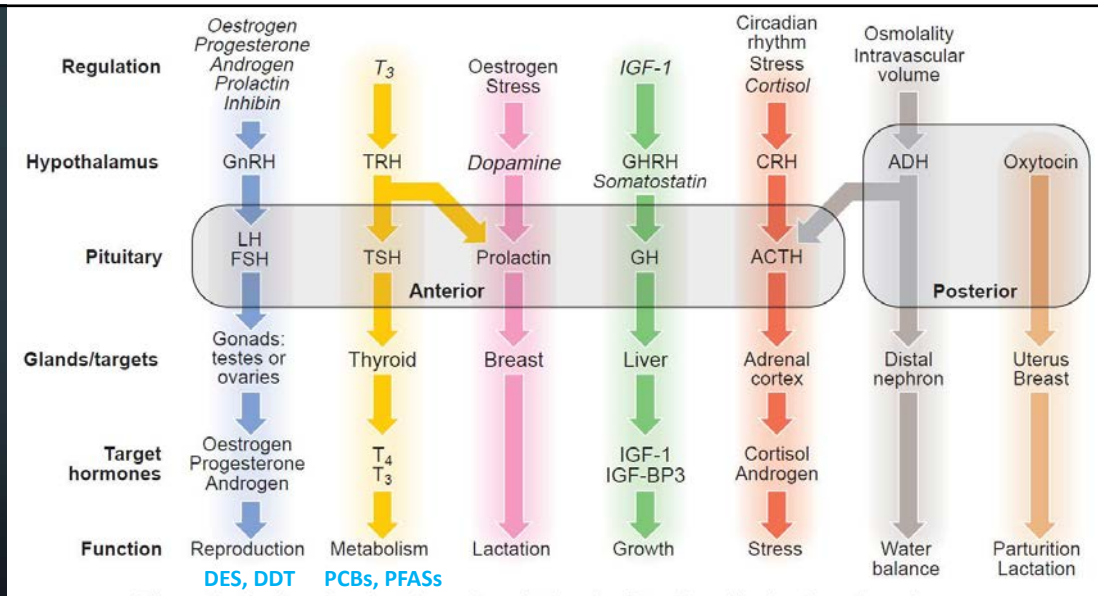


**The principal endocrine 'axes' and glands.** Parathyroid glands, adrenal zona glomerulosa and endocrine pancreas are not controlled by the pituitary. Italics show negative regulation. (GnRH = gonadotrophin-releasing hormone. For other abbreviations see text.)

Source : Davidsons Essentials of Medicine, 2e

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# Lecture overview

Lecture #5

A. Introduction: classifying toxicants
B. Endocrine disruption – Generic considerations
C. Disrupting the estrogenic axis: DES, DDT
D. Disrupting the thyroid axis: PCBs, PFASs

Interactions with nuclear receptors *(seminar of W. Bourguet)*

Lecture #6

E. Characterizing effects of non-persistent compounds in humans
F. Triclosan and bisphenols
G. Social inequalities in exposure
H. Health and societal impact
I. Evaluation of risk management options
J. Risk management

Mixture effects *(seminar of Pr. A. Kortenkamp)*

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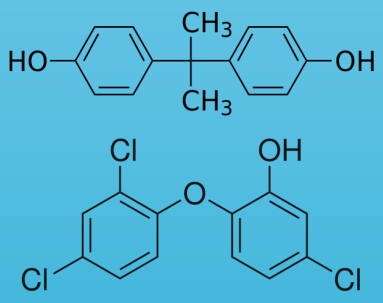
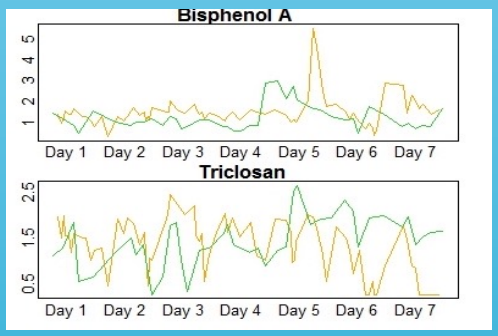
## E. Characterizing the effects of non-persistent compounds in humans

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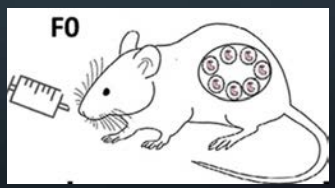
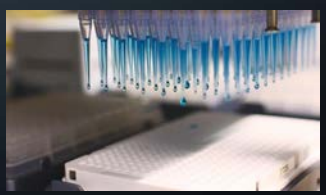
## Characterizing the effect of chemicals on health, from the molecular to the population scales

Individual scale (cohorts) | Individual scale (in vivo toxicology) | Cellular scale (in vitro toxicology) | Molecular scale

Uncontrolled (real-life) exposure

Controlled exposure



(in silico/QSAR approaches)

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Commentary

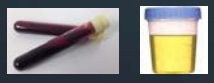
(wileyonlinelibrary.com) DOI: 10.1002/sim.5499

Published online in W

# The biomarker revolution

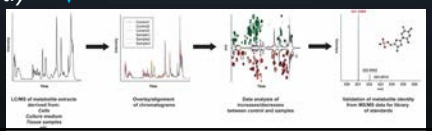
Enrique F. Schisterman[a*†] and Paul S. Albert[b]

(Schilsterman, *Stat Med*, 2012)



5 ml

**Untargeted analysis** (thousands of chemicals, *not always quantitative, partly annotated*)



**Targeted analyses** (hundreds of chemicals), *very sensitive, annotated*

| Compound | | Maternal samples P25 | P50 | P75 | Max | n analyzed | % quantifiable samples |
|---|---|---|---|---|---|---|---|
| PCB 118 | ng/g lipid | 1.57 | 2.64 | 4.82 | 39.0 | 829 | 79.1 |
| PCB 138 | ng/g lipid | 5.54 | 9.10 | 16.1 | 132 | 1048 | 96.5 |
| PCB 153 | ng/g lipid | 10.4 | 17.6 | 30.5 | 214 | 1048 | 99.6 |
| PCB 170 | ng/g lipid | 1.84 | 3.69 | 7.06 | 84.5 | 826 | 99.5 |
| PCB 180 | ng/g lipid | 5.78 | 10.4 | 18.6 | 201 | 1048 | 97.6 |
| DDT | ng/g lipid | 0.82 | 1.33 | 3.06 | 94.1 | 826 | 65.6 |
| DDE | ng/g lipid | 25.9 | 52.3 | 111 | 1903 | 1048 | 99.9 |
| HCB | ng/g lipid | 5.59 | 8.16 | 13.0 | 164 | 1048 | 99.1 |
| PBDE 47 | ng/g lipid | 0.27 | 0.43 | 0.75 | 34.74 | 684 | 80.8 |
| PBDE 153 | ng/g lipid | 0.03 | 0.45 | 0.66 | 198 | 648 | 72.9 |
| PFOA | µg/L | 1.38 | 2.30 | 3.34 | 31.6 | 1240 | 99.7 |
| PFNA | µg/L | 0.43 | 0.69 | 1.08 | 5.92 | 1240 | 97.9 |
| PFUnDA | µg/L | 0.10 | 0.19 | 0.29 | 2.80 | 1032 | 95.4 |
| PFHxS | µg/L | 0.31 | 0.55 | 0.91 | 21.0 | 1240 | 97.5 |
| PFOS | µg/L | 4.12 | 6.41 | 9.63 | 48.0 | 1240 | 100 |
| As | µg/L | 0.28 | 1.19 | 2.27 | 90.1 | 833 | 58.5 |
| Cd | µg/L | 0.15 | 0.22 | 0.33 | 27.9 | 833 | 99.6 |
| Cs | µg/L | 1.19 | 1.56 | 2.15 | 10.9 | 833 | 100 |
| Hg | µg/L | 0.98 | 1.90 | 3.45 | 43.5 | 1020 | 98.9 |
| Pb | µg/L | 7.14 | 9.66 | 13.20 | 187 | 833 | 100 |
| Tl | µg/L | | | | | 833 | 1.1 |
| MEP | µg/g creat. | 72.0 | 179 | 469 | 17,733 | 1080 | 99.0 |
| MiBP | µg/g creat. | 23.3 | 38.7 | 60.7 | 705 | 1088 | 99.9 |
| MnBP | µg/g creat. | 18.3 | 29.6 | 47.3 | 6445 | 1089 | 100 |
| MBzP | µg/g creat. | 3.63 | 7.33 | 15.3 | 775.1 | 1088 | 99.7 |
| MEHP | µg/g creat. | 4.42 | 8.73 | 15.3 | 417 | 1085 | 99.5 |
| MEHHP | µg/g creat. | 10.5 | 18.2 | 31.2 | 967 | 1089 | 100 |
| MEOHP | µg/g creat. | 8.29 | 14.1 | 23.7 | 783 | 1089 | 100 |
| MECPP | µg/g creat. | 22.4 | 33.6 | 52.3 | 1361 | 913 | 99.9 |
| oh-MiNP | µg/g creat. | 0.61 | 0.91 | 1.47 | 66.5 | 914 | 92.6 |
| oxo-MiNP | µg/g creat. | 0.62 | 1.03 | 1.75 | 75.1 | 914 | 95.7 |
| MEPA | µg/g creat. | 39.5 | 167 | 389 | 39,241 | 815 | 99.8 |
| ETPA | µg/g creat. | 1.14 | 6.26 | 26.72 | 6774 | 817 | 97.4 |
| PRPA | µg/g creat. | 8.87 | 44.2 | 134 | 12,463 | 1083 | 97.3 |
| BUPA | µg/g creat. | 0.36 | 3.37 | 14.4 | 371 | 1083 | 97.0 |
| BPA | µg/g creat. | 1.55 | 2.82 | 6.60 | 107 | 1084 | 99.4 |
| OXBE | µg/g creat. | 1.46 | 4.90 | 27.5 | 12,837 | 1085 | 99.3 |
| TCS | µg/g creat. | 1.50 | 6.28 | 79.9 | 1653 | 1085 | 98.5 |
| DMP | µg/g creat. | 4.13 | 8.37 | 16.4 | 321 | 1080 | 90.8 |
| DMTP | µg/g creat. | 2.05 | 4.96 | 12.4 | 220 | 1084 | 88.9 |
| DMDTP | µg/g creat. | 0.05 | 0.19 | 1.54 | 134 | 969 | 41.6 |
| DEP | µg/g creat. | 1.86 | 3.33 | 6.44 | 198 | 1082 | 97.8 |
| DETP | µg/g creat. | 0.12 | 0.58 | 2.56 | 44.3 | 1037 | 50 |
| DEDTP | µg/g creat. | | | | | 1084 | 1.7 |
| Cotinine | µg/g creat. | 1.49 | 5.25 | 23.7 | 15,410 | 1093 | 43.7 |

(Haug, *Env Int*, 2018)

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## Some issues related to the use of exposure biomarkers in human studies

- Link between biomarkers (urinary) *concentrations* and *exposure* and relevance of biomarkers-based studies for regulation
- Confounding by genetic and physiological factors (e.g., Verner, *EHP*, 2013, Weisskopf, *Epidemiology*, 2017)
- Multiple testing (if multiple biomarkers are assayed)
- Exposure misclassification
  - Method analytical accuracy
  - Batch effects (repeatability)
  - Choice of biomarker and biological matrix
  - Biospecimen collection (mode, timing…), transport, storage, freezing/thawing…

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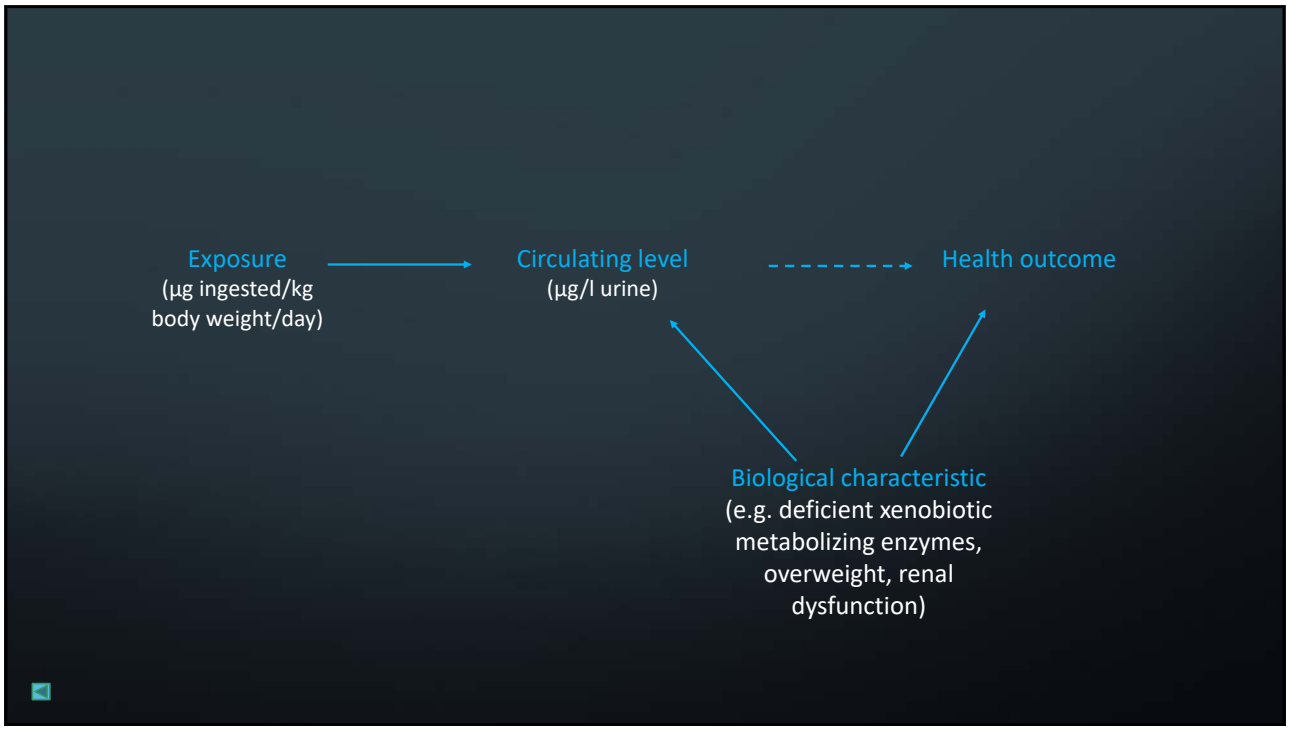


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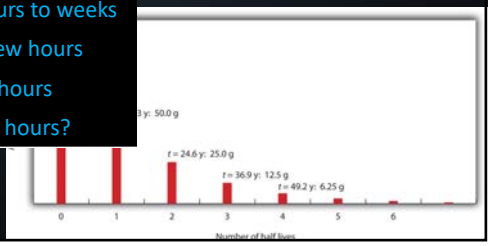
## Half-life of some compounds in the human body

| | Compound | Matrix | Half-life |
|---|---|---|---|
| "Legacy chemicals" (exposure existed before 1950s) | DDE | | 10 years |
| | DDT (organochlorine pesticide) | Blood | 5 years |
| | Cadmium (Cd) | Urine | 10-30 years |
| | Cotinine (metabolite of nicotine) | Urine | 20 h. |
| | Elemental Mercury (Hg) | Urine | 1-3 months |
| | Methylmercury | Blood | 50 days |
| | Lead (Pb) | Blood | Around 40 days |
| More recent chemicals | Organophosphate pesticides | Urine | Hours to weeks |
| | DEHP (phthalate) | Urine | A few hours |
| | Triclosan | Blood | 21 hours |
| | Bisphenol A | Urine | 2-4 hours? |



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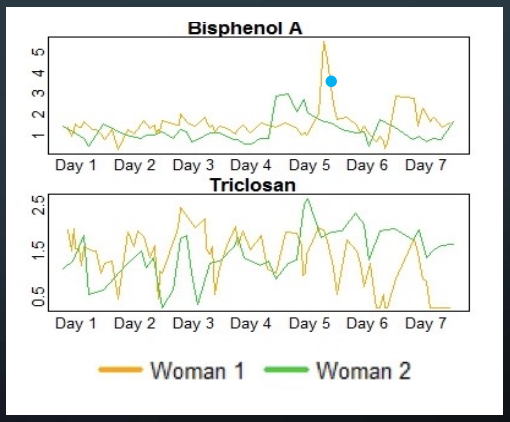
# High production chemicals are moving targets in the body

SEPAGES-feasibility study, sampling of all urine samples for 2 women during a week (140 urine samples). A Calafat's lab (CDC, Atlanta)




(Vernet, *EHP*, 2018)

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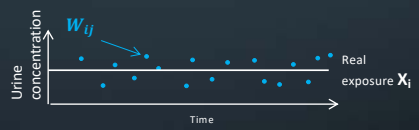
# A simulation study to estimate the impact of reliance on a spot biospecimen to assess exposure

**1. Simulation of $X_i$ (mean, 0; SD, 1)**

Real exposure of subject i measured without error
e.g., average of the urinary concentrations over the whole pregnancy in subject $i$

**2. Simulations of error-prone variables $W_{ij}$**

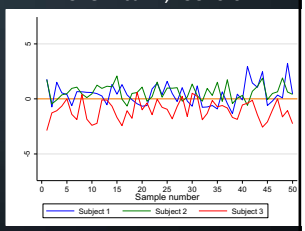
Biomarker concentrations measured in spot urine samples collected at different time points of pregnancy
$W_{ij}$ randomly varies around $X_i$



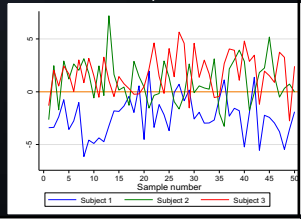

Error of classical type: $W_{ij} = X_i + U_{ij}$, $U_{ij}$, random error, independent of X, $j = 1 \ldots 50$

Intra-class correlation coefficient (ICC):
either **0.6** (chemical A) or **0.2** (chemical B).

Chemical A, ICC: 0.6




Chemical B, ICC: 0.2

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# Simulation study (2): Health outcome generation

**3. We then generate the health outcome $Y_i$** assumed to linearly depend on the real (unmeasured) exposure $X_i$

$$Y_i = \alpha + \beta X_i + \varepsilon_i$$

with slope $\beta$=-100 and random error $\varepsilon$ (Gaussian)

**4. Model efficiency** is estimated by regressing the generated outcome $Y_i$ on $W_i$, the within-subject mean of the **observed (error-prone) exposures $W_{ij}$**

$$Y_i = \hat{\alpha} + \hat{\beta}_1 \bar{W}_i + \varepsilon_i$$

**5. Steps 2-4 are repeated 1000 times** and the mean of $\hat{\beta}$ is compared to its expected value -100

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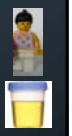
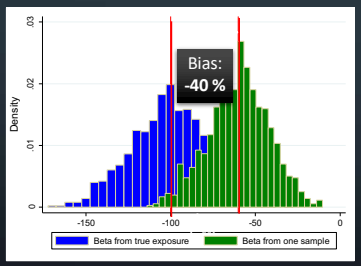
# Simulation study (3): Results - Impact of using a spot urine sample to assess exposure on bias

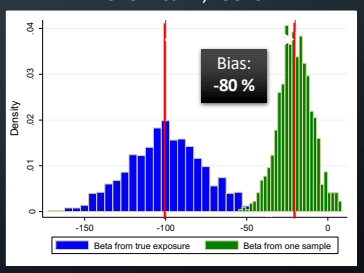


Distribution of the health effect estimates β obtained using the **true (unknown) exposure** or the concentration measured in **one sample**

Chemical A, **ICC=0.6**




Chemical B, **ICC=0.2**




1000 simulations, each with 500 subjects; real effect $\beta_{True}$ = -100 g

If we assume a lack of effect of A and B on Y, then the false positive rate is 5% (not increased compared to a situation without measurement error) (Perrier, *Epidemiology*, 2016)

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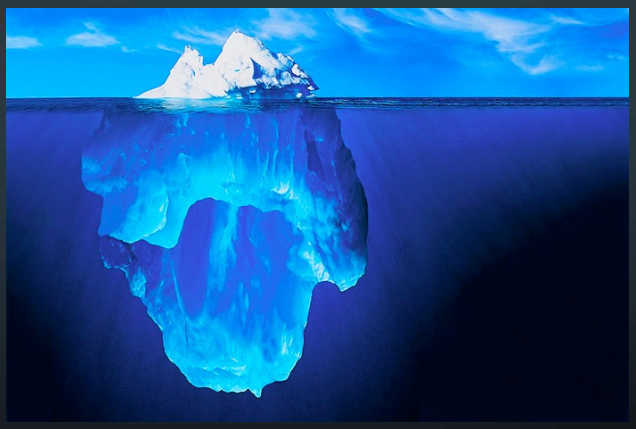
## Attenuation bias



What epidemiologists see

What may be the true effect

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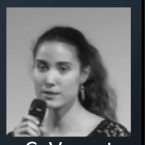
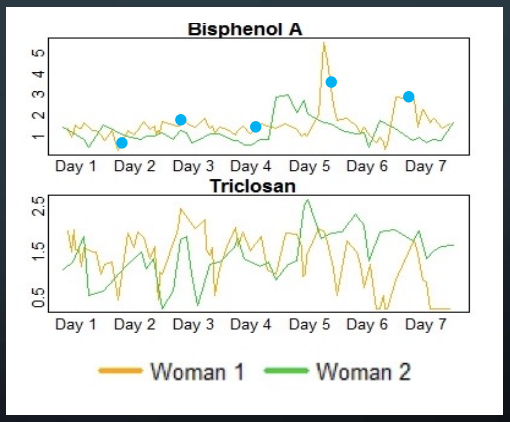
## Is there a way to see the whole iceberg?


C. Philippat


C. Vernet




(Vernet, *EHP*, 2018)

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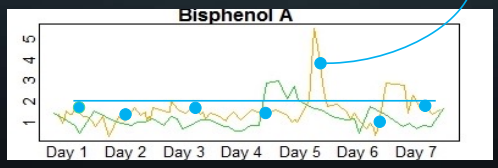
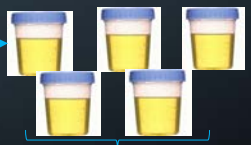
## *Moving forward:* How to relate exposures varying on an hourly basis to biological phenomena spanning over several months?

The *within-subject pooling of biospecimens* approach
(Perrier, *Epidemiology*, 2016)




1. Collect repeated samples for each subject



2. *(optional)* Pool samples *within-subject*

3. Assay phenols in each (pooled) sample

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## Increasing the number of biospecimens per subject


**ICC = 0.6**

| Number of biospecimens per subject | Real effect[a] | Effect estimate[a] |
|---|---|---|
| 1 | -100 | -60[c] |

**ICC = 0.2**

| Bias (%)[d] | Effect estimate[a] | 95% CI[b] | Power[c] |
|---|---|---|---|
| 80 | -20[c] | [-45; 7.6] | 0.32 |
| 66 | -34 | [-67; 1.8] | 0.50 |
| 58 | -43 | [-83; -3.1] | 0.58 |
| 49 | -52 | [-92; -8.7] | 0.68 |
| 43 | -56 | [-105; -13] | 0.71 |
| 40 | -60 | [-108; -16] | 0.70 |
| 35 | -64 | [-113; -15] | 0.77 |
| 33 | -66 | [-112; -17] | 0.74 |
| 30 | -71 | [-121; -20] | 0.81 |
| 28 | -72 | [-119; -24] | 0.80 |
| 25 | -75 | [-129; -22] | 0.82 |
| 21 | -79 | [-130; -29] | 0.86 |
| 18 | -81 | [-135; -30] | 0.85 |
| 16 | -83 | [-139; -29] | 0.85 |
| 14 | -85 | [-139; -31] | 0.88 |
| 12 | -89 | [-143; -31] | 0.88 |
| 10 | -91 | [-145; -39] | 0.89 |
| 9 | -92 | [-153; -35] | 0.88 |
| 8 | -91 | [-146; -34] | 0.88 |

*Within-subject pooling* reduces bias and increases power …without increasing assay costs

Effect estimate: mean of 1000 simulations, each with 500 subjects

(Perrier, *Epidemiology*, 2016)

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# Improving the within-subject pooling approach?

If the ICC is known, then the bias of the within-subject pooling approach relying on k samples per subject is such that:

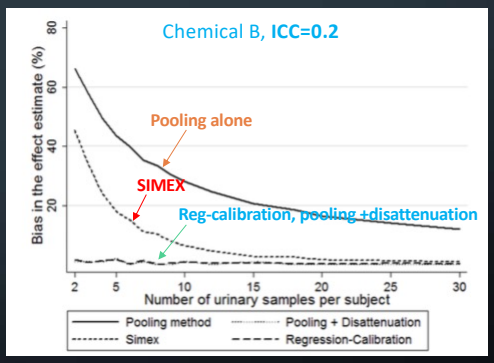
$$\beta_{true} = \beta_{obs} \cdot \frac{1}{k}\left(k - 1 + \frac{1}{ICC}\right)$$

(Rappaport, *EHP*, 1995)

It follows that

$$\hat{\beta}_{corr} = \hat{\beta}_{obs} \cdot \left(\frac{k-1}{k} + \frac{1}{k\,ICC}\right)$$

is an unbiased estimated of $\beta_{true}$




We will call this estimator *a posteriori disattenuation*

(Perrier, *Epidemiology*, 2016)

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# *More subjects or more biospecimens per subject?*

| Sample size | Number of specimens per subject | Real effect[a] | Chemical B, ICC of 0.2 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Within-subject pooling | | | Within-subject pooling + dissatenuation | | | Simex | | | Regression calibration | | |
| | | | Effect estimate[a] | Power[b] | Bias (%)[c] | Effect estimate[a] | Power[b] | Bias (%)[c] | Effect estimate[a] | Power[b] | Bias (%)[c] | Effect estimate[a] | Power[b] | Bias (%)[c] |
| 500 | 1 | -97 | -21[d] | 0.10 | 79 | -104[d] | 0.10 | 7 | | | | | | |
| | 2 | -101 | -34 | 0.12 | 66 | -102 | 0.12 | 1 | -55 | 0.14 | 46 | -108 | 0.10 | 6 |
| | 5 | -99 | -53 | 0.16 | 47 | -95 | 0.16 | 4 | -75 | 0.18 | 24 | -95 | 0.19 | 4 |
| | 10 | -101 | -72 | 0.22 | 29 | -101 | 0.22 | 0 | -93 | 0.24 | 8 | -101 | 0.25 | 0 |
| | 50 | -101 | -94 | 0.27 | 7 | -102 | 0.27 | 0 | -101 | 0.30 | 0 | -102 | 0.30 | 0 |
| 1000 | 1 | -100 | -21[d] | 0.13 | 79 | -107[d] | 0.13 | 6 | | | | | | |
| | 2 | -100 | -34 | 0.21 | 66 | -103 | 0.21 | 3 | -56 | 0.24 | 44 | -105 | 0.22 | 5 |
| | 5 | -100 | -56 | 0.29 | 44 | -100 | 0.29 | 1 | -81 | 0.31 | 19 | -101 | 0.32 | 1 |
| | 10 | -101 | -71 | 0.36 | 29 | -99 | 0.37 | 1 | -92 | 0.40 | 8 | -99 | 0.42 | 1 |
| | 50 | -101 | -93 | 0.45 | 7 | -101 | 0.46 | 0 | -100 | 0.50 | 1 | -101 | 0.50 | 0 |
| 2000 | 1 | -98 | -20[d] | 0.22 | 80 | -101[d] | 0.22 | 2 | | | | | | |
| | 2 | -100 | -33 | 0.33 | 67 | -99 | 0.34 | 1 | -53 | 0.39 | 47 | -100 | 0.37 | 1 |
| | 5 | -100 | -56 | 0.54 | 44 | -101 | 0.54 | 1 | -81 | 0.58 | 19 | -101 | 0.59 | 1 |
| | 10 | -100 | -72 | 0.63 | 28 | -101 | 0.63 | 1 | -94 | 0.67 | 6 | -101 | 0.67 | 1 |
| | 50 | -99 | -92 | 0.74 | 7 | -99 | 0.74 | 0 | -99 | 0.78 | 0 | -99 | 0.78 | 0 |
| 3000 | 1 | -100 | -20[d] | 0.32 | 80 | -100[d] | 0.32 | 0 | | | | | | |
| | 2 | -100 | -34 | 0.50 | 66 | -101 | 0.50 | 1 | -54 | 0.52 | 45 | -101 | 0.53 | 2 |
| | 5 | -100 | -56 | 0.71 | 43 | -101 | 0.71 | 1 | -82 | 0.72 | 18 | -102 | 0.74 | 2 |
| | 10 | -99 | -72 | 0.80 | 28 | -100 | 0.80 | 1 | -93 | 0.82 | 6 | -100 | 0.83 | 1 |
| | 50 | -99 | -91 | 0.88 | 8 | -98 | 0.88 | 1 | -98 | 0.90 | 1 | -98 | 0.90 | 0 |
| 4000 | 1 | -98 | -19[d] | 0.37 | 80 | -96[d] | 0.37 | 2 | | | | | | |
| | 2 | -100 | -33 | 0.59 | 67 | -99 | 0.59 | 1 | -53 | 0.63 | 47 | -99 | 0.63 | 1 |
| | 5 | -100 | -56 | 0.83 | 44 | -101 | 0.83 | 1 | -82 | 0.85 | 19 | -102 | 0.86 | 1 |
| | 10 | -100 | -72 | 0.91 | 28 | -100 | 0.91 | 1 | -93 | 0.91 | 7 | -101 | 0.93 | 1 |
| | 50 | -100 | -93 | 0.96 | 7 | -100 | 0.96 | 0 | -100 | 0.96 | 0 | -100 | 0.97 | 0 |

For compounds with a low ICC (e.g., 0.2), doubling the number of biospecimens per subject can be more efficient (and is cheaper) than doubling the number of subjects

(Perrier, *Epidemiology*, 2016)

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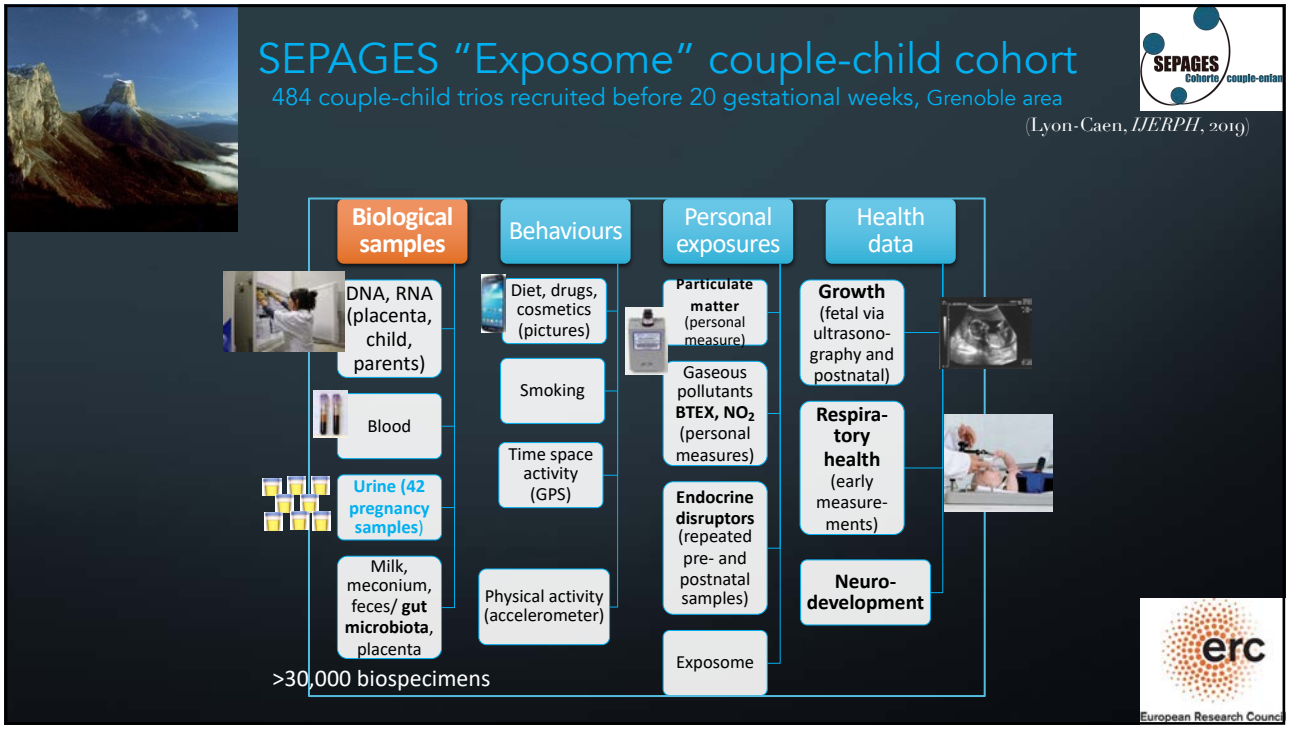
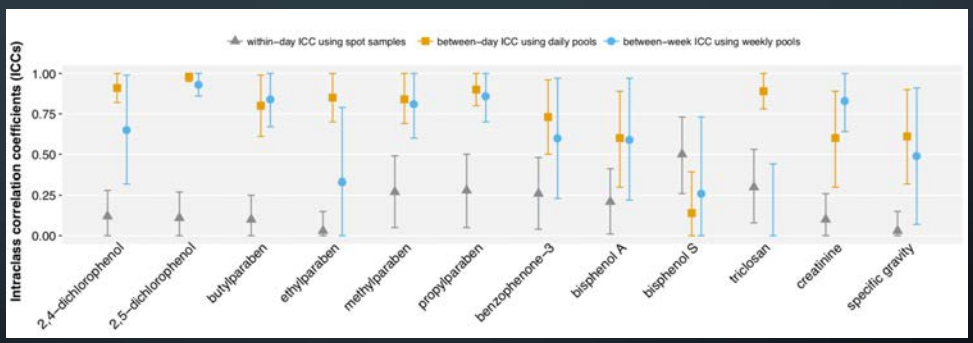



95

## Within-, between-day and between-week variability of phenols during pregnancy

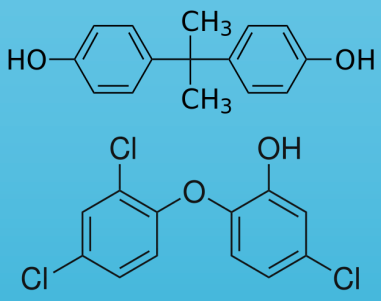
8 women with repeated measurements from SEPAGES-feasibility study




(Vernet, *EHP*, 2018)

96

# F. Phenols (bisphenols, triclosan) and health

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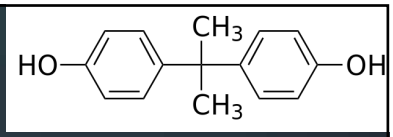
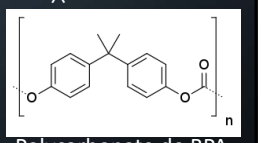
## Bisphenol A (BPA)



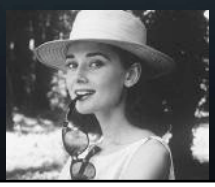
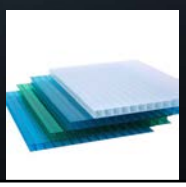

- 1891: Chemical synthesis of BPA (A Dianin)
- 1930s: Identification of BPA's estrogenic properties
  - Not used as a drug because DES was then identified as a more potent synthetic oestrogen
- End of 20th Century: 2/3 used to synthetise polycarbonate (transparent plastic used in glasses, food containers…), in epoxy-ester and vinyl-ester resins (lining of cans)(25-30% of BPA production), thermal inks …
- World production: 2.2 million t in 2016



Polycarbonate de BPA

- Toxicokinetics: Half-life <24 h
- Reaches the placenta in the case of exposure during pregnancy (Grandin, *Env Int*, 2018)

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0013-7227/93/1326-2279$03.00/0
Endocrinology


Vol. 132, No. 6
Printed in U.S.A.

# Bisphenol-A: An Estrogenic Substance Is Released from Polycarbonate Flasks during Autoclaving*

ARUNA V. KRISHNAN, PETER STATHIS, SUZANNE F. PERMUTH, LASZLO TOKES, AND DAVID FELDMAN

*Division of Endocrinology, Stanford University School of Medicine, Stanford, California 94305; and the Institute of Analytical Research (L.T.), Syntex Discovery Research, Palo Alto, California 94304*

**ABSTRACT**

In studies to determine whether *Saccharomyces cerevisiae* produced estrogens, the organism was grown in culture media prepared using distilled water autoclaved in polycarbonate flasks. The yeast-conditioned media showed the presence of a substance that competed with [$^3$H]estradiol for binding to estrogen receptors (ER) from rat uterus. However, it soon became clear that the estrogenic substance in the conditioned media was not a product of the yeast grown in culture, but was leached out of the polycarbonate flasks during the autoclaving procedure. [$^3$H]Estradiol displacement activity was monitored by ER proximately 1:2000 that of estradiol for ER. In functional assays, BPA (10–25 nM) induced progesterone receptors in cultured human mammary cancer cells (MCF-7) at a potency of approximately 1:5000 compared to that of estradiol. The BPA effect on PR induction was blocked by tamoxifen. In addition, BPA (25 nM) increased the rate of proliferation of MCF-7 cells assessed by [$^3$H]thymidine incorporation. Thus, BPA exhibited estrogenic activity by both RRA and two functional bioresponse assays. Finally, MCF-7 cells grown in media prepared with water autoclaved in polycarbonate exhibited higher progesterone receptor levels than cells grown in media prepared with water autoclaved in glass, suggesting an estrogenic effect of the water auto-

(Krishnan, *Endocrinology*, 1993)

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# BPA controversy between regulatory and academic toxicology (2000s-2022)

TOXICOLOGICAL SCIENCES 104(2), 362–384 (2008)
doi:10.1093/toxsci/kfn084
Advance Access publication April 29, 2008

## Two-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD-1 (Swiss) Mice

Rochelle W. Tyl,*[,1] Christina B. Myers,* Melissa C. Marr,* Carol S. Sloan,* Nora P. Castillo,* M. Michael Veselica,* John C. Seely,† Stephen S. Dimond,‡ John P. Van Miller,§ Ronald N. Shiotsuka,¶ Dieter Beyer,‖ Steven G. Hentges,‖‖ and John M. Waechter, Jr‖‖‖

*Health Sciences Unit, RTI International, Research Triangle Park, North Carolina 27709; †Experimental Pathology Laboratories, Inc., Research Triangle Park, North Carolina 27709; ‡SABIC Innovative Plastics, Pittsfield, Massachusetts 02101; §Toxicology/Regulatory Services, Inc., Charlottesville, Virginia 22911; ¶Bayer Material Science, Pittsburgh, Pennsylvania 15205; ‖Bayer Healthcare AG, Wuppertal, Germany D-42096; ‖‖American Chemistry Council, Arlington, Virginia 22209; and ‖‖‖The Dow Chemical Co., Midland, Michigan 48674

"At lower doses (0.018-30 ppm), there were no treatment-related effects and no evidence of nonmonotonic dose-response curves for any parameter. The systemic no observable effect level (NOEL) was 30 ppm BPA (approximately 5 mg/kg/day); the reproductive/developmental NOEL was 300 ppm (approximately 50 mg/kg/day). Therefore, BPA is not considered a selective reproductive or developmental toxicant in mice."

(Tyl, *Tox Sci*, 2008)

"BPA can be a weak estrogen mimic, and is ubiquitous in humans (in 93% US population; ...). European/US food/drug agencies conclude that current BPA levels present no risk to the general population (some include infants/children); basic endocrine disruption (ED) researchers state that entire populations are at risk from these levels. Basic ED researchers report reproductive/developmental effects from perinatal BPA exposure in mice at very low doses, e.g. 2 ng/g body weight (0.002 mg/kg body weight), with non-monotonic dose-response (NMDR) curves, using few animals per group and few groups; contract research organizations, in good laboratory practice- and guideline-compliant large studies in rats and mice, report no low-dose effects or NMDR curves. The argument rages!"

(Tyl, *Semin Fetal Neonatal Med*, 2014)

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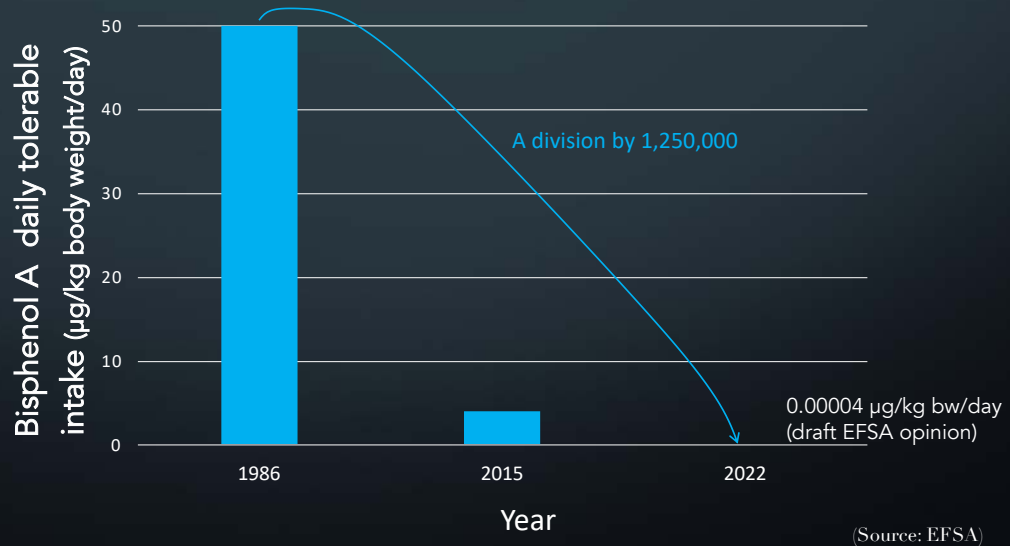
## Evolution of the bisphenol A Daily Tolerable Intake (EFSA, EU)




(Source: EFSA)

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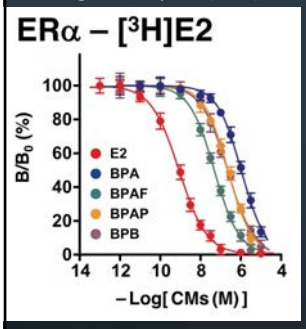
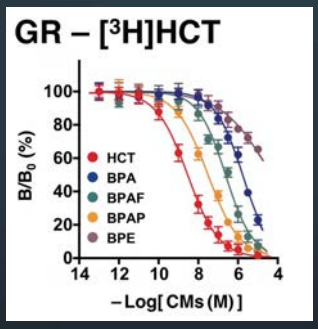
## Bisphenol A affinity to nuclear receptors

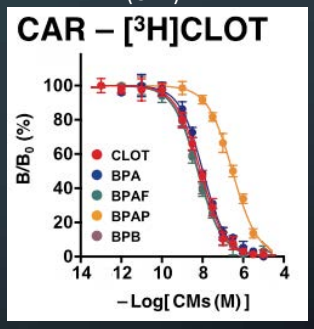
Estrogen receptor (ERα)



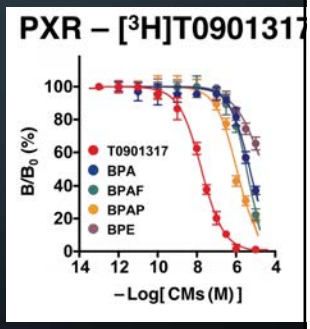

Glucocorticoid receptor (GR)

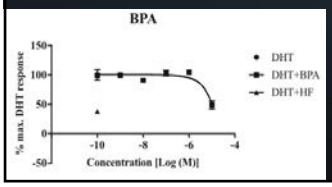



Constitutive androstane receptor (CAR)




Pregnane-X receptor (PXR)




BPA also has an anti-androgenic activity.
(Park, *Env Poll*, 2020)

(Liu, *Tox Appl Pharmacol*, 2017)

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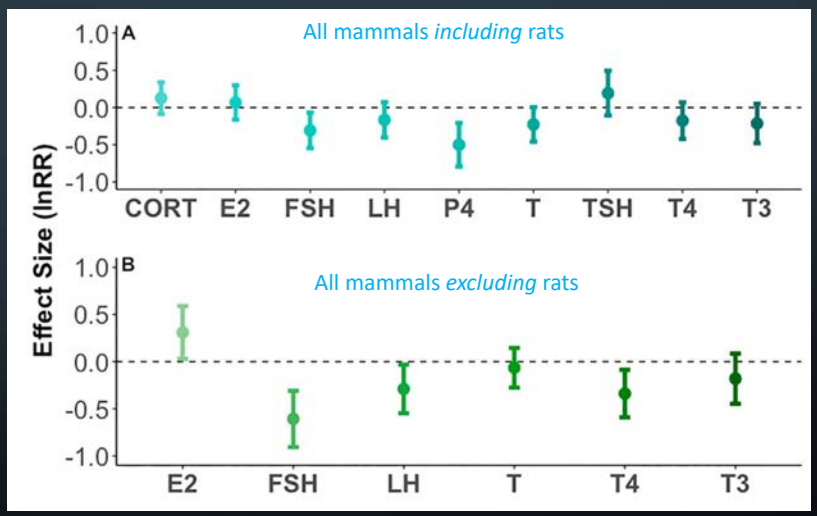
# Effects of bisphenols on hormone levels in mammals (meta-analysis)




(Rubin, *Sc Tot Env*, 2022)

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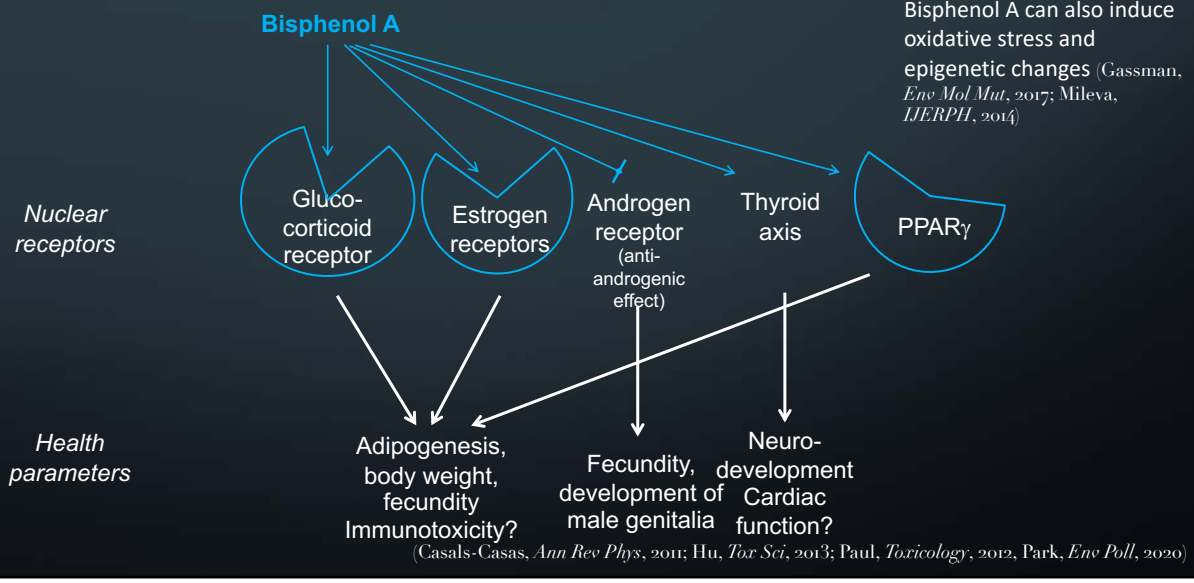
# Interaction of bisphenol A with endocrine modalities




(Casals-Casas, *Ann Rev Phys*, 2011; Hu, *Tox Sci*, 2013; Paul, *Toxicology*, 2012, Park, *Env Poll*, 2020)

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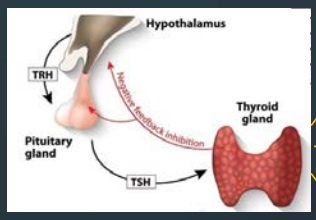
## Thyroid hormone has different roles in different time periods and can act non-linearly at very low concentration

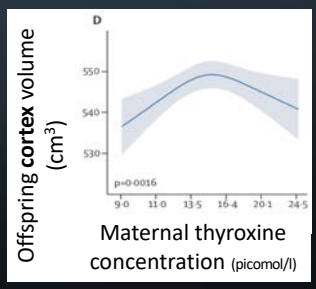
*In adults*

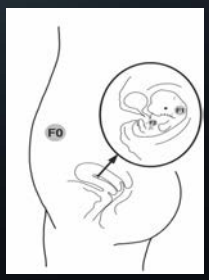
Controls body temperature
Controls heart and breathing rates
Mood, anxiety, concentration
Metabolism
…

*During development*

Growth
Fetal brain development




(Korevaar, *Lancet Diab Endo*, 2016)

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## Possible hazards of bisphenol A according to EFSA 2022 synthesis

### Metabolic disorders
(ALAN effects, unless otherwise indicated)

Obesity
Fat deposition in the liver
Glucose regulation
Blood lipids
Uric acid (likely)
Type 1 diabetes mellitus
Type 2 diabetes mellitus

### Carcinogenicity

Mammary gland histology (ALAN)
Prostate histology (ALAN)
Uterus histology (likely)

### Reprotoxicity

Female fertility (likely)
Male fertility (likely)

### Neurotoxicity
(all effects judged to be *likely*)

Neuromorphology (number of neurons in hippocampus, other)
Nervous system functionality (acetylcholinesterase activity)
Behavior (anxiety/emotionality; learning/memory)

### Immunotoxicity
(all effects judged to be *likely*)

Allergic lung inflammation
Cellular immunity
Inflammation

*ALAN*: As Likely As Not

(EFSA, 2022)

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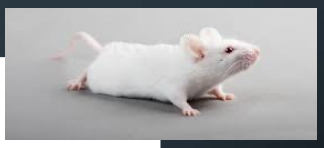
# Bisphenol A perinatal exposure and offspring anxiety in rodents



Toxicology
Volume 378, 1 March 2017, Pages 107–113

Anxiety like behavior due to perinatal exposure to Bisphenol-A is associated with decrease in excitatory to inhibitory synaptic density of male mouse brain

Dhiraj Kumar, M.K. Thakur


Effect of perinatal exposure to BPA on the behaviour of 8 weeks postnatal male mice in Open Field test (A) Path tracking of mice (B)

(Kumar, *Toxicology*, 2017)

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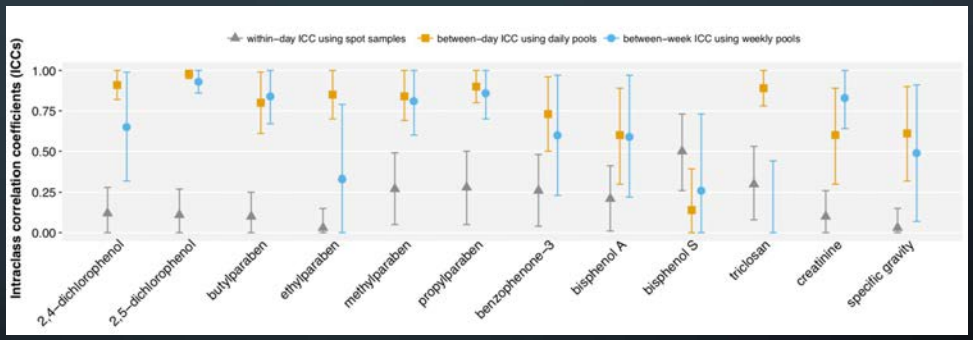
# Within-, between-day and between-week variability of phenols during pregnancy

8 women with repeated measurements from SEPAGES-feasibility study




(Vernet, *EHP*, 2018)

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# Phenols (BPA) pregnancy levels and offspring behavior – *Results from epidemiological cohorts*

*(reviewed by Mustieles, 2015)*

| | Age (yrs) | n | Assessment of behaviour | Main result |
|---|---|---|---|---|
| **Braun 2011** | 2 | 244 boys and girls | Behavioural assessment for children (BASC-2) | No clear association |
| **Braun 2011** | 3 | 237 boys and girls | Behavioural assessment for children (BASC-2) Behaviour Rating Inventory of Executive Function-Preschool (BRIEF) | Decreased hyperactivity scores |
| **Perera 2012** | 3 to 5 | 198 boys and girls | Child Behaviour Checklist (CBCL) | Increased internalizing, externalizing, emotionally reactive, withdrawn/depressed and aggressive behaviour scores |
| **Casas 2015** | 4 and 7 | 438 boys and girls | McCarthy Scales of Children's Abilities (MSCA) ADHD Criteria of DSM-IV | Increased hyperactivity and inattention scores (4 years) |
| **Roen 2015** | 7 to 9 | 250 boys and girls | Child Behaviour Check List (CBCL) | Increased internalizing, externalizing, anxious/depressed, withdrawn/depressed, somatic complaints, thought problems, rule-breaking and aggressive behaviour scores |
| **Harley 2013** | 7 to 9 | 292 boys and girls | Behaviour Assessment System for Children (BASC-2) Conners' ADHD/DSM-IV Scales (CADS) | Increased internalizing, aggressive behaviour, depression, anxiety and somatization problem scores. |
| **Evans 2014** | 6 to 10 | 153 boys and girls | Child Behaviour Check List ( CBCL) | Increased internalizing, externalizing, somatic, oppositional/defiant problem scores |
| **Perez-Lobato 2016** | 9 to 11 | 300 boys and girls | Child Behaviour Check List (CBCL) | Increased somatic, thought and social problems |
| **Perera 2016** | 10 to 12 | 241 boys and girls | Revised Children's Manifest Anxiety Scale (RCMAS) Children's Depression Rating Scale (CDRS) | Increased symptoms of depression and anxiety |

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# Exposure to phenols, phthalates and behaviour at 3 years of age in humans (Sépages cohort)

N = 227 mother-boy and 189 mother-girl pairs from the SEPAGES cohort.
Exposure assessed from 42 pooled repeated within-subject pregnancy urinary samples.

WQS: Weighted Quantile Sum;
CI: Confidence Interval; SE: Standard Error; MEP: Monoethyl phthalate; MiBP: Mono-isobutyl phthalate; MnBP: Mono-n-butyl phthalate; MBzP: Mono-benzyl phthalate; ohMPHP: 6-hydroxy-mono-propyl-heptyl phthalate; ΣDEHP: Molar sum of di(2-ethylhexyl) phthalate; ΣDiNP: Molar sum of diisononyl phthalate; ΣDiNCH Molar sum of di(isononyl)cyclohexane-1,2-dicarboxylate.
a Models adjusted on maternal age at conception, level of education, body mass index before pregnancy, psychological difficulties during the third trimester, parity(, child sex) and specific gravity.

(Guilbert, *Env Int*, 2021)

| CBCL score | Child sex | Effect estimate (95 %CI)[a, b] | Biomarkers included in the WQS index[c, d] | Average weight ± SE |
|---|---|---|---|---|
| Externalizing score | Boys and girls together | 1.95 (0.20, 3.70)** | Benzophenone-3 | 0.17 ± 0.09 |
| | | | ΣDiNP | 0.15 ± 0.08 |
| | | | Triclosan | 0.14 ± 0.08 |
| | | | Ethylparaben | 0.12 ± 0.08 |
| | | | MBzP | 0.12 ± 0.08 |
| | | | Methylparaben | 0.11 ± 0.07 |
| | | | ΣDiNCH | 0.10 ± 0.07 |
| | | | MEP | 0.10 ± 0.07 |
| | Boys | 1.70 (-0.42, 3.81) | Benzophenone-3 | 0.22 ± 0.11 |
| | | | ΣDiNP | 0.19 ± 0.10 |
| | | | Methylparaben | 0.12 ± 0.09 |
| | | | ΣDiNCH | 0.11 ± 0.09 |
| | | | Triclosan | 0.11 ± 0.08 |
| | | | Ethylparaben | 0.10 ± 0.08 |
| | | | Propylparaben | 0.08 ± 0.08 |
| | | | ohMPHP | 0.07 ± 0.06 |
| | Girls | 3.67 (1.24, 6.10)** | Bisphenol A | 0.18 ± 0.09 |
| | | | Triclosan | 0.17 ± 0.09 |
| | | | MEP | 0.15 ± 0.09 |
| | | | MnBP | 0.13 ± 0.09 |
| | | | Ethylparaben | 0.10 ± 0.07 |
| | | | MBzP | 0.10 ± 0.07 |
| | | | Methylparaben | 0.09 ± 0.07 |
| | | | Benzophenone-3 | 0.08 ± 0.07 |
| Internalizing score | Boys and girls together | 1.31 (0.05, 2.58)** | Methylparaben | 0.20 ± 0.10 |
| | | | MEP | 0.15 ± 0.09 |
| | | | Triclosan | 0.13 ± 0.08 |
| | | | MBzP | 0.12 ± 0.08 |
| | | | ΣDEHP | 0.10 ± 0.08 |
| | | | ΣDiNCH | 0.09 ± 0.07 |
| | | | MnBP | 0.08 ± 0.07 |
| | | | Propylparaben | 0.08 ± 0.07 |
| | | | Bisphenol A | 0.06 ± 0.06 |
| | Boys | 1.17 (-0.50, 2.84) | Methylparaben | 0.42 ± 0.15 |
| | | | Triclosan | 0.22 ± 0.13 |
| | | | ΣDiNP | 0.17 ± 0.10 |
| | | | MnBP | 0.10 ± 0.08 |
| | | | ΣDiNCH | 0.10 ± 0.08 |
| | Girls | 2.47 (0.60, 4.33)** | MEP | 0.19 ± 0.10 |
| | | | MBzP | 0.19 ± 0.10 |
| | | | MnBP | 0.16 ± 0.09 |
| | | | Bisphenol A | 0.11 ± 0.08 |
| | | | Ethylparaben | 0.09 ± 0.08 |
| | | | Methylparaben | 0.09 ± 0.07 |
| | | | Propylparaben | 0.09 ± 0.07 |
| | | | ΣDEHP | 0.07 ± 0.06 |

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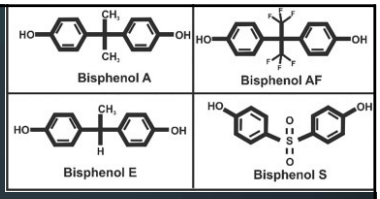
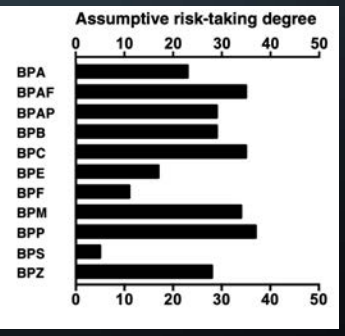
## *A dangerous family?* Other bisphenols have some affinity to several nuclear receptors…




| BPs \ NRs | LXRα | LXRβ | PXR | CAR | ERα | ERβ | ERRγ | GR | PR | AR |
|---|---|---|---|---|---|---|---|---|---|---|
| BPA | + (1+) | + (1+) | ++ (2+) | +++++ (5+) | ++ (2+) | +++ (3+) | ++++++ (6+) | ++ (2+) | + (1+) | |
| BPAF | + (1+) | + (1+) | ++ (2+) | ++++++ (6+) | +++++ (5+) | +++++ (5+) | ++++ (4+) | ++++ (4+) | ++ (2+) | ++ (2+) |
| BPAP | | | ++ (2+) | ++++ (4+) | ++++ (4+) | +++++ (5+) | ++++ (4+) | +++++ (5+) | +++ (3+) | + (1+) |
| BPB | | | ++ (2+) | ++++++ (6+) | ++++ (4+) | +++++ (5+) | ++++++ (6+) | +++ (3+) | ++ (2+) | + (1+) |
| BPC | | | + (1+) | +++++ (5+) | ++++++ (6+) | ++++++ (6+) | +++++ (5+) | +++ (3+) | ++ (2+) | +++ (3+) |
| BPE | | | + (1+) | ++++ (4+) | ++ (2+) | ++ (2+) | ++++++ (6+) | + (1+) | | + (1+) |
| BPF | | | + (1+) | | ++ (2+) | ++ (2+) | ++++ (4+) | + (1+) | | + (1+) |
| BPM | +++(3+) | ++ (2+) | ++ (2+) | ++ (2+) | ++++ (4+) | ++++ (4+) | + (1+) | ++ (2+) | § | § |
| BPP | ++++ (4+) | +++ (3+) | ++ (2+) | + (1+) | ++++ (4+) | ++++ (4+) | +++ (3+) | ++++ (4+) | +++ (3+) | +++ (3+) |
| BPS | | | + (1+) | | + (1+) | + (1+) | ++ (2+) | | § | § |
| BPZ | | | ++ (2+) | ++++ (4+) | +++++ (5+) | ++++ (4+) | +++++ (5+) | ++++ (4+) | ++ (2+) | ++ (2+) |




(Note that disruption of the thyroid axis is not considered here)

(Liu, *Tox Appl Pharmacol*, 2017)

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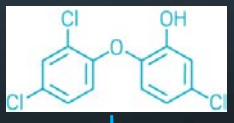
## Production and toxicokinetics of triclosan

- Synthetic chemical produced for its antimicrobial/antiseptic properties
- Antimicrobial efficiency is debated
- Worldwide production: 10 million pounds (2015)
- Very long persistence in anaerobic soil, but not in aerobic conditions
- Toxicological half-life (humans): short (days)
- Several metabolites in the body or environment




2,4 DCP (endocrine disruptor)

Dioxin-like compounds

Chloroform (in drinking water)

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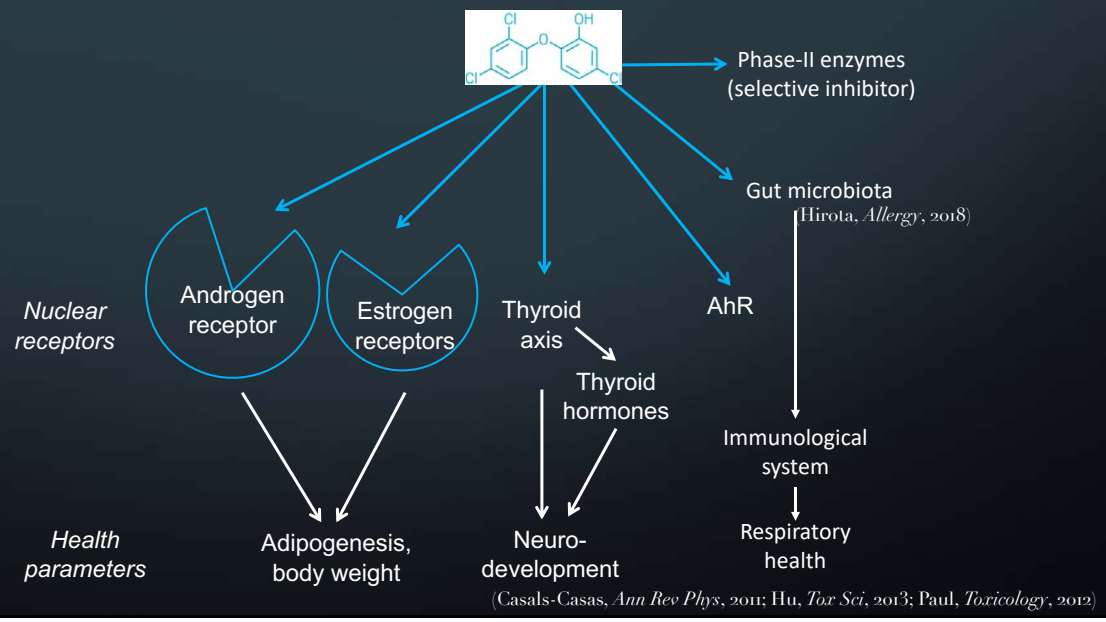
## Effects of triclosan at the molecular and subclinical levels




(Casals-Casas, *Ann Rev Phys*, 2011; Hu, *Tox Sci*, 2013; Paul, *Toxicology*, 2012)

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## Suspected health effects of triclosan

- Allergy and asthma (Clayton, *EHP*, 2011)
- Alteration of the microbiome (Hirota, *Allergy*, 2018)
- Fetal growth (Philippat, *Epidemiology*, 2014)
- Obesity
- Neurodevelopment
- Fecundity (Hipwell, *Hum Reprod Update*, 2018)

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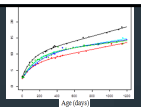
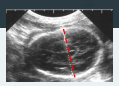
## Adjusted* association between phenol concentrations and biparietal diameter








*Adjustment factors: *Prenatal growth:* maternal and paternal height and weight, maternal active and passive smoking, maternal education level, parity, gestational age at measurement and recruitment center.

*For postnatal growth:* maternal and paternal height and weight, maternal active and passive smoking, maternal education level, recruitment center, parity and breastfeeding.

(Philippat, *Epidemiology*, 2014)

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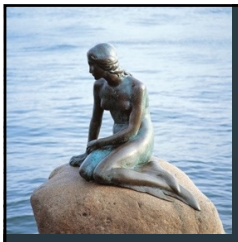
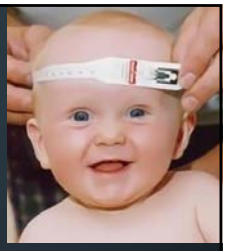
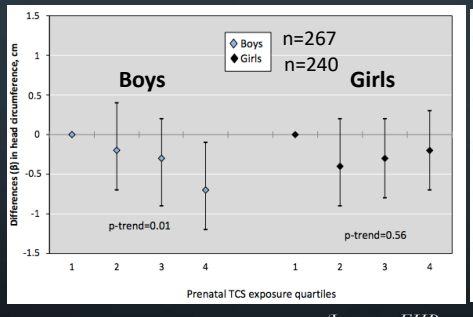


## Triclosan pregnancy levels and head circumference in other birth cohorts

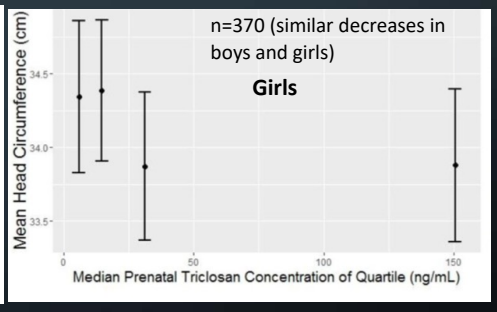


Odense cohort (Denmark)

MIREC cohort (USA)




(Lassen, *EHP*, 2016)




(Etzel, *Env Res*, 2017)

No evidence of association with head circumference in Sépages cohort (based on repeated within-subject biospecimen pooling) (Jedynak, *Epidemiology*, in press)

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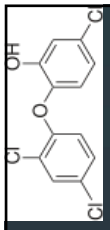
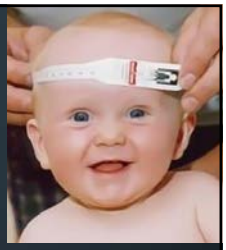



## Plausibility and possible implications of an association between triclosan and fetal head circumference



- Eden cohort and Odense Danish birth cohort suggested deleterious associations of triclosan with measures of head circumference at birth (Philippat, *Epidemiology*, 2014; Lassen, *EHP*, 2016)
- (Slightly) reduced head circumference is not directly an adverse clinical outcome
- Head circumference is correlated with brain volume (Bartholomeusz, *Neuroped*, 2002)
- *In vitro studies:* Anti-androgenic properties, disruption of the thyroid axis (Axelstat, *Food Chem Toxicol*, 2013)
- Thyroid hormones control fetal brain development

**Could pregnancy triclosan exposure alter neurodevelopment?**

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## Exposure to phenols, phthalates and behaviour at 3 years of age in humans

N = 227 mother-boy and 189 mother-girl pairs from the SEPAGES cohort.
Exposure assessed from pooled repeated within-subject pregnancy urinary samples.

WQS: Weighted Quantile Sum;
CI: Confidence Interval; SE: Standard Error; MEP: Monoethyl phthalate; MiBP: Mono-isobutyl phthalate; MnBP: Mono-n-butyl phthalate; MBzP: Mono-benzyl phthalate; ohMPHP: 6-hydroxy-mono-propyl-heptyl phthalate; ΣDEHP: Molar sum of di(2-ethylhexyl) phthalate; ΣDiNP: Molar sum of diisononyl phthalate; ΣDiNCH Molar sum of di(isononyl)cyclohexane-1,2-dicarboxylate.
a Models adjusted on maternal age at conception, level of education, body mass index before pregnancy, psychological difficulties during the third trimester, parity(, child sex) and specific gravity.

(Guilbert, *Env Int*, 2021)

| CBCL score | Child sex | Effect estimate (95 %CI)[a, b] | Biomarkers included in the WQS index[c, d] | Average weight ± SE |
|---|---|---|---|---|
| Externalizing score | Boys and girls together | 1.95 (0.20, 3.70)** | Benzophenone-3 | 0.17 ± 0.09 |
| | | | ΣDiNP | 0.15 ± 0.08 |
| | | | Triclosan | 0.14 ± 0.08 |
| | | | Ethylparaben | 0.12 ± 0.08 |
| | | | MBzP | 0.12 ± 0.08 |
| | | | Methylparaben | 0.11 ± 0.07 |
| | | | ΣDiNCH | 0.10 ± 0.07 |
| | | | MEP | 0.10 ± 0.07 |
| | Boys | 1.70 (-0.42, 3.81) | Benzophenone-3 | 0.22 ± 0.11 |
| | | | ΣDiNP | 0.19 ± 0.10 |
| | | | Methylparaben | 0.12 ± 0.09 |
| | | | ΣDiNCH | 0.11 ± 0.09 |
| | | | Triclosan | 0.11 ± 0.08 |
| | | | Ethylparaben | 0.10 ± 0.08 |
| | | | Propylparaben | 0.08 ± 0.08 |
| | | | ohMPHP | 0.07 ± 0.06 |
| | Girls | 3.67 (1.24, 6.10)** | Bisphenol A | 0.18 ± 0.09 |
| | | | Triclosan | 0.17 ± 0.09 |
| | | | MEP | 0.15 ± 0.09 |
| | | | MnBP | 0.13 ± 0.09 |
| | | | Ethylparaben | 0.10 ± 0.07 |
| | | | MBzP | 0.10 ± 0.07 |
| | | | Methylparaben | 0.09 ± 0.07 |
| | | | Benzophenone-3 | 0.08 ± 0.07 |
| Internalizing score | Boys and girls together | 1.31 (0.05, 2.58)** | Methylparaben | 0.20 ± 0.10 |
| | | | MEP | 0.15 ± 0.09 |
| | | | Triclosan | 0.13 ± 0.08 |
| | | | MBzP | 0.12 ± 0.08 |
| | | | ΣDEHP | 0.10 ± 0.08 |
| | | | ΣDiNCH | 0.09 ± 0.07 |
| | | | MnBP | 0.08 ± 0.07 |
| | | | Propylparaben | 0.08 ± 0.07 |
| | | | Bisphenol A | 0.06 ± 0.06 |
| | Boys | 1.17 (-0.50, 2.84) | Methylparaben | 0.42 ± 0.15 |
| | | | Triclosan | 0.22 ± 0.13 |
| | | | ΣDiNP | 0.17 ± 0.10 |
| | | | MnBP | 0.10 ± 0.08 |
| | | | ΣDiNCH | 0.10 ± 0.08 |
| | Girls | 2.47 (0.60, 4.33)** | MEP | 0.19 ± 0.10 |
| | | | MBzP | 0.19 ± 0.10 |
| | | | MnBP | 0.16 ± 0.09 |
| | | | Bisphenol A | 0.11 ± 0.08 |
| | | | Ethylparaben | 0.09 ± 0.08 |
| | | | Methylparaben | 0.09 ± 0.07 |
| | | | Propylparaben | 0.09 ± 0.07 |
| | | | ΣDEHP | 0.07 ± 0.06 |

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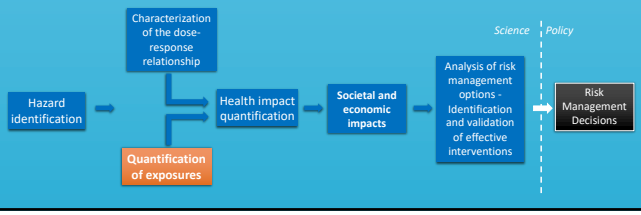
# G. Social inequalities in exposure

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# Social exposure gradients in exposure to select endocrine disruptors

| DES | PCBs | PFAS | DDT, Bisphenol A |
|---|---|---|---|
| Mostly an issue of "white women" in the USA | Exposure possibly increased in rather wealthy populations (fish and dairy products as sources of exposure) | Variable according to compound. PFOA and PFOS levels tend to increase with income in USA | |

Exposure still widespread in the general population
(Santé publique France, 2019)

(Montazeri, *Int J Hyg Env Heal*, 2019
Tyrell, *Env Health*, 2013)

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# Bisphenol A levels in children in France (2014-2016)

(Detection rate: 100%)

**Distribution du BPA total (µg/L) des enfants âgés de 6 à 17 ans, France continentale (2014-2016)**

| | n | MG | IC 95 % MG | P10 | P25 | P50 | P75 | P90 | P95 | IC 95 % P95 |
|---|---|---|---|---|---|---|---|---|---|---|
| Total | 500 | **2,26** | [2,05 ; 2,50] | 0.91 | 1.35 | 2,12 | 3,71 | 5,56 | 7,09 | [6,03 ; 8,72] |

| Variable qualitative | Effectif dans l'échantillon (% dans la population) | BPA |
|---|---|---|
| **Sexe*** | | |
| Garçon | 258 (50,6) | |
| Fille | 242 (49,4) | 1,49 [-16,5 ; 23,3] |
| **Etat matrimonial du référent (en couple)*** | | |
| Oui | 447 (81,1) | |
| Non | 53 (18,9) | -1,74 [-28,3 ; 34,6 |
| **Ressenti sur l'état financier du foyer*** | | |
| « Vous êtes à l'aise » | 102 (14,2) | 0 (reference) |
| « Ça va » | 188 (33,6) | 13,2 [-9,5 ; 41,6] |
| « C'est juste » | 54 (11,1) | 22,5 [-9,3 ; 65,6] |
| « Il faut faire attention/difficile/avec des dettes » | 156 (41,1) | 19,7 [-4,9 ; 50,8] |

(Santé publique France, 2019)

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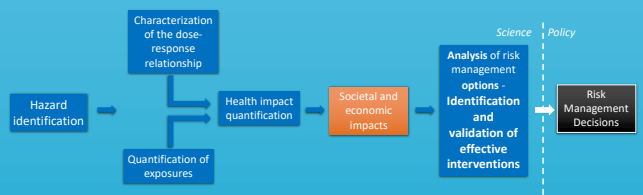
# H. Health and societal impacts

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# Examples of (un)/official EDs

- Drugs
  - DES, ethynyl-oestradiol…
- Chemicals found in consumers products
  - Phthalates (e.g. DEHP)
  - Phenols (Bisphenol A)
  - Flame retardants (PCB, PBDE…)
  - Perfluorinated compounds (PFOA, PFOS…)
- Combustion by-products
  - Dioxin
- Pesticides
  - Organochlorine pesticides (DDT, chlordecone…)
  - Vinclozolin, linuron
- Phytoestrogens
  - Isoflavones
- Mycotoxins
  - Zearalenone

ECHA EUROPEAN CHEMICALS AGENCY

*Official lists:*

EU substances of very high concern:
12 EDs (BPA, DEHP, nonylphenols…)
UN ED list: 45 substances (parabens…)

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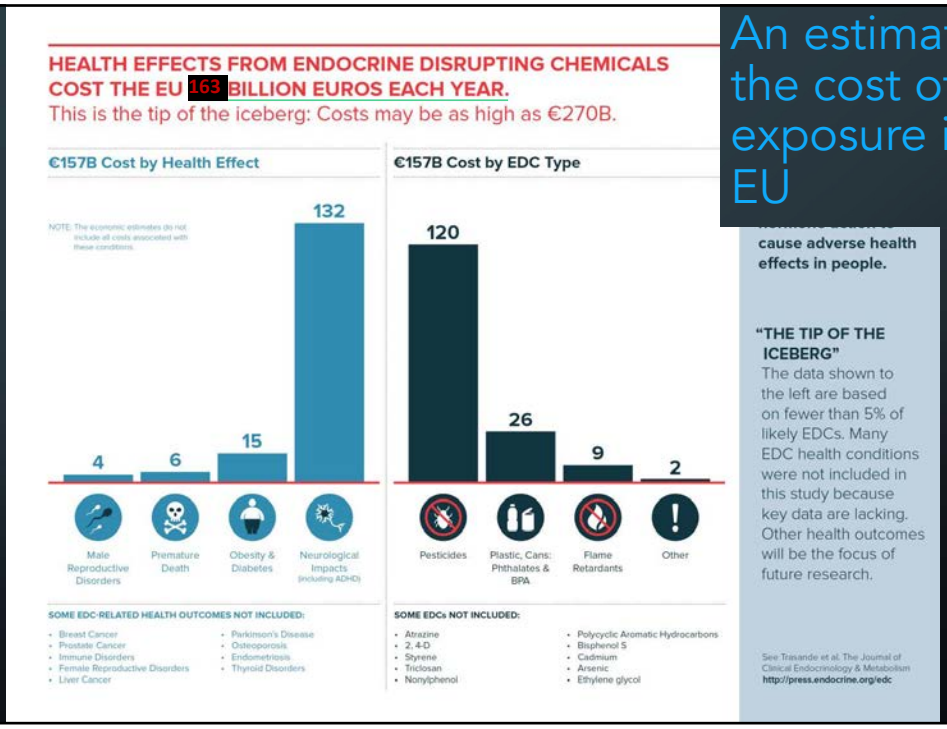
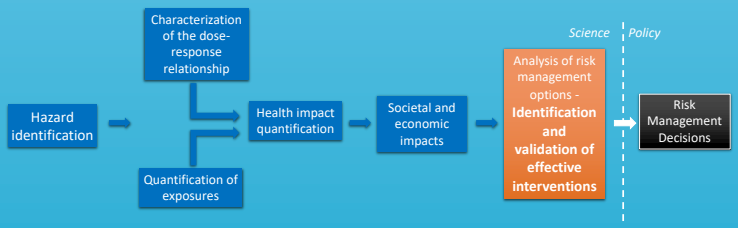
# An estimation of the cost of EDs exposure in the EU




124

# I. Identification of efficient interventions




127

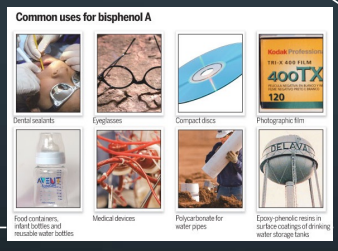
Acting on ED sources as the main option?

***A. Environmental intervention***
(primary or primordial prevention)

***Environment***

Human activities, pollution sources…

Media




***Prevention***

***Therapy***

Many suspected effects of EDs are hard to counter or cure (e.g., decreases in IQ, altered behaviours…)

***Individuals***

Very high number of suspected EDs, present in many sectors (diet, consumers products, air, water, toys, cosmetics…). Exposure is not easy to control for individuals in the absence of compulsory labelling

Behaviours ← ***B. Intervention on behaviours*** (primary prevention)

Exposures

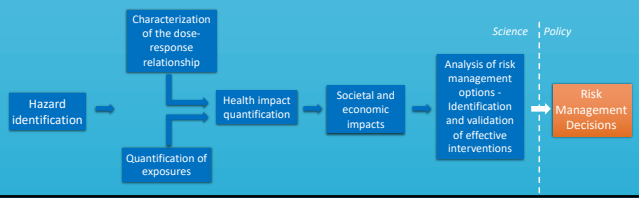
Pre-clinical effects ← ***C. Pre-clinical intervention*** (secondary prevention)

Diseases ← ***D. Clinical intervention*** (tertiary prevention)

Death

128

# J. Risk management

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## Which scientific properties of EDs should be kept in mind to define regulations protective of health?

- Very low dose effects of hormones
- Effects of some recognized endocrine disruptors identified at very low doses (e.g. for bisphenol A)
- Complex feedback mechanisms in the endocrine system and non-monotonic effects of many hormones
- Dose-additivity as a relevant toxicological "default" model

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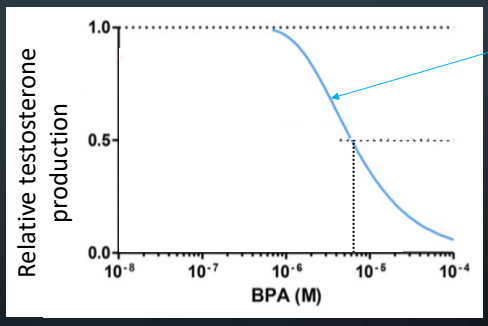
# The biological effect of a compound…




**Effect of bisphenol A (BPA) alone**

A dose of ≅$5x10^{-5}$ M is required to lower testosterone level by 50%

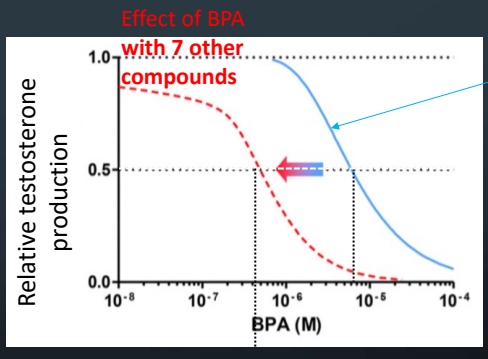
*model: human foetal testis explants.

(Gaudriault, *EHP*, 2017)

131

# The biological effect of a compound…

**can be altered in the case of co-exposure to other compounds**




**Effect of bisphenol A (BPA) alone**

A dose of ≅$5x10^{-5}$ M is required to lower testosterone level by 50%

Dose lowering testosterone by 50% is divided by 10, Compared to when BPA acts alone

*model: human foetal testis explants.

(Gaudriault, *EHP*, 2017)

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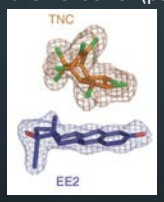
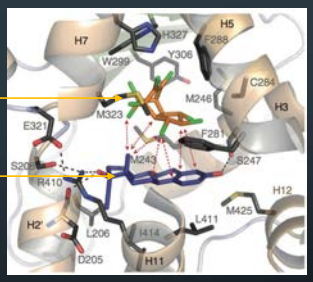
## Examples of issues that could hamper identification of health effects of non-persistent chemicals (1)

- Chemicals could act (mostly) in **synergy** with each other (or with other types of factors)

*Trans*-nonachlor (pesticide)

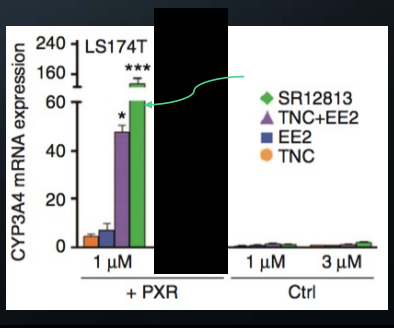



Ethinylestradiol




TNC and EE2 bind together to build a supramolecular ligand acting on PXR nuclear receptor (Delfosse, *Nature Comm*, 2015)

**"1+1=50"**

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## Endocrine disruptors: singularity of a hazard definition

| Carcinogens | Mutagens | Reprotoxicants | EDs | Explosives, inflammable substances | Persistent compounds |
|---|---|---|---|---|---|
| | Mode of action | | Mode of action | | |
| Adverse effect | | Adverse effect | X Adverse effect | Physical or chemical properties | |

…an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.

(WHO/IPCS, 2002)

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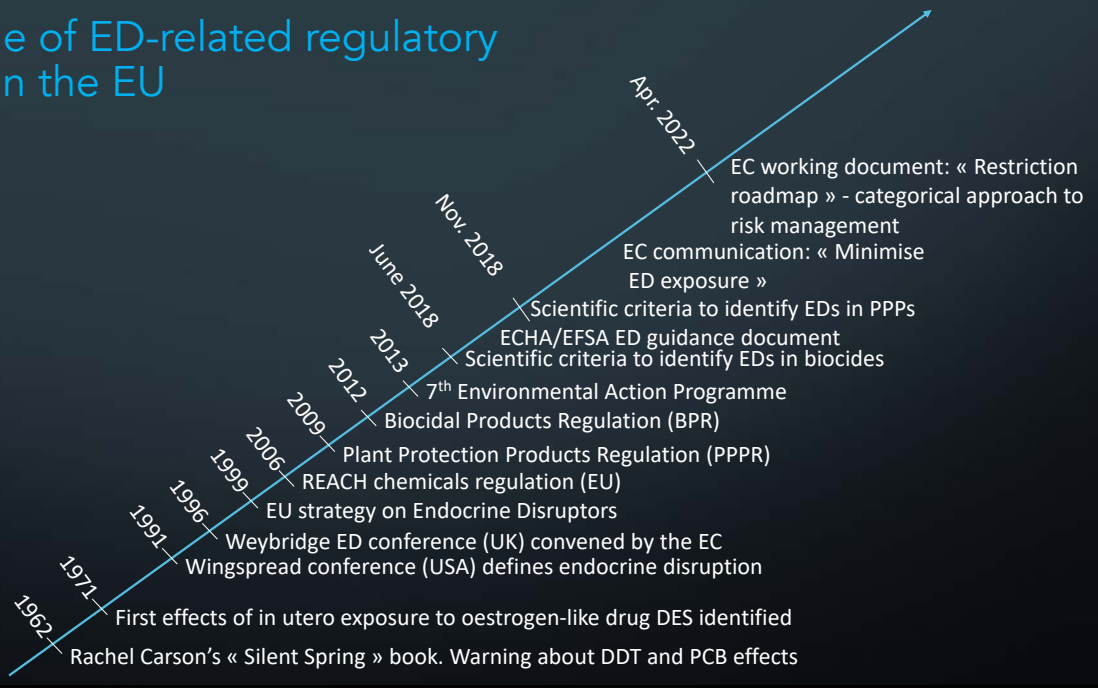
## Timeline of ED-related regulatory action in the EU

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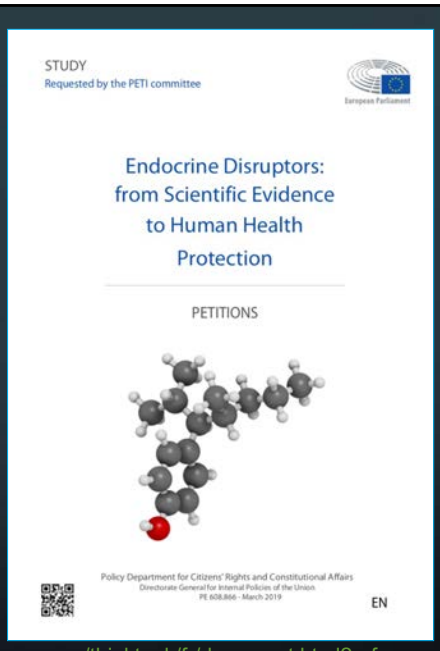


(Demeneix & Slama, 2019)

http://www.europarl.europa.eu/thinktank/fr/document.html?reference=IPOL_STU(2019)608866

POLICY DEPARTMENT CITIZENS' RIGHTS AND CONSTITUTIONAL AFFAIRS

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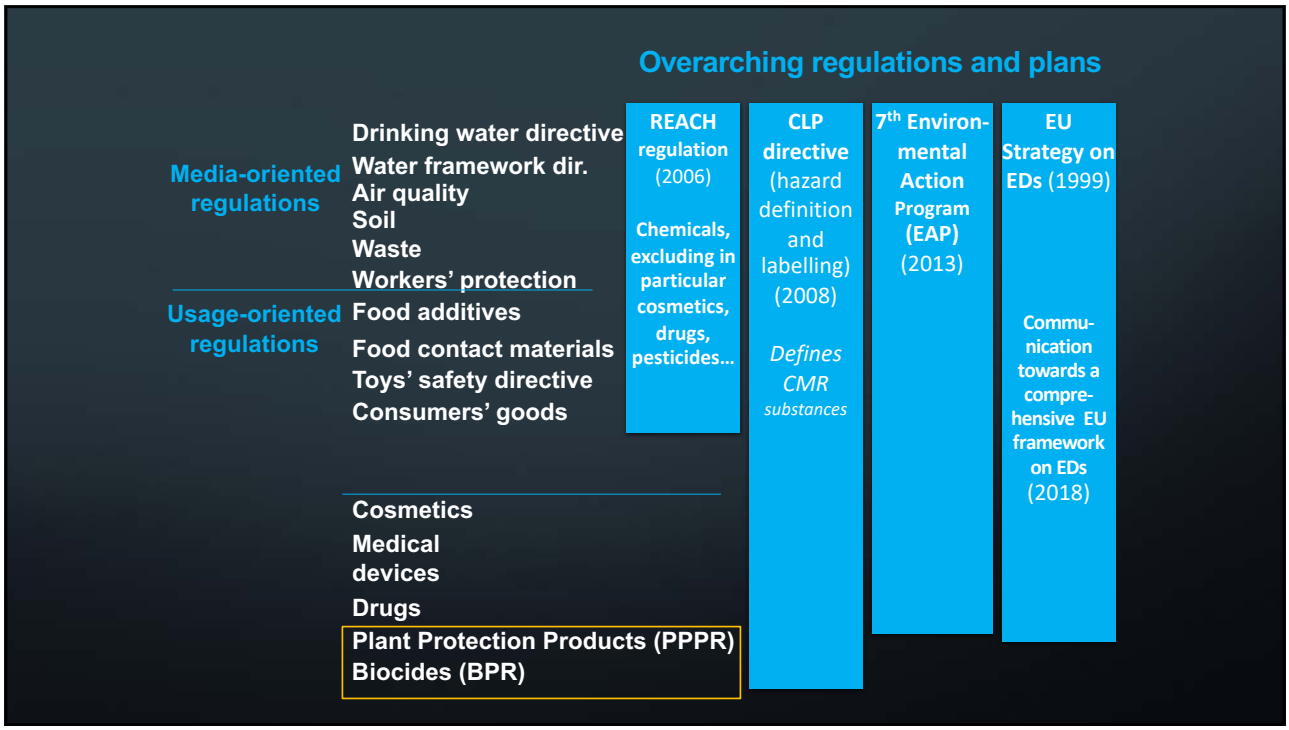


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## Recommendations for efficient regulations to minimise overall exposure of humans and the environment to EDs

| | 5 regulatory steps to protect health | | | | |
|---|---|---|---|---|---|
| | 1. Definition of EDs | 2. Guidance document | 3. Tests | 4. Test requirements | 5. Risk management logic |
| | Y | Y | I | I | Y |
| | Y | Y | | I | Y |
| | N | N | | N | Y |
| | N | N | | N | N |
| | N | N | | N | N |
| | N | N | | N | N |
| | N | N | | N | N |

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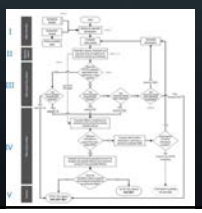
## Sector-specific regulations: the example of the plant protection products regulation (PPPR, 2009)

| 5 regulatory steps to protect health | | | | |
|---|---|---|---|---|
| **1. Definition of EDs** | **2. Guidance document** | **3. Tests** | **4. Test requirements** | **5. Risk management logic** |
| Definition of EDs valid in the context of plant protection products as of 2018 | ECHA/EFSA guidance document (2018) | Existing tests allow to cover some (but not all) ED modalities | Few tests are required in the plant protection products homologation dossiers | Plant protection products containing EDs should not be authorized (PPPR, 2009) |



Limitation

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## Sector-specific regulations: the example of REACH chemicals

| 5 regulatory steps to protect health | | | | |
|---|---|---|---|---|
| **1. Definition of EDs** | **2. Guidance document** | **3. Tests** | **4. Test requirements** | **5. Risk management logic** |
| No definition of EDs legally valid – WHO definition used in practice | No legally valid guidance document | Existing tests allow to cover some (but not all) ED modalities | Very limited requirements when it comes to ED action identification in homologation dossiers | Rather complex and lengthy management logic ("authorization list") |

13 EDs currently on the SVHC list. Scientific evidence suggests that there are more than 13 EDs on the market. All EDs are unlikely to be on REACH SVHC list by 2020 as required by the 7th EAP.

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# Overview of the regulatory framework regarding protection from ED health effects

| | 5 regulatory steps to protect health | | | | |
|---|---|---|---|---|---|
| Sector | 1. Definition of EDs | 2. Guidance document | 3. Tests | 4. Test requirements | 5. Risk management logic |
| Plant protection products | Y | Y | I | I | Y |
| Biocides | Y | Y | | I | Y |
| REACH chemicals | I | I | | I | I |
| Cosmetics | N | N | | N | N |
| Food additives | N | N | | N | N |
| Food packaging | N | N | | N | N |
| Workers' regulations | N | N | | N | N |
| Medical devices | Y | N | | N | Y |

I: Insufficient/needs reinforcement. N: None or very limited. Y: Yes, satisfying existing regulation.

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# Sector-specific regulations: cosmetics (2006)

| 5 regulatory steps to protect health | | | | |
|---|---|---|---|---|
| 1. Definition of EDs | 2. Guidance document | 3. Tests | 4. Test requirements | 5. Risk management logic |
| No definition of EDs | No legally valid guidance document | | Very limited requirements when it comes to ED action identification in homologation dossiers | No management logic specific to EDs (while carcinogens and suspected carcinogens are not authorized) |

➔ Compound-by-compound and "safe thresholds" logic currently applied for EDs in cosmetics

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## Overview of the regulatory framework regarding protection from ED health effects

| | 5 regulatory steps to protect health | | | | |
|---|---|---|---|---|---|
| Sector | 1. Definition of EDs | 2. Guidance document | 3. Tests | 4. Test requirements | 5. Risk management logic |
| Plant protection products | Y | Y | I | I | Y |
| Biocides | Y | Y | | I | Y |
| REACH chemicals | I | I | | I | I |
| Cosmetics | N | N | | N | N |
| Food additives | N | N | | N | N |
| Food packaging | N | N | | N | N |
| Workers' regulations | N | N | | N | N |
| Medical devices | Y | N | | N | Y |

I: Insufficient/needs reinforcement. N: None or very limited. Y: Yes, satisfying existing regulation.

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## The generic approach to risk management

- Automatic trigger of pre-determined risk management measures (e.g. packaging requirements, restrictions, bans, etc.) based on the hazardous properties of the chemical and generic considerations of their exposure (e.g. widespread uses, uses in products destined to children, difficult to control exposure).
- In working documents, the European commission suggested that such a generic approach may be the default option for the main hazard categories (carcinogens, reprotoxicants, mutagens, endocrine disruptors, persistent and bioaccumulative substances, neurotoxicants…) in consumer products.

(European Commission, Oct. 2020 ; April 2022)

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# K. Conclusion

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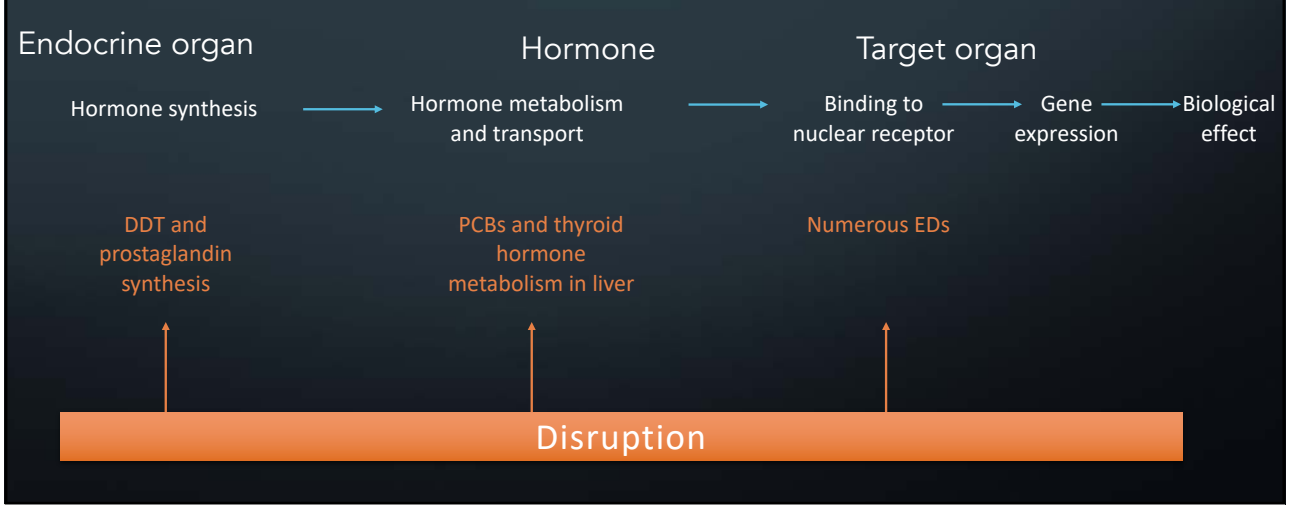
## The endocrine system: *a dynamic view*

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# Conclusion

- Endocrine disruption is a new class of health and environmental hazard identified in the 1990s (WHO, 2002, 2010)
- Endocrine disruption research builds on numerous complementary disciplines and approaches
- Many substances can disrupt the functioning of the endocrine system
  - Disruption can occur at various steps of the endocrine system signalling, from hormone synthesis to metabolism or interaction with endocrine disruptors
  - Disruption can affect any endocrine modality: estrogen, testosterone, thyroid, prostaglandin… pathways
  - A large diversity of adverse effects can be expected from these interactions with the endocrine system, in particular but not only following early-life exposure
  - Of course, substances disrupting the endocrine system can also affect health via other biological mechanisms
  - In the absence of institution officially in charge of ED identification worldwide, there is no unique list of EDs. In the EU, a dozen EDs are officially recognized. Hundreds of suspected EDs have been identified by scientists.
- From a regulatory perspective, endocrine disruption has been identified as a concern in the EU and has entered the regulatory framework at least since the 2010s
  - Currently their regulation is heterogeneous across domains, with compound-by-compound approaches in some and more generic ("group") approaches in others (e.g. pesticides)
  - There is a trend for endocrine disruptors being more often regulated similarly to CMRs, on a "hazard-based" basis
  - Efficient regulation of EDs requires recognized test methods covering all ED modalities

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The relations between human health and the environment in the Anthropocene

# Course overview

COLLÈGE DE FRANCE 1530

**#1 – 31 March 2022**
Inaugural lecture: Causes and external conditions of diseases and health

**#2 - 6 April 2022**
Lead: the oldest enemy of human health

***Seminar:*** **Lead, legal poison: uses and regulations of toxic in the nineteenth century**
**Pr. Judith Rainhorn**, Université Paris-1 Panthéon-Sorbonne (Paris)

**#3 - 13 April 2022**
Fine particulate matter: effects on mortality and cardiovascular and respiratory morbidity

***Seminar:*** Air pollution effects on the central nervous system
**Pr. Marc Weisskopf**, Cecil K. and Philip Drinker Professor of Environmental Epidemiology and Physiology, Harvard TH Chan School of Public Health (Boston)

**#4 - 20 April 2022**
Fine particulate matter: new metrics, recently identified targets

***Seminar:*** The Human Sensor – Toxicology in Real People in the Real World
**Pr. Ian Mudway**, Imperial College London, MRC for Environment and Health (London)

**#5 - 11 May 2022**
'Legacy' endocrine disruptors: the convergence between basic biology, (eco)toxicology, clinical research and epidemiology

***Seminar:*** Endocrine disruption and nuclear receptors: mechanisms and impact on health
**Dr. William Bourget**, Centre de Biologie Structurale, Univ Montpellier, CNRS, Inserm (Montpellier)

**#6 - 18 May 2022**
Contemporary endocrine disruptors: assessing the health effects of non-persistent compounds

*Seminar:* Bad cocktails – the evaluation of combined exposures
**Pr. Andreas Kortenkamp**, Brunell University (London)

**#7 - 25 May 2022**
The Exposome: Promises and Challenges of a New Concept

*Seminar:* Protéger la santé des populations exposées aux substances chimiques - Enseignement et perspectives du programme national de biosurveillance
**Dr. Clémence Fillol**, Santé publique France

**#8 – 1 June 2022**
A Global Vision: The Burden of Disease Attributable to the Environment

**Seminar:** Causal pluralism and public health.
**Pr. Federica Russo**, Philosophe des Sciences, Techniques, et Information, Université d'Amsterdam

**#9 - 8 June 2022**
Climate change and human health

***Seminar:*** L'anthropocène est un accumulocène
**Dr. Jean-Baptiste Fressoz**, CNRS et EHESS

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