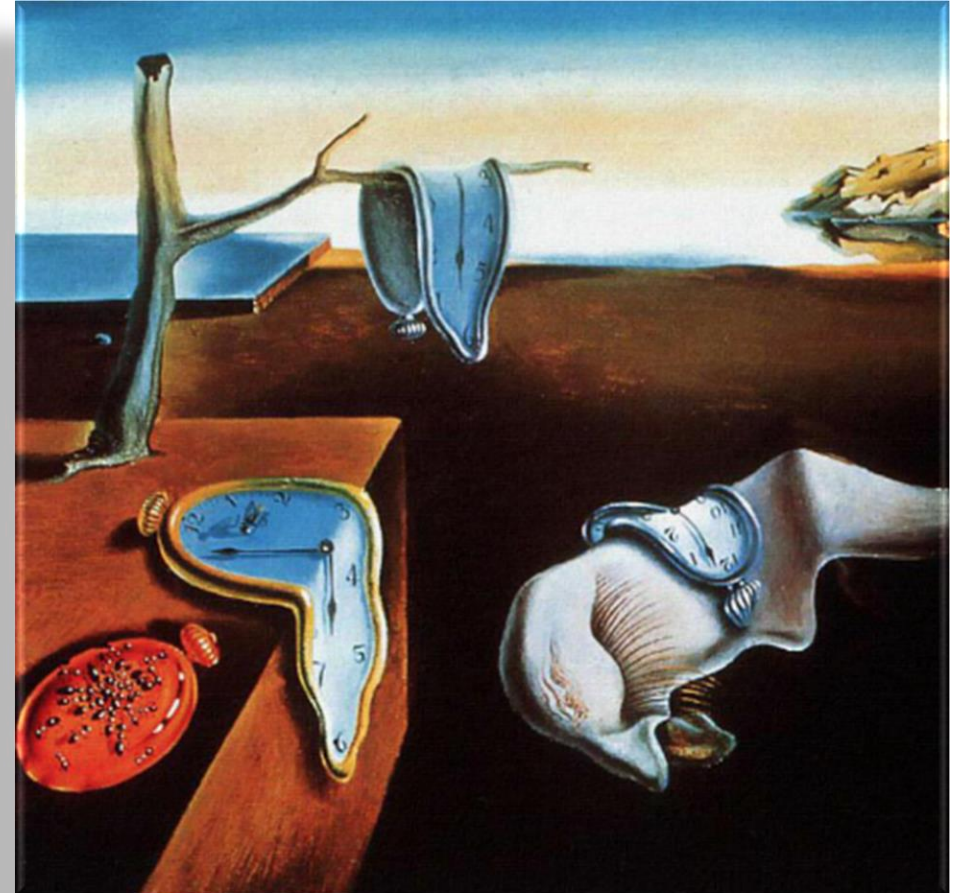


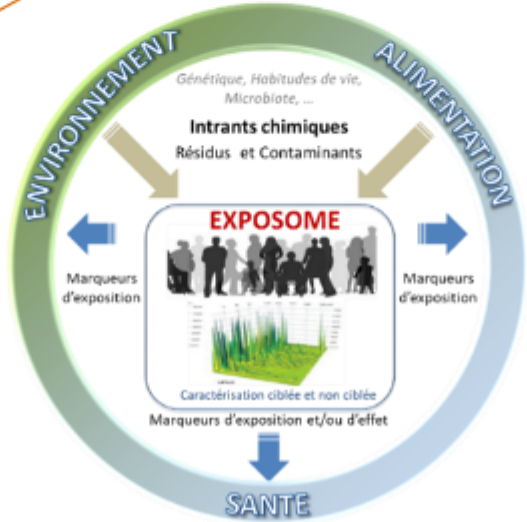
- Introduction
- What measuring ?
- How measuring ?
- Where measuring ?
- Real case studies
- Conclusion





UMR 1329 Oniris-INRAE

Laboratoire d'Etude des Résidus et Contaminants dans les Aliments



- 3 EC
- 4 IR
- 1 CR

- 4 Post-Doc
- 8 PhD
- 4 Master



LABERCA



Laboratoire National de Référence
Ministère de l'Agriculture – EU DG SANCO

National Reference
Laboratory

Mixed Research Unit

PLATFORMS

UPC

21

UCO

FOOD

HEALTH

HBM

MELISA



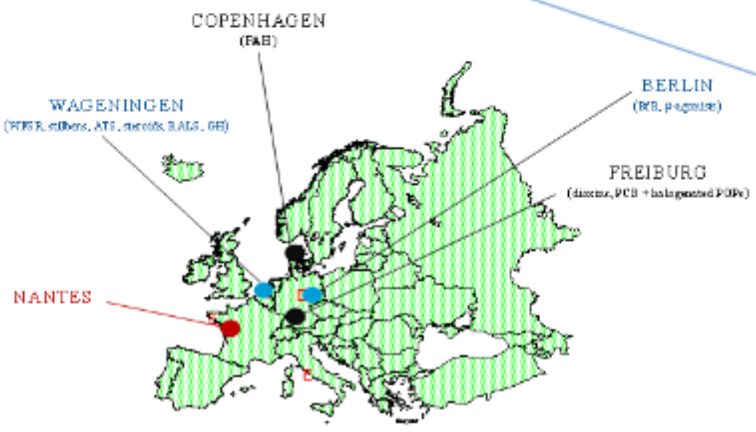
30 novembre 2018 JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE Texte 82 sur 108

Décrets, arrêtés, circulaires

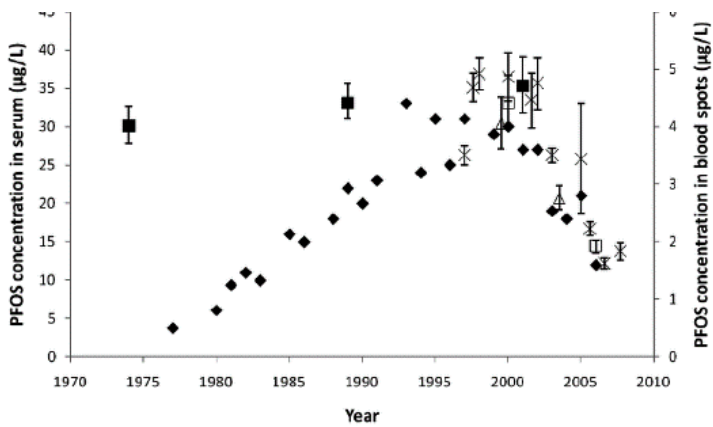
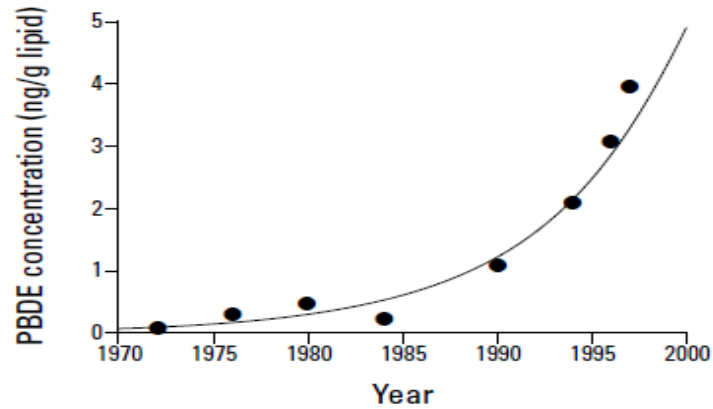
TEXTES GÉNÉRAUX

MINISTÈRE DE L'AGRICULTURE ET DE L'ALIMENTATION

Arrêté du 26 novembre 2018 modifiant l'arrêté du 29 décembre 2009 désignant les laboratoires nationaux de référence dans le domaine de la santé publique vétérinaire et phytosanitaire



Temporal increase of human exposure to environmental chemicals



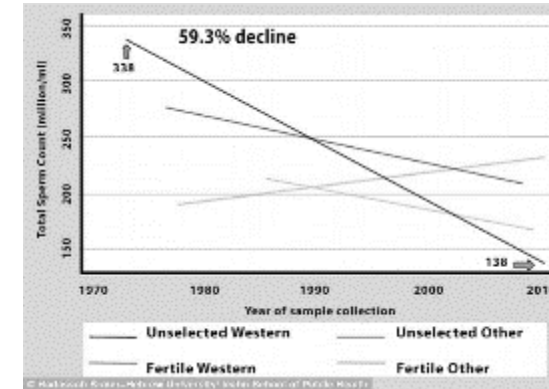
◆ Pooled serum, Norway △ NHANES, US
 ■ Red Cross blood donors, US □ Red Cross blood donors, US
 × Infant blood spots, US



Coincidence ?
 Association ?
 Causality ?

Temporal increase of some human health outcomes

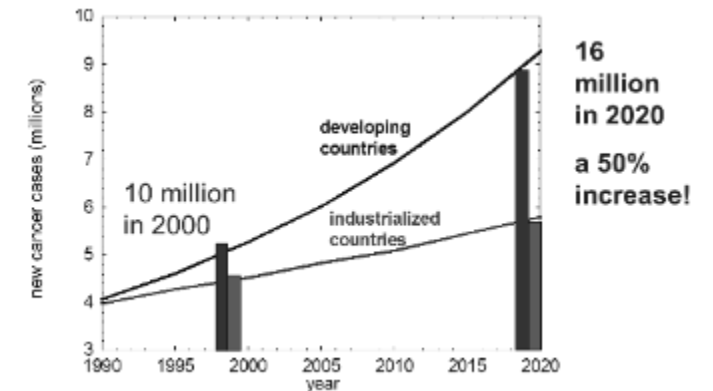
Reproduction & development
 (∇ sperm quality, age of puberty...)

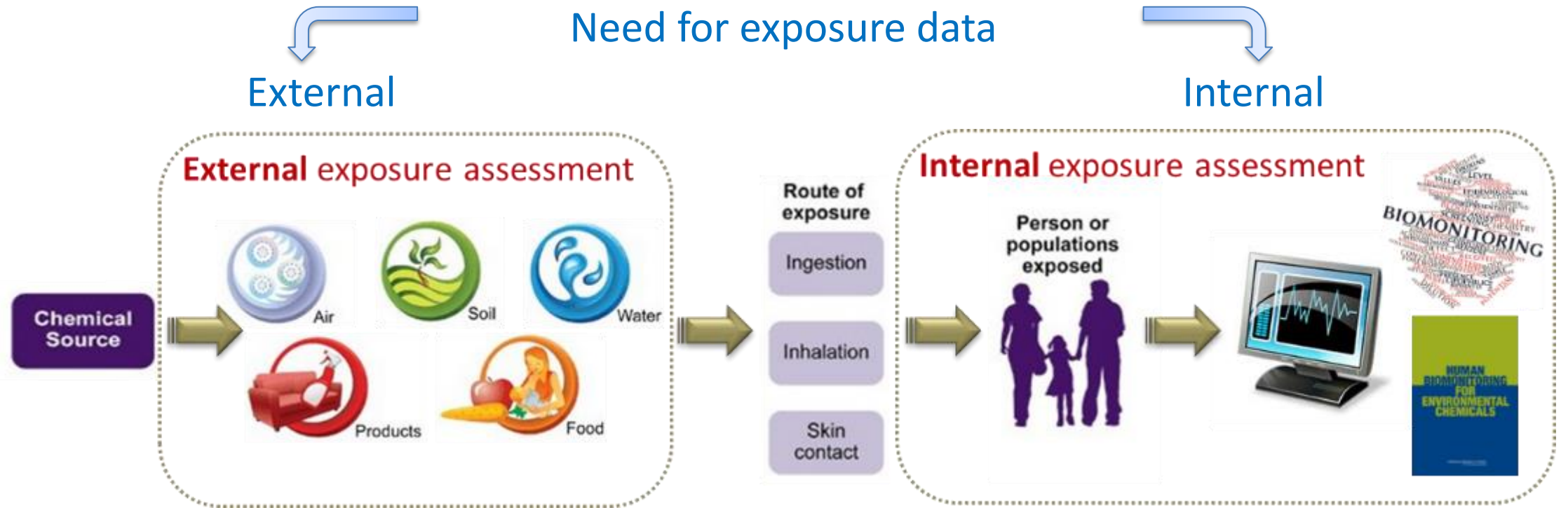


Metabolism & immune system
 (obesity, metabolic syndrome, allergy...)



Cancer
 (↗ breast & prostate cancers incidence)

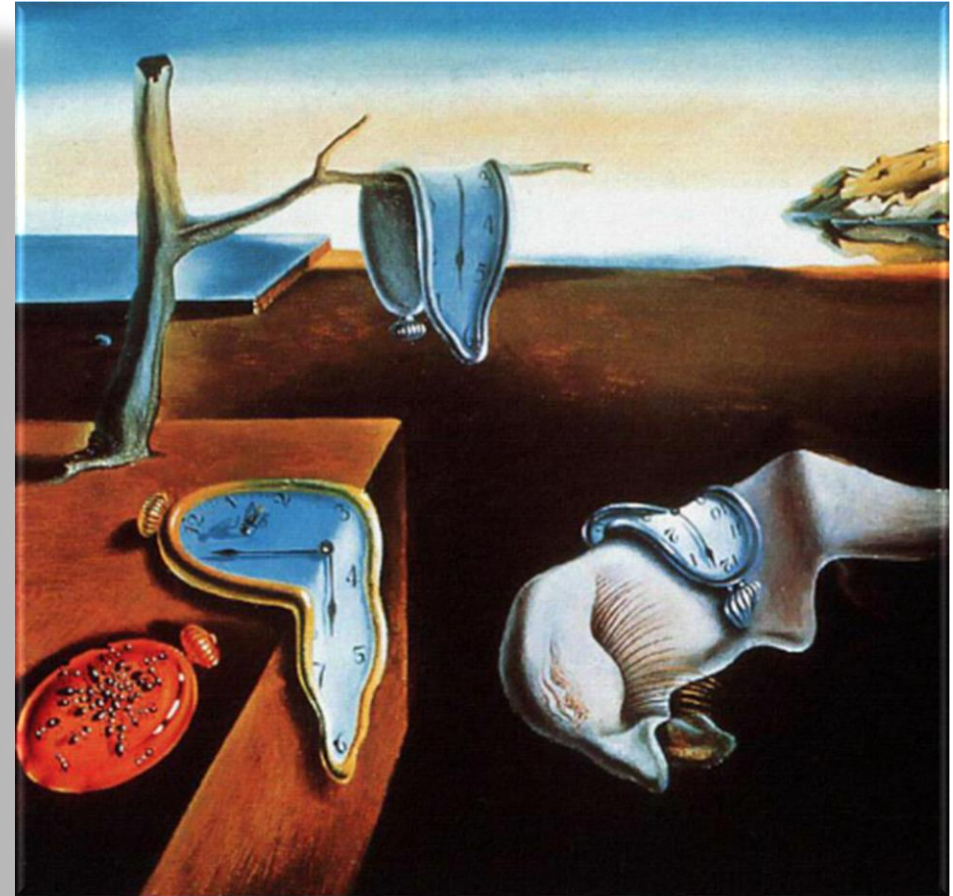


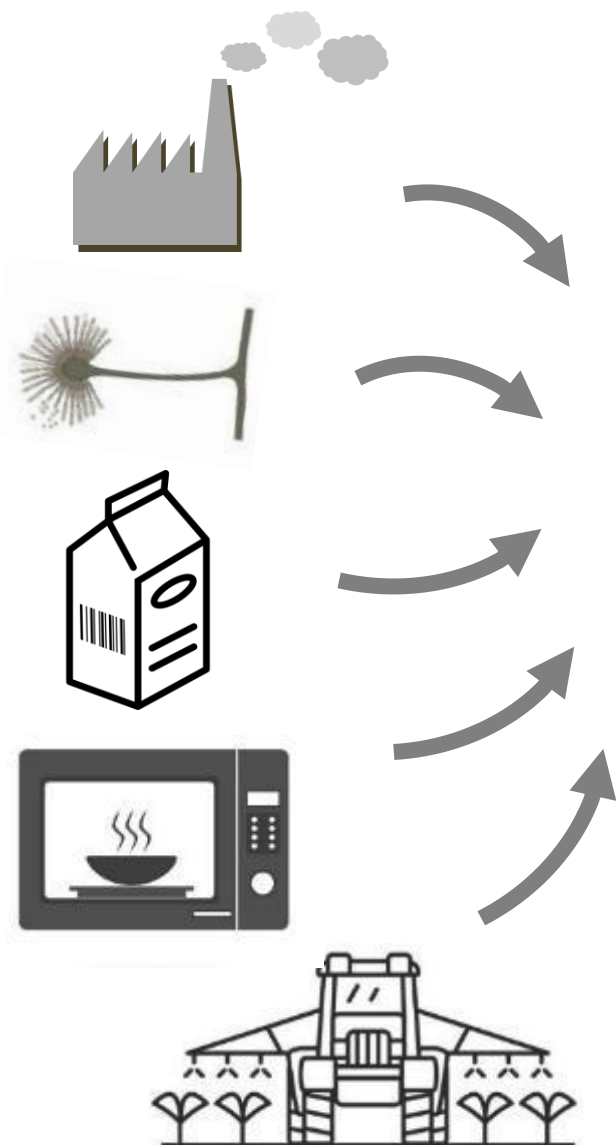


But... how, where, and when measuring what ?



- Introduction
- What measuring ?
- How measuring ?
- Where measuring ?
- Real case studies
- Conclusion





Etude Alimentation Totale 2
445 composés analysés
(dont 361 composés règlementés)



Number of chemicals (% samples detected)

16 Métaux lourds (70%)

11 Phytoestrogènes (20%)

25 Mycotoxines (6%)

283 Pesticides (1%)

12 Additifs (42%)

Acrylamide (11%)

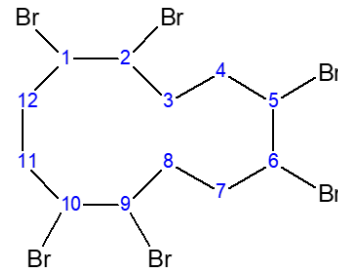
20 Hydrocarbures Aromatiques Polycycliques (49%)

65 Polluants Organiques Persistants (86%)

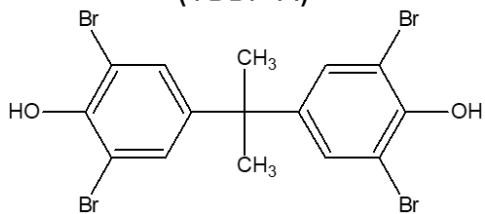
Les retardateurs de flamme bromés (RFBs)



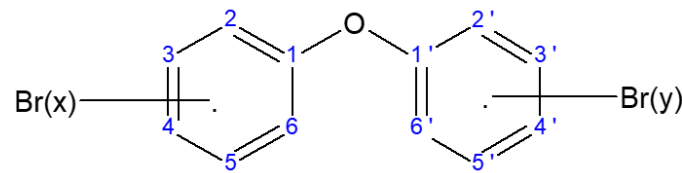
Hexabromocyclododecane (HBCD)



Tetrabromo-bisphenol-A (TBBP-A)



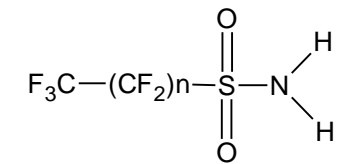
Polybrominated diphenylethers (PBDE)



Les substances perfluoroalkylés (PFAS)



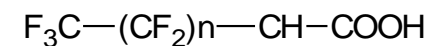
PerfluoroalkylSulfonic acids



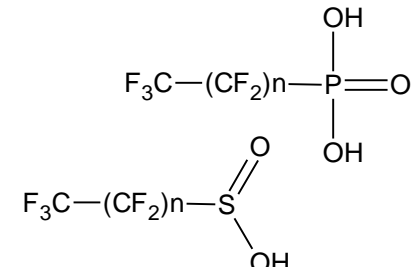
PFOS



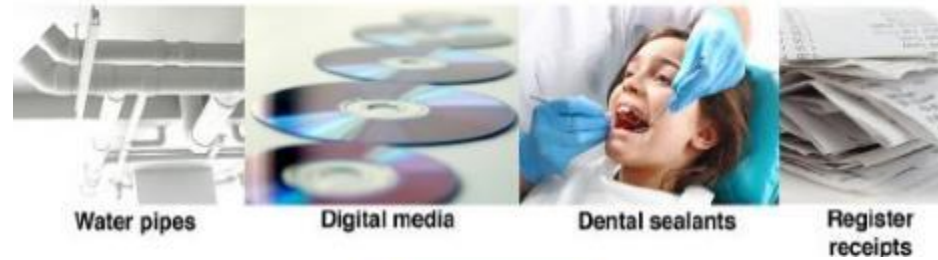
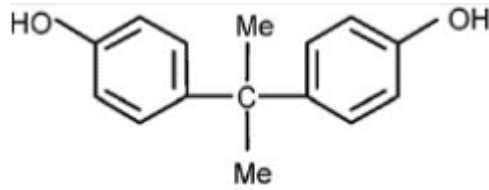
PerfluoroalkylCarboxylic acids



PFOA



Bisphenols (BPA and substitutes BPF / BPS)

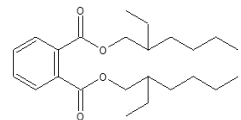
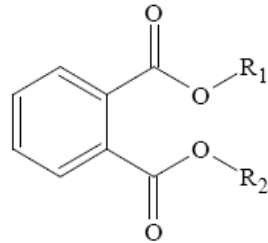


Personal care related contaminants

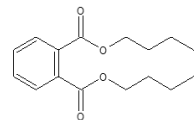
Preservatives (Parabènes, triclosan)



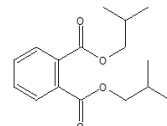
Phthalates



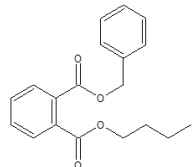
Di-2-EthylHexyl Phthalate (DEHP)



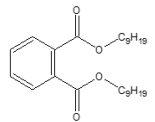
Di-n-Butyl Phthalate (DnBP)



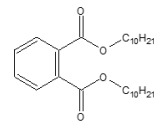
Di-iso-Butyl Phthalate (DiBP)



ButylBenzyl Phthalate (BBzP)



Di-iso-Nonyl Phthalate (DiNP)



Di-iso-Decyl Phthalate (DiDP)



UV-filters (Benzophenone-3)



« Un perturbateur endocrinien est une substance ou un mélange de substances, qui altère les fonctions du système endocrinien et de ce fait induit des effets néfastes dans un organisme intact, chez sa progéniture ou au sein de (sous)- populations. OMS2002 »

800-1200 substances suspectées
163 milliards d'euros par an pour
le système de santé européen

Santé de l'enfant

Neuro-développement

(Berghuis et al 2015, doi: 10.1007/s00204-015-1463-3)

Troubles de la reproduction

(Bonde 2016, 10.1093/humupd/dmw036.)

Allergies

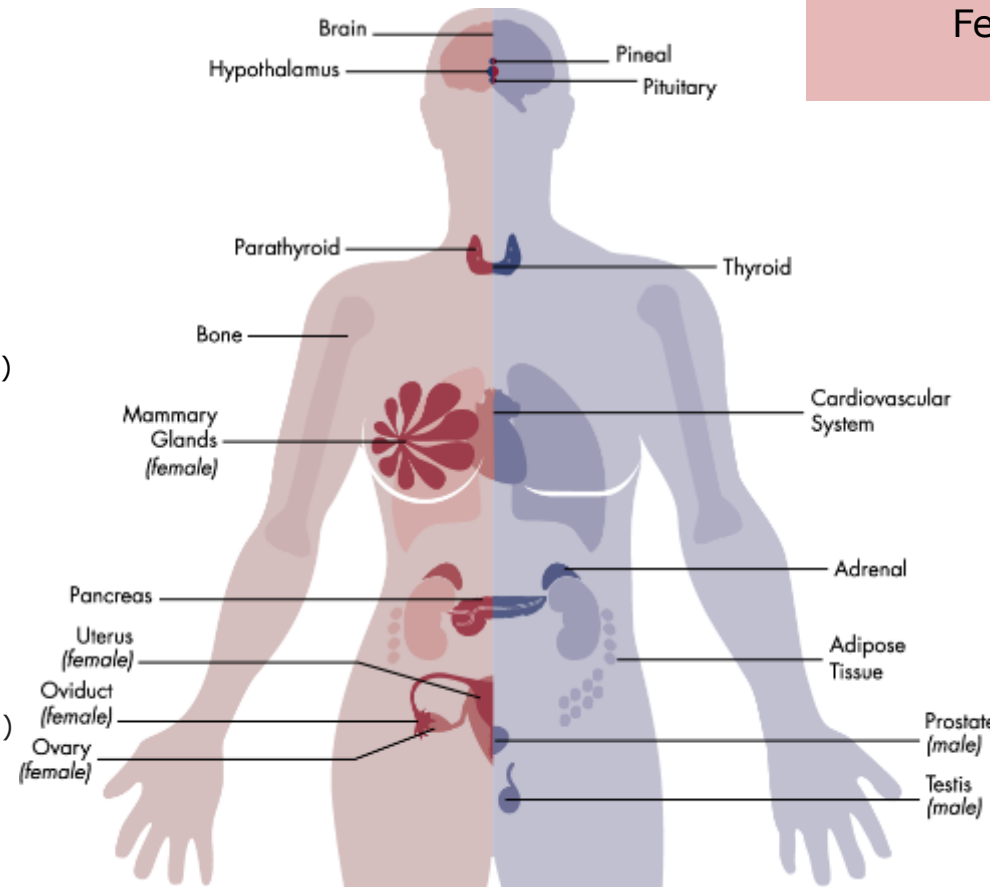
(Luo et al 2020,
10.1016/j.envres.2020.110145)

Troubles respiratoires

(Gascon et al 2013, doi: 10.1016/j.envint.2012.11.005.)

Perturbation métabolique, obésité

(Stratakis et al 2022, doi:10.1111/obr.13383)



Présents et actifs à très Faible dose
Relation dose-réponse non monotones
Fenêtres d'exposition spécifiques
« Effets cocktail » complexes

Santé de l'adulte

Perturbation métabolique

Maladies Cardiovasculaires

(Mendes et al 2021; Cano-Sancho et al 2017)

Cancer

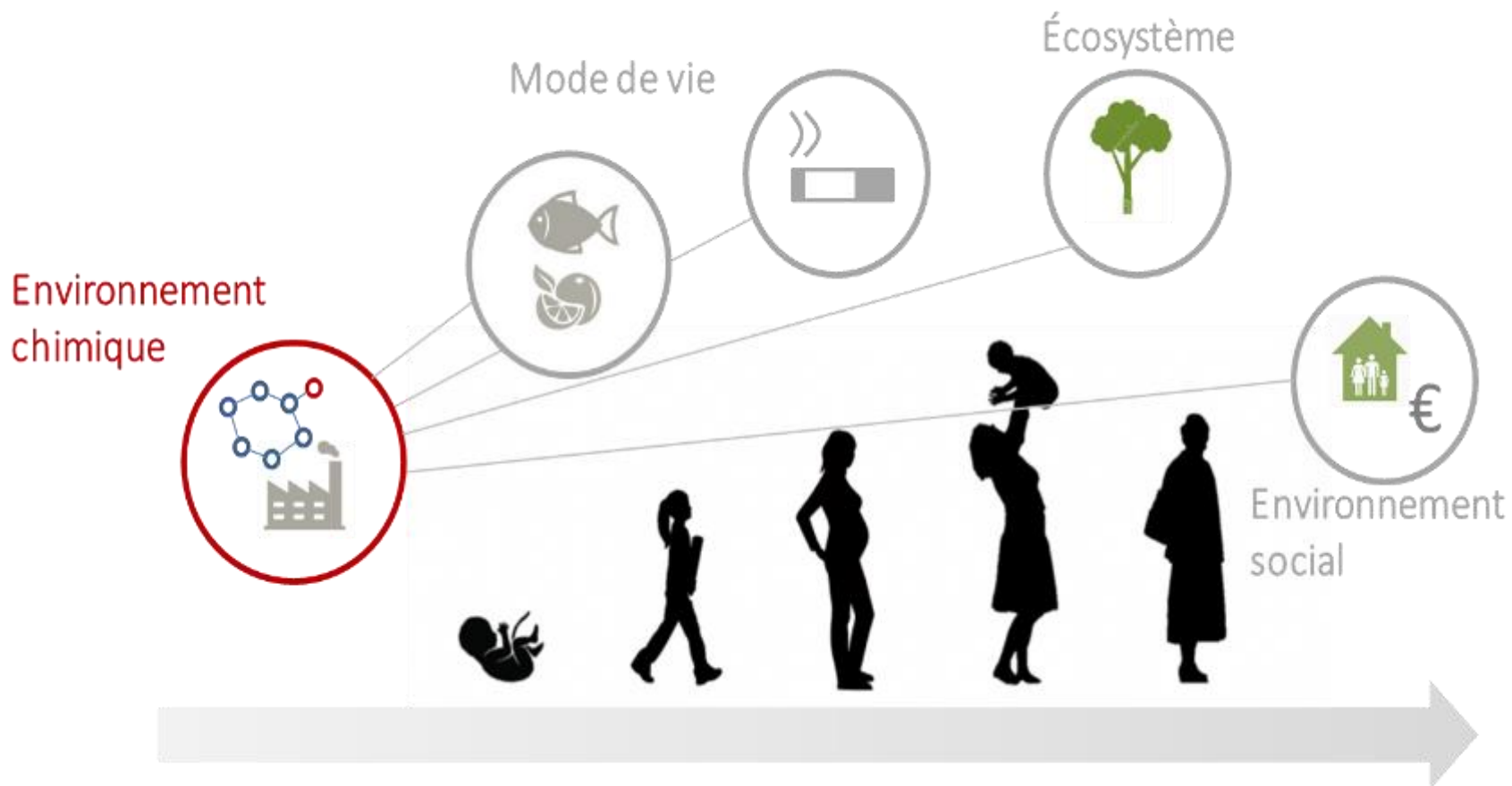
(Ennour-Idrissi et al 2019;
Han et al 2019)

Infertilité

(Khan et al 2021; Lefebvre 2021)

Endométriose

(Cano-Sancho et al 2019)



« Le concept d'exposome prend en compte notre exposition aux agents chimiques, présents dans notre environnement et notre alimentation, physiques avec par exemple le bruit, biologiques via les microorganismes avec lesquels nous sommes en contact mais aussi les carences alimentaires au cours du développement et des facteurs psycho-socio-économiques (stress, inégalités sociales). » Wild 2005



Christopher Wild

Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology

Christopher Paul Wild
Molecular Epidemiology Unit, Centre for Epidemiology and Statistics, Leeds Institute of Health and Therapeutics, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom



REVIEW

The exposome: from concept to utility

Christopher Paul Wild



Stephen Rappaport

REVIEW

Implications of the exposome for exposure science

STEPHEN M. RAPPAPORT



EPIDEMIOLOGY

Environment and Disease Risks

Stephen M. Rappaport and Marilyn T. Smith



Garry Miller



Roel Vermeulen

REVIEW

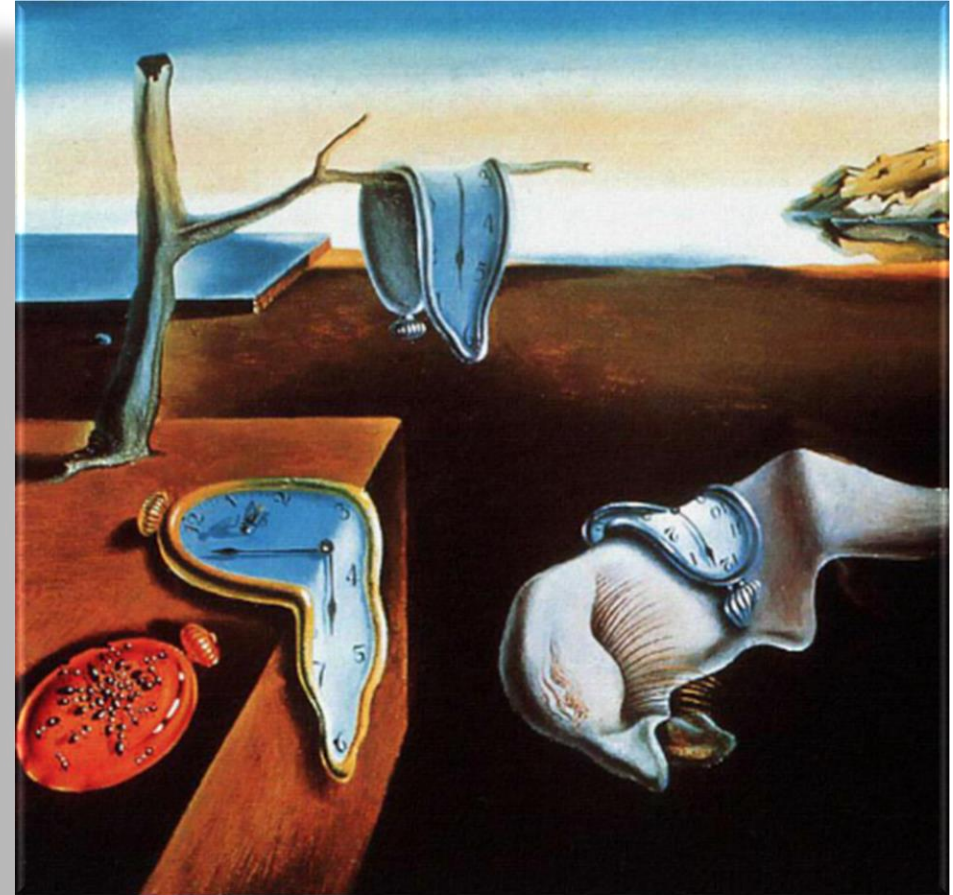
The exposome and health: Where chemistry meets biology

Roel Vermeulen^{1,2*}, Emma L. Schymanski¹, Albert-László Barabási^{3,4,5}, Gary W. Miller^{2,6*}

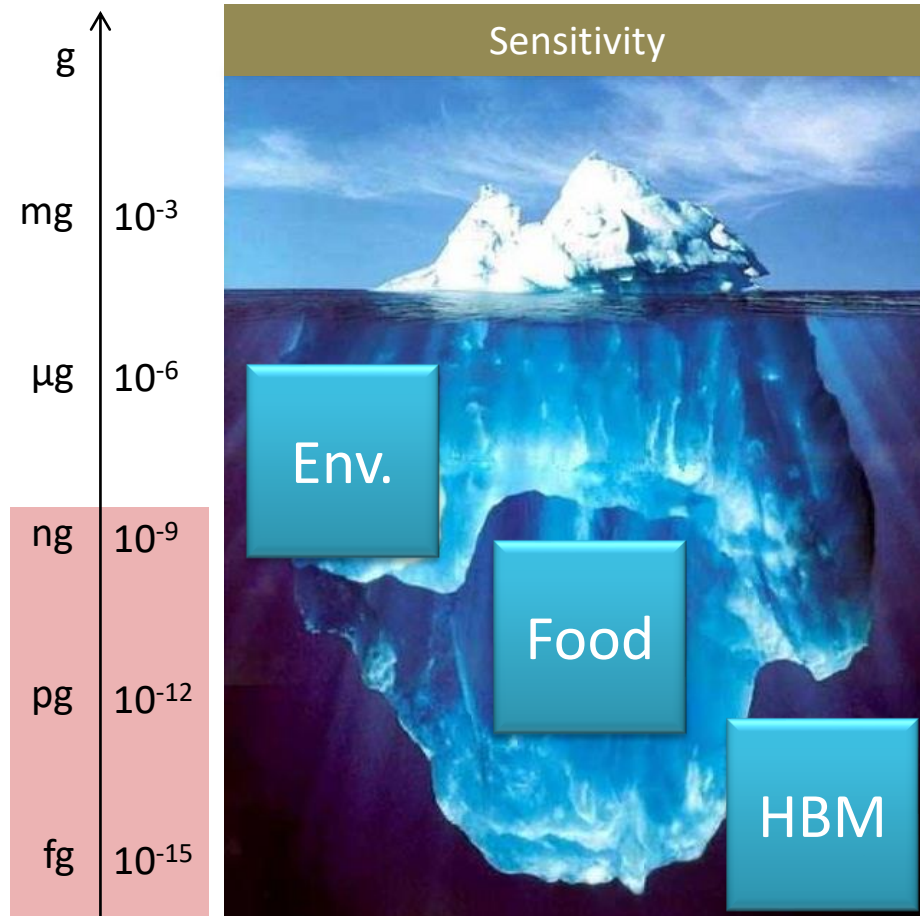


Universiteit Utrecht

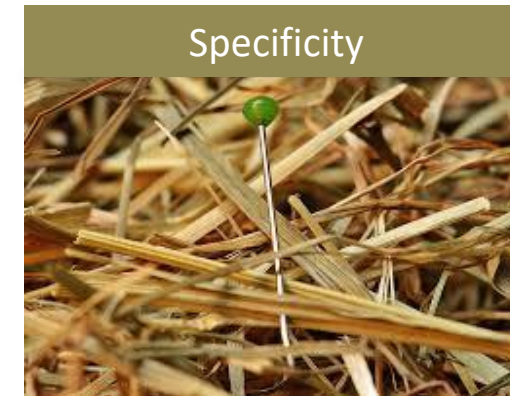
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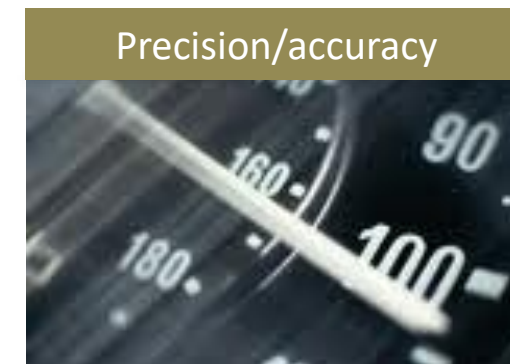
Extremely low concentration levels



Very complex biological matrices



Need for unambiguous identification and precise/accurate quantification





LC-QTOF (IMS)



GCxGC-TOF



GC- and LC-HRMSⁿ (x 4, Orbitrap systems)



LC-MS/MS (x 3, QqQ)



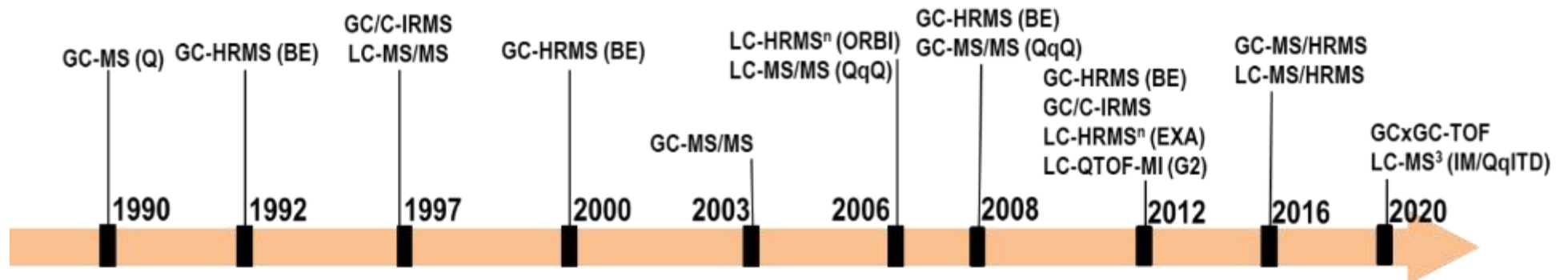
GC-HRMS (x 3, BE)



GC-C-IRMS (x 2)



GC-MS/MS (x 3, QqQ)

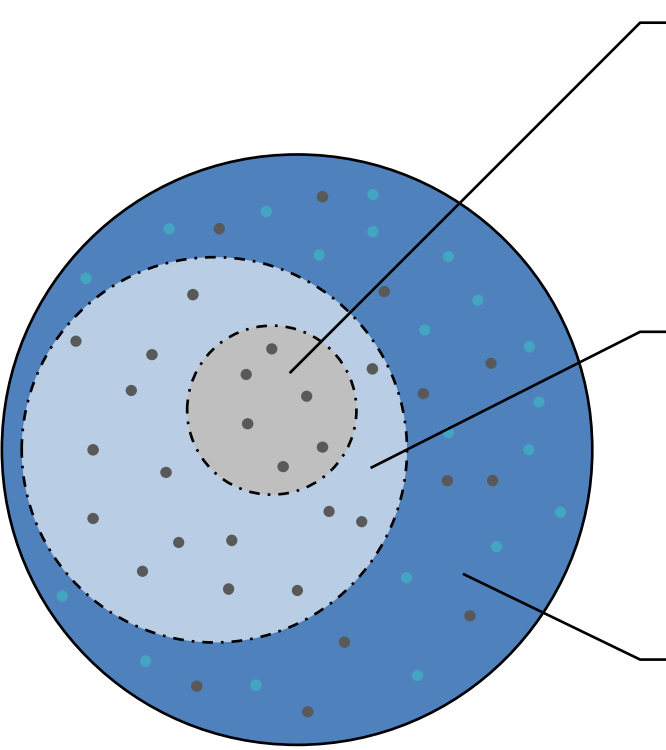


Stratification of the human chemical exposome

Methodological approaches

Objectives

Research and support to policy outputs



Known

Well established and focused quantitative method

Known unknown

Known structure but still no established quantitative method

Unknown unknown

Still unknown marker of exposure



Targeted measurement

Suspect screening

Non-targeted screening (NTS)

Unambiguous identification and quantification

Qualitative detection rates or semi-quantitative data

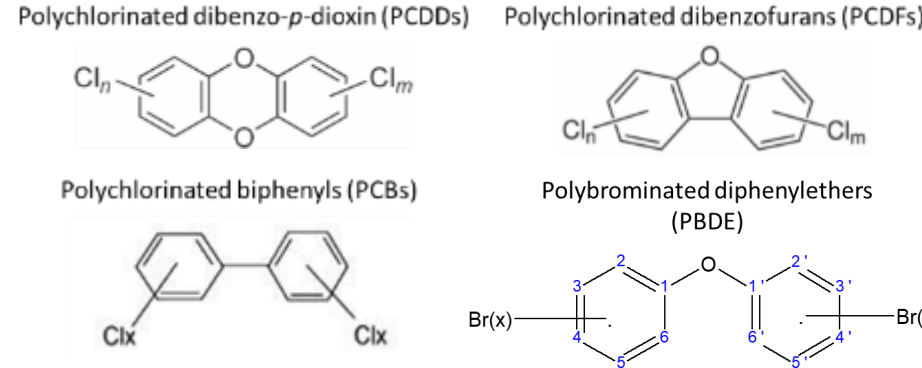
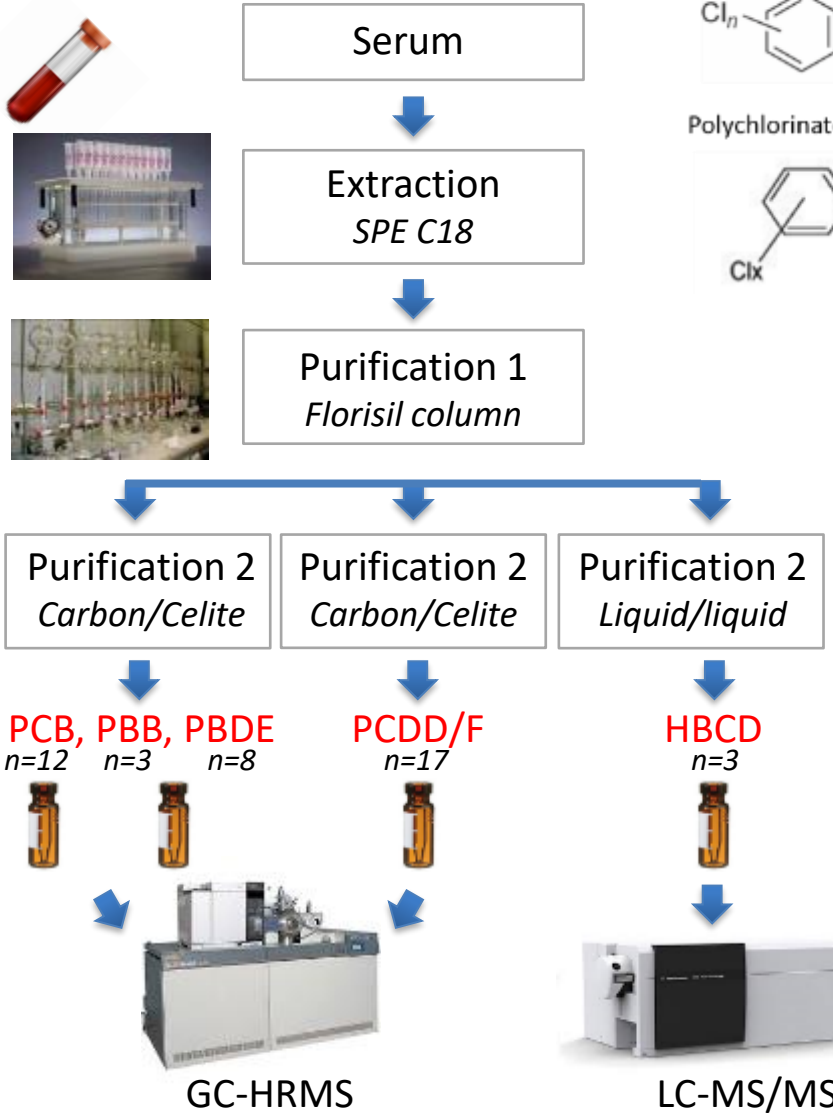
Detection of new exposure markers of concern

Short term: regular quantitative exposure data

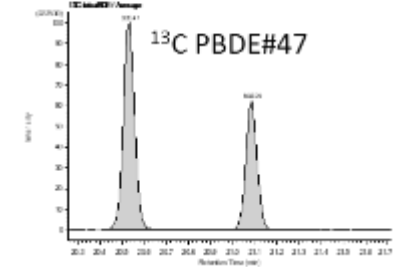
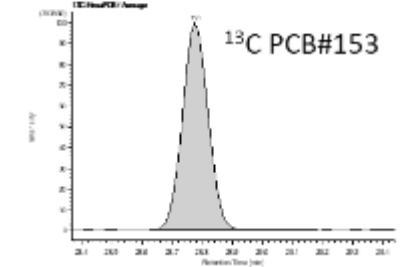
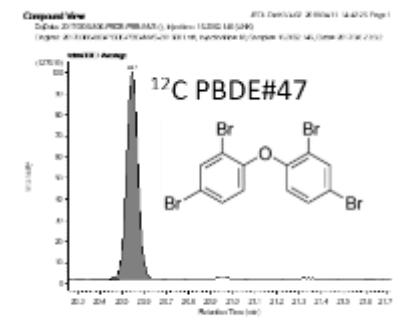
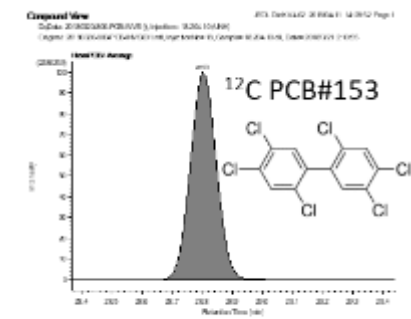
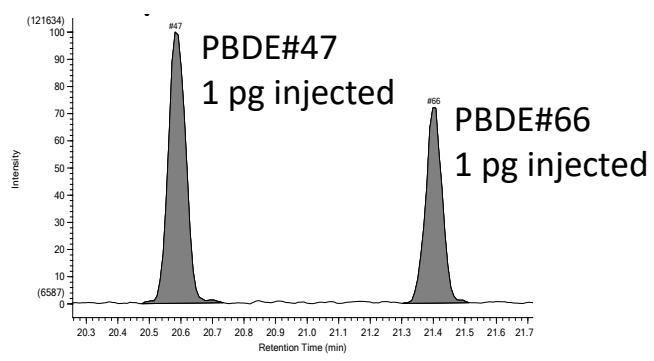
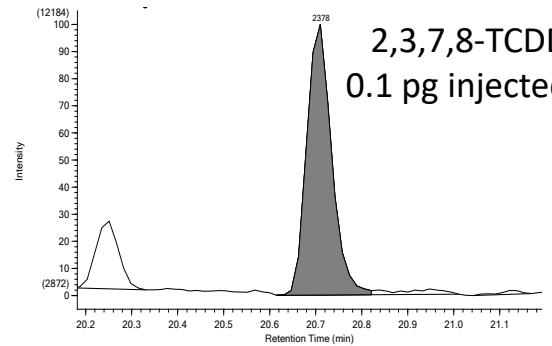
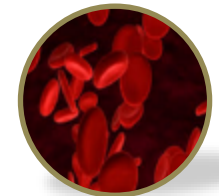
Medium term: prioritizing further targeted analytical developments, rationalizing content of HBM programmes, documenting exposure patterns / trends

Sustainable: developing an opened and early warning capability, new marker discovery, generating new research hypotheses

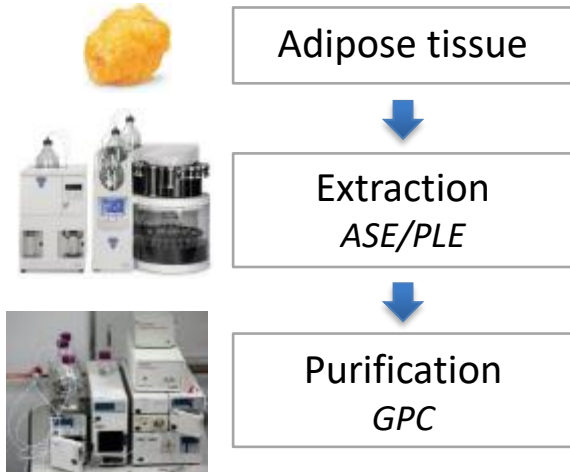
Dioxins/PCB/PBDE



Real serum sample

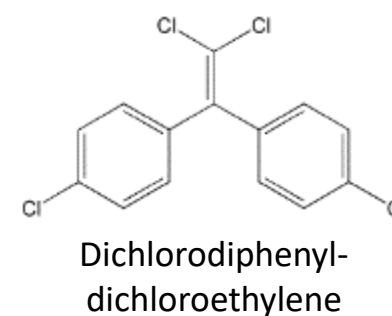
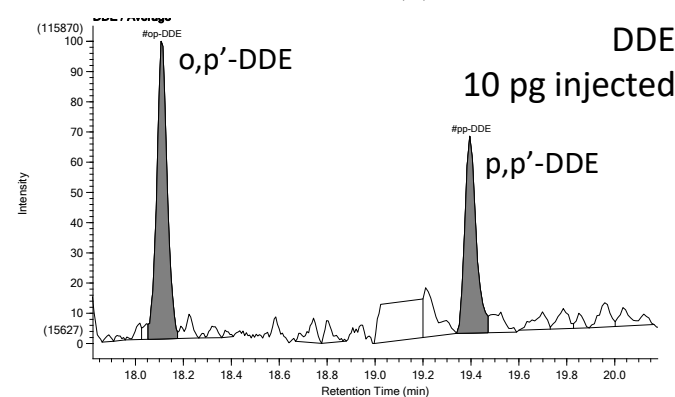
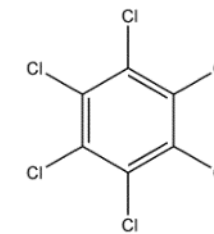
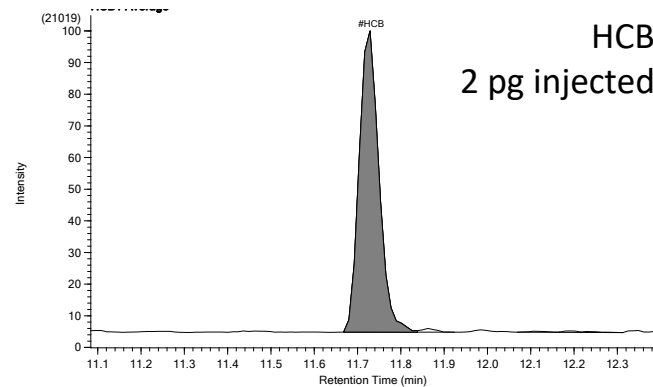
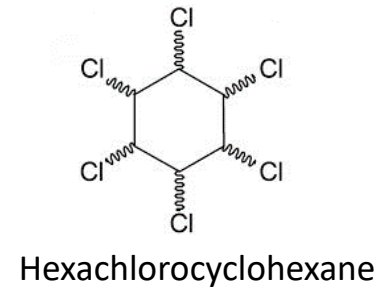
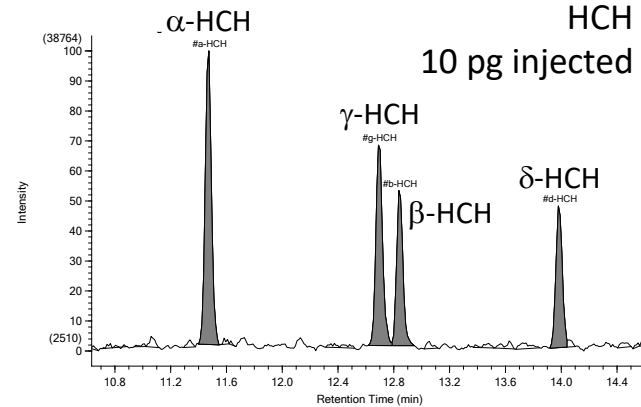
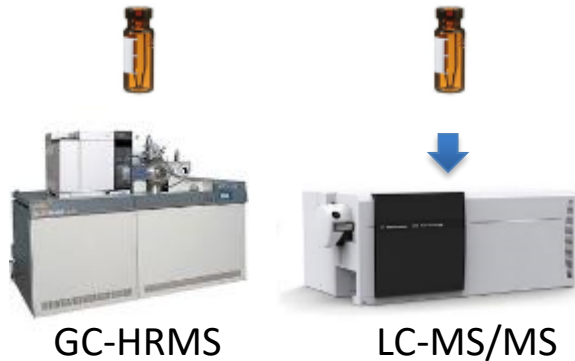


Organochlorine pesticides



Other OCs
n=28

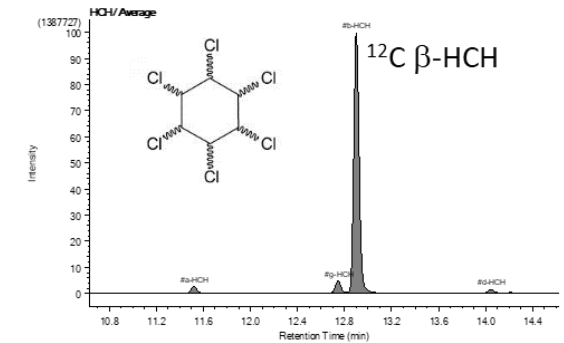
Chlordecone



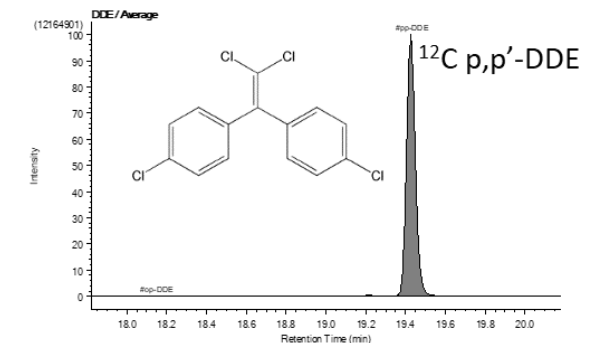
Real adipose
tissue sample



Compound View
JEOL DaK V4.02 2018/04/11 14:51:06 Page 1
DaData: 20170502-700-POC(), Injection= 17.236.5 (LINK)
Original: 20170502-700-POC001.mf, InjectionNo= 14, Sampler= 17.236.5, Date= 2017/5/2 8:12:37



Compound View
JEOL DaK V4.02 2018/04/11 15:51:31 Page 1
DaData: 20170502-700-POC(), Injection= 17.236.4 (LINK)
Original: 20170502-700-POC001.mf, InjectionNo= 13, Sampler= 17.236.4, Date= 2017/5/2 7:37:6

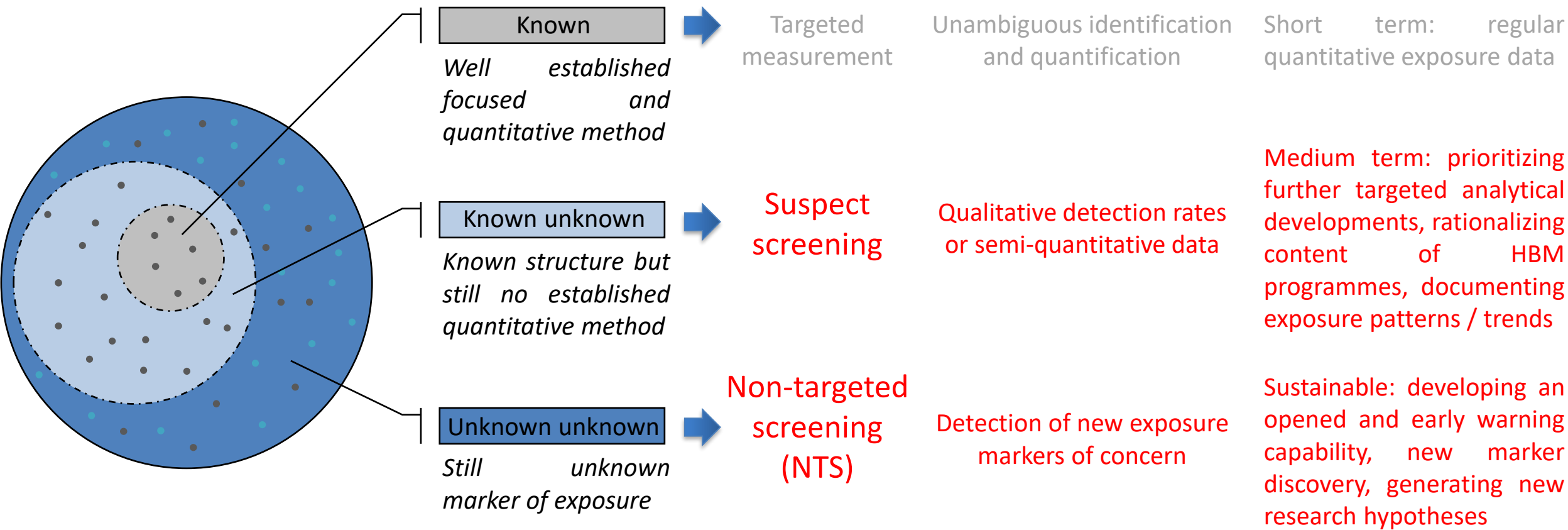


Stratification of the human chemical exposome

Methodological approaches

Objectives

Research and support to policy outputs



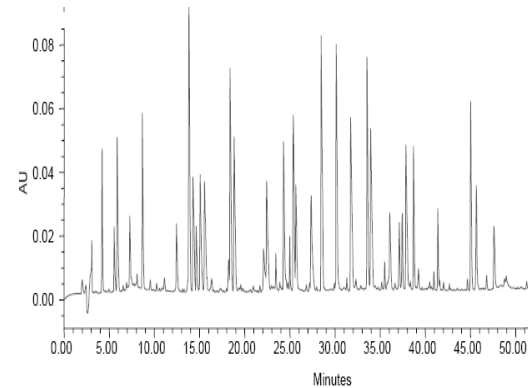
Environmental matrices
Food matrices
Human matrices



Non-selective
sample preparation



Chromatography-high resolution
mass spectrometry profiling
(*LC-HRMS, GC-HRMS*)



Non-selective generation
of chemical descriptors

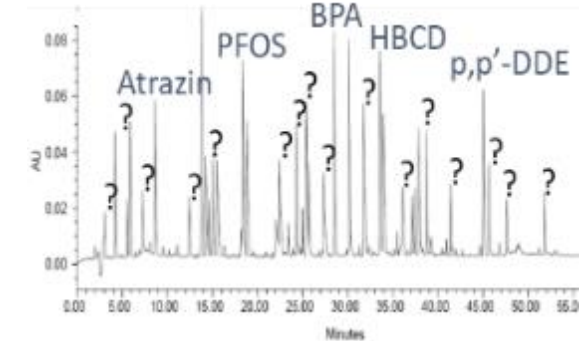


Annotation of the generated
descriptors through comparison
with reference MS data

predefined list of
suspect -> target
markers

Accurate mass
Retention time
MS spectrum
MS/MS spectrum

Annotation MS
reference library
(suspect list)



Annotation of the
suspect markers

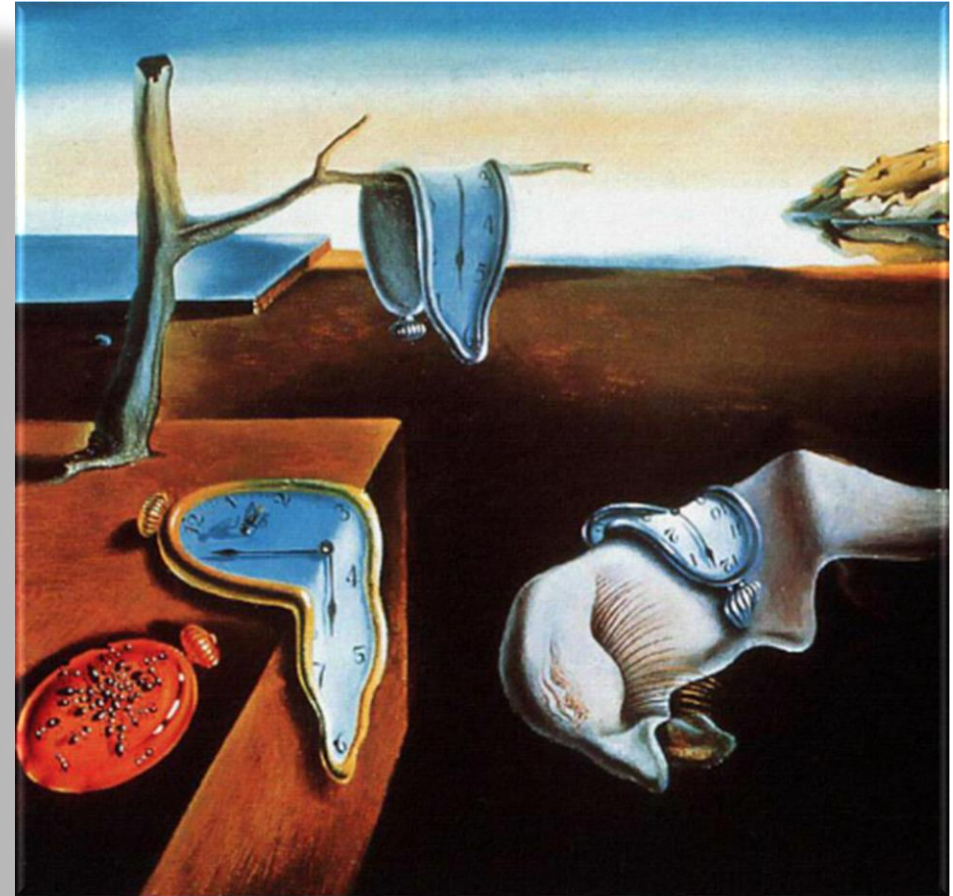


Human Biomonitoring for Europe
EU H2020, 2017-2022, 50 M€
WP16 « emergng chemicals »
17 partners, 5 M€



Partnership for assessment of risk of
chemicals, Horizon EU, 2022-2029, 400 M€
Task 4.3 « innovative methods »
60 partners, 30 M€

- Introduction
- What measuring ?
- How measuring ?
- **Where measuring ?**
- Real case studies
- Conclusion



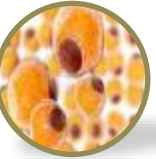


ENDOMET "Association between POP exposure and endometriosis"
 Coord. LABERCA, Collab. CHU Nantes (PhD Pr. Stéphane Ploteau)



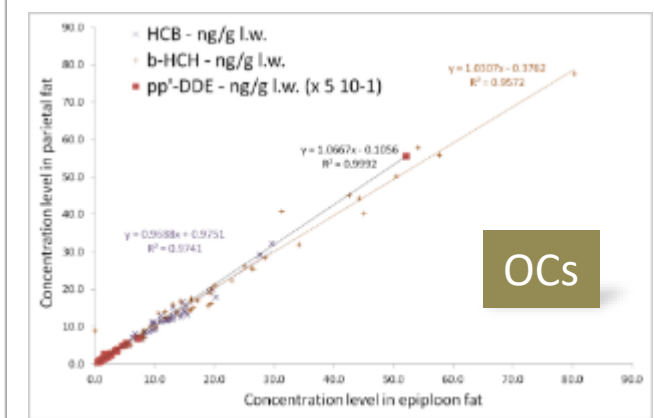
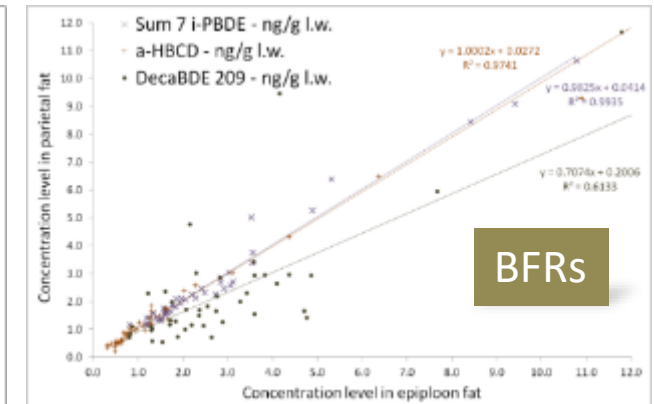
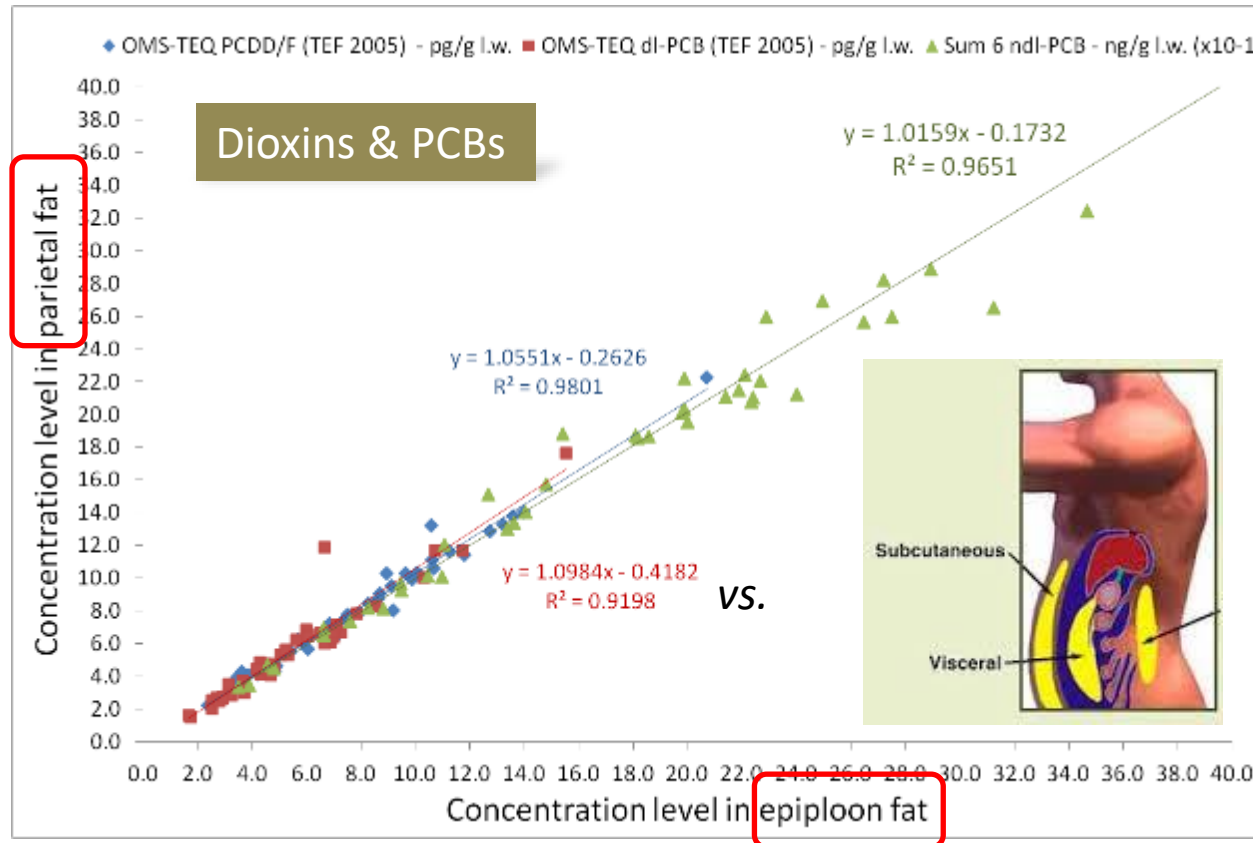
PhD
 Pr. S. Ploteau
 LABERCA / CHU Nantes

Are different adipose tissue depots equivalent in terms of POPs concentration levels?



- POPs levels in superficial and deep AT appeared equivalent in steady-state individuals.
- No necessarily the case for all chemicals and depends on individual's weight stability and diet.

Ploteau et al., *Env. Int.*
 2016:97;125-136.





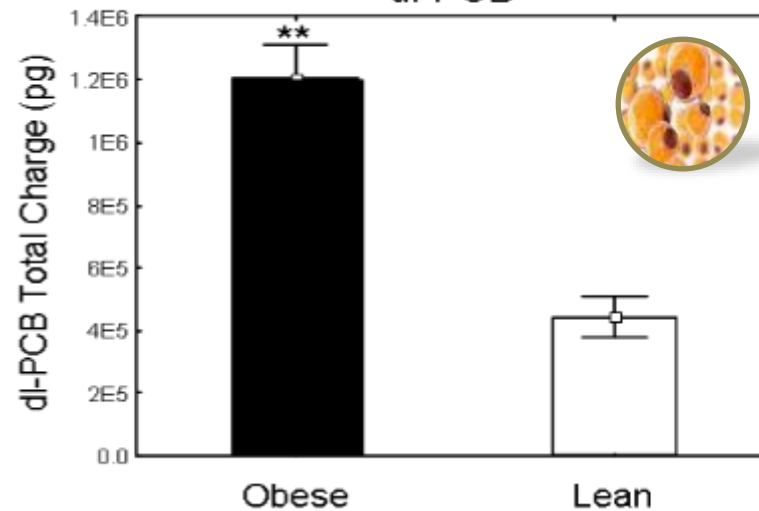
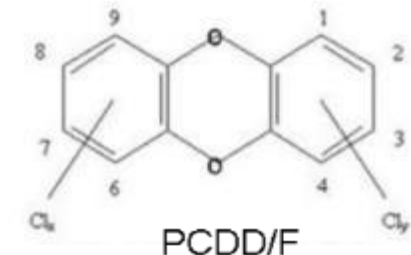
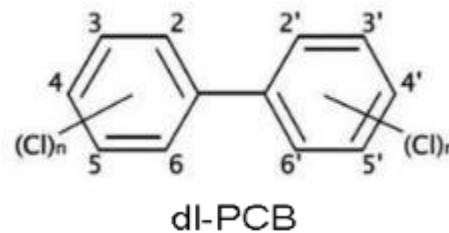
ADIPOTOX "Distribution of POPs after drastic weight loss" - // POLOB "polluants organiques lipophiles et obésité morbide"
 Coord. : INSERM U747 (Robert Barouki), Collab.: INSERM U755 (Karine Clément) // Coord. CHU Nice (Patrick Fénichel)



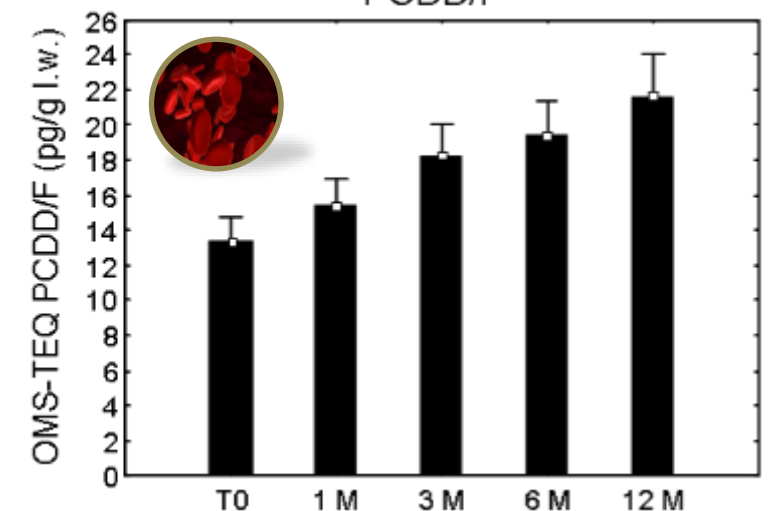
Pr. R. Barouki
 INSERM 1124, Paris

What relationship between POPs levels in adipose tissue versus serum in case of drastic weight loss?

- Higher total body burden of POPs in obese subjects, increased serum levels of POPs after surgery.
- The internal POPs levels vary according to the weight loss/gain of individuals.



Amounts (total charge) of POPs (mean ± SEM) measured in adipose tissue of lean versus obese patients (before surgery) (i.e. reported to the total fat mass in pg or ng).



Evolution of the concentrations of POPs (mean ± SEM) measured in serum of obese patients before (T0) and after (1, 3, 6, or 12 months) surgery expressed on a lipid weight basis (i.e. in pg or ng / g fat).

Kim et al., EHP 2011;119:377-383.

La Merrill et al., EHP 2013;121(2):162-169.

Fénichel et al., Env. Int. 2021;151:106400



Des sous-population particulièrement sensibles vis-à-vis du risque chimique

Plus exposées

Plus vulnérables



Alimentation particulière

Exposition occupationnelle

Puberté

Période périnatale

Période fœtale



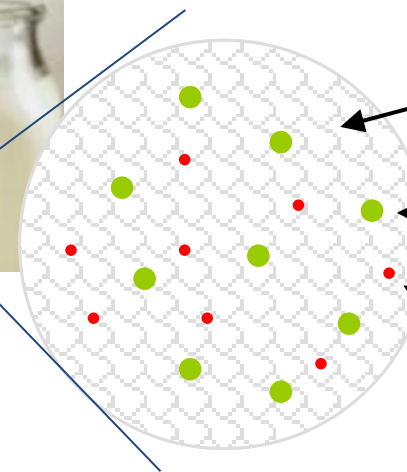
Lait Maternel



Vecteur d'exposition directe du nourrisson allaité
+
Indicateur de l'imprégnation de la mère et du fœtus



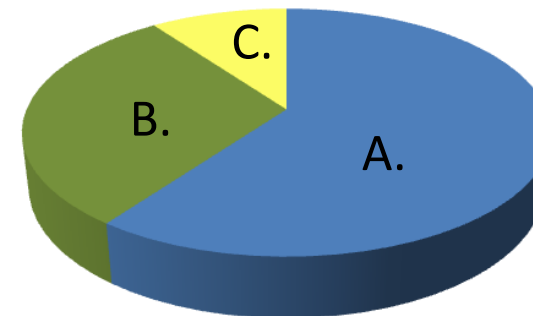
Le lait : un milieu propice à la présence de résidus et contaminants chimiques



Macroconstituants (polysaccharides, protéines...)

Micronutriments (AGPI, vitamines...)

Résidus et contaminants chimiques



A. Fraction aqueuse
Certaines hormones, phytoestrogènes, métabolites

B. Fraction protéique
Contaminants perfluorés (PFAS)

C. Fraction lipidique
Certaines hormones, contaminants lipophiles (POPs)



LACTACOL project - CPP N°2011-S4

Collab. INRA PHAN (CY Boquien), CHU Nantes (JC Rozé, C Boscher), Lactarium Nantes (A Legrand)



DEER project - FP7-ENV-2007-1 (212844)

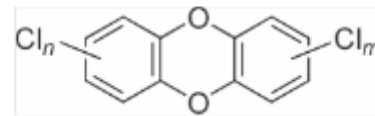
Collab. Righospitalet, Copenhagen (K. Main, Niels E Skakkebaeck)



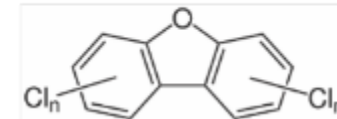
Pr. N.E. Skakkebaeck
Righospitalet, DK
Testicular Dysgenesis Syndrome

What are the exposure levels of Dioxins in Danish/finish vs. French mothers breast milk?

Polychlorinated dibenzo-*p*-dioxin (PCDDs)



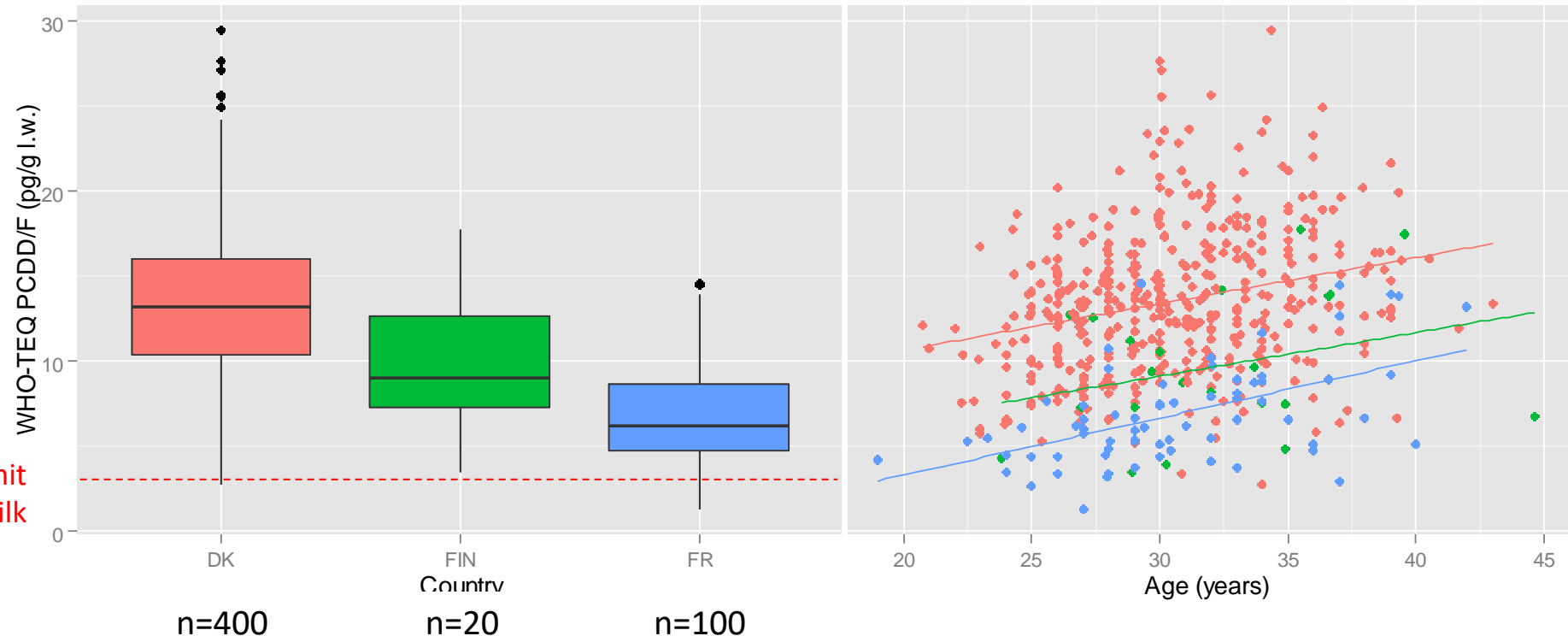
Polychlorinated dibenzofurans (PCDFs)



- Higher levels of POPs in breast milk than regulatory limit for cow milk.
- Correlation between POP levels and age.
- Different exposure levels and patterns among different countries

Regulated Limit
in cow milk

Antignac et al., *Env. Pol.*
2016:218;728-738.





LACTACOL project - CPP N°2011-S4

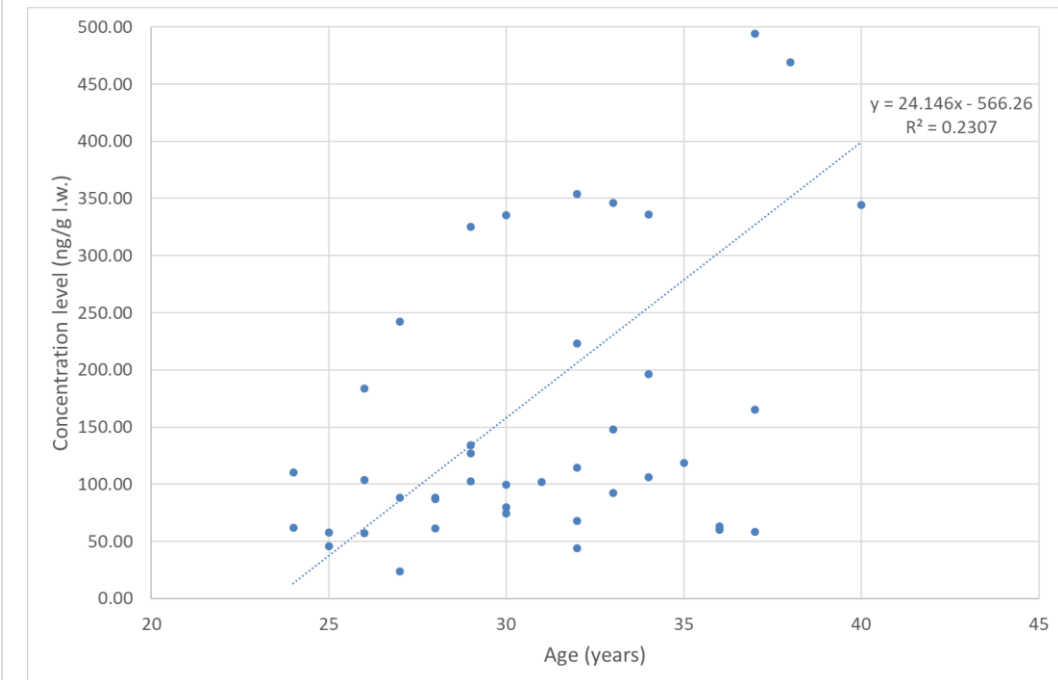
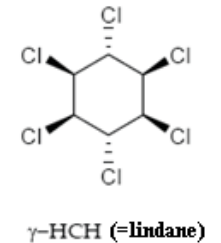
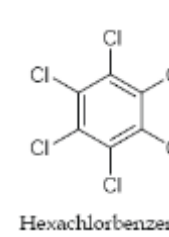
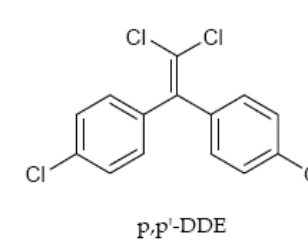
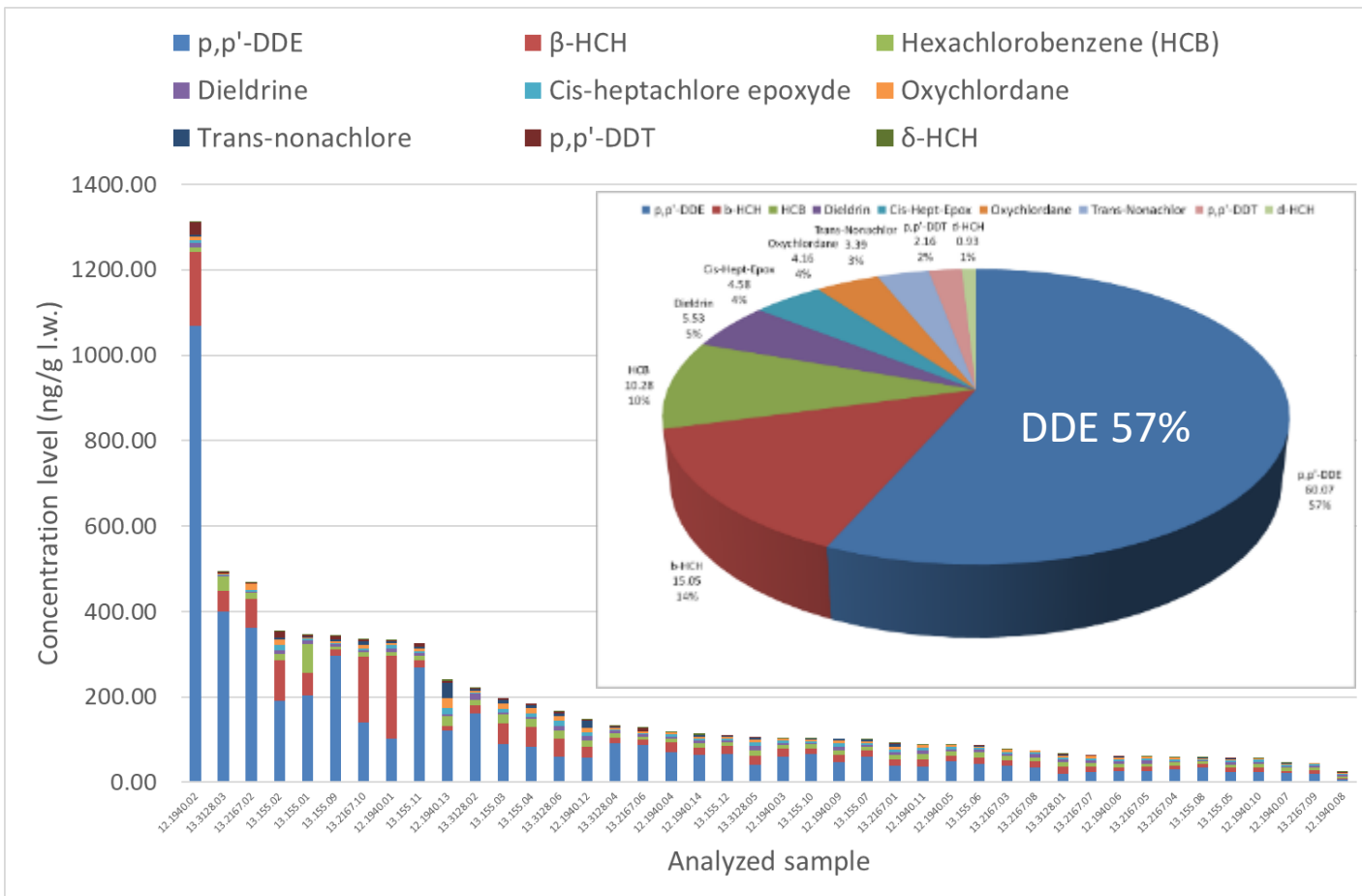
Collab. INRA PHAN (CY Boquien), CHU Nantes
(JC Rozé, C Boscher), Lactarium Nantes (A Legrand)



DEER project - FP7-ENV-2007-1 (212844)

Collab. Righospitalet, Copenhagen
(K. Main, Niels E Skakkebaeck)

What are the exposure levels of OCPs in French mothers breast milk?





“Etude de l'exposition du fœtus et du nourrisson aux retardateurs de flamme bromés.”

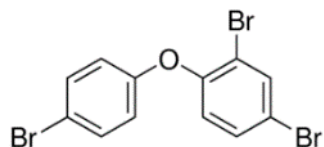
Contrat AFSSET RD-2004-011 “BED”

PhD Ronan Cariou, co-dir. LABERCA-TOXALIM

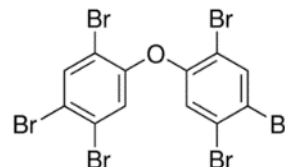
Collab. CHU Toulouse (A. Berrebi), INRA UMR 1331 Toxalim (D. Zalko)

What are the relationships between PBDE levels in breast milk and in other biological compartments?

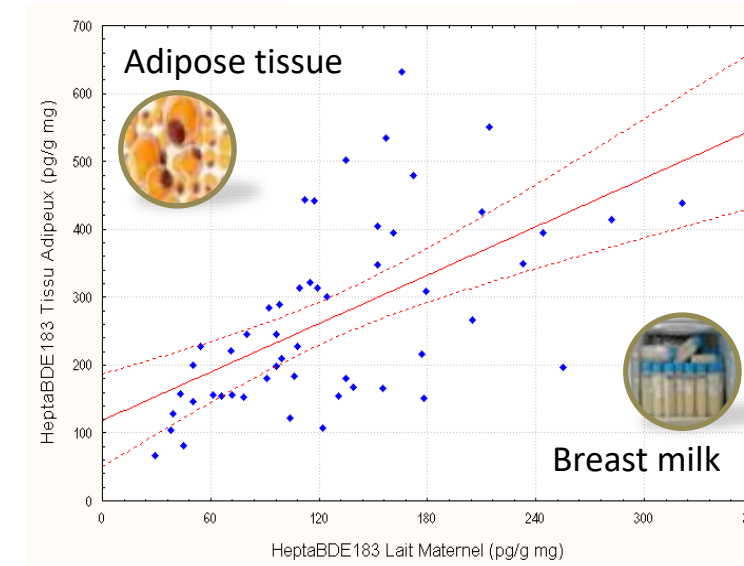
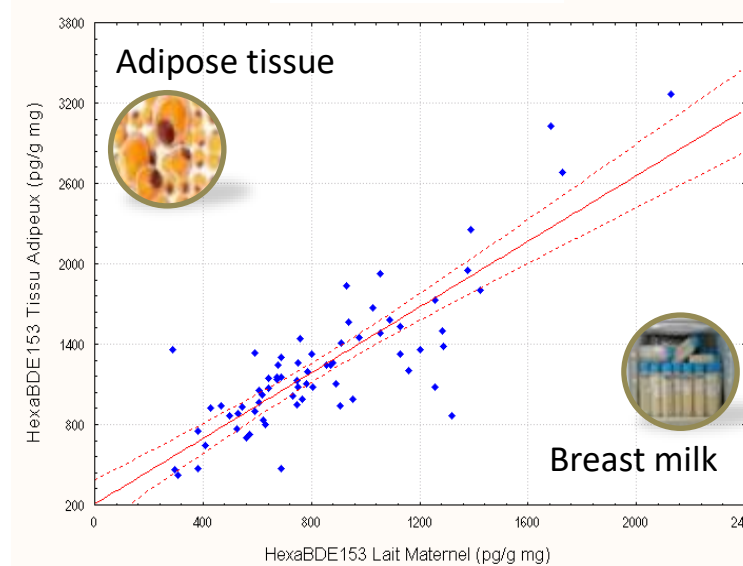
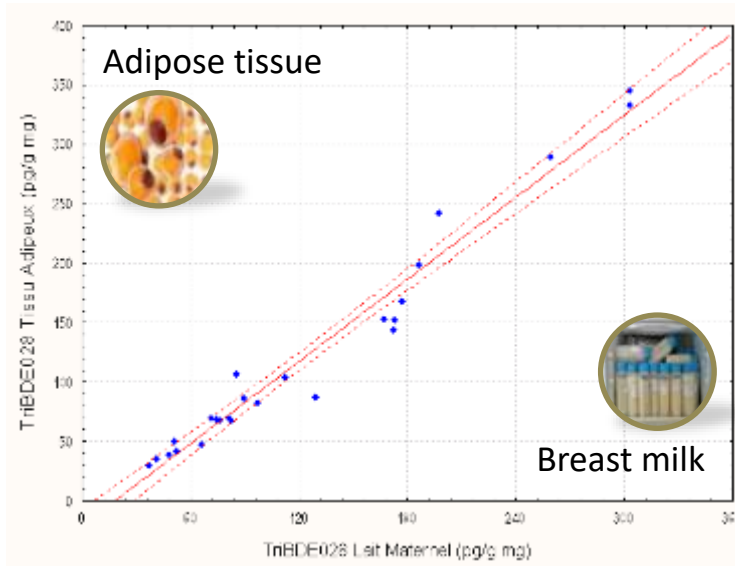
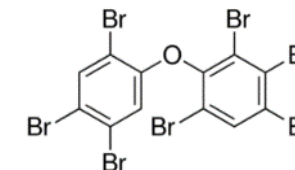
PBDE#28 (tri-BDE)



PBDE#153 (Hexa-BDE)



PBDE#183 (Hepta-BDE)



Antignac et al., *Env. Pol.*
2009:157;164–173.





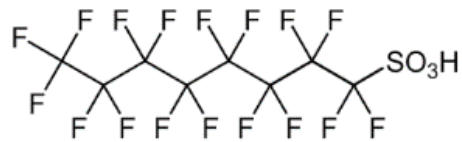
Coord. LABERCA

CONTREPERF project - "Emerging perfluorinated contaminants: contribution to the human exposure assessment, to the study of their metabolism and to the characterization of their toxicological impact." - ANR-10-CESA-008

Collab. CHU Toulouse (Alain Berrebi), INRA UMR 1331 Toxalim (Daniel Zalko)

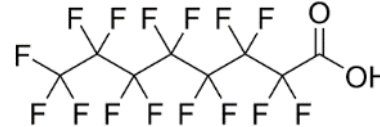
What relationship between POP levels in maternal versus foetal compartments?

PFOS

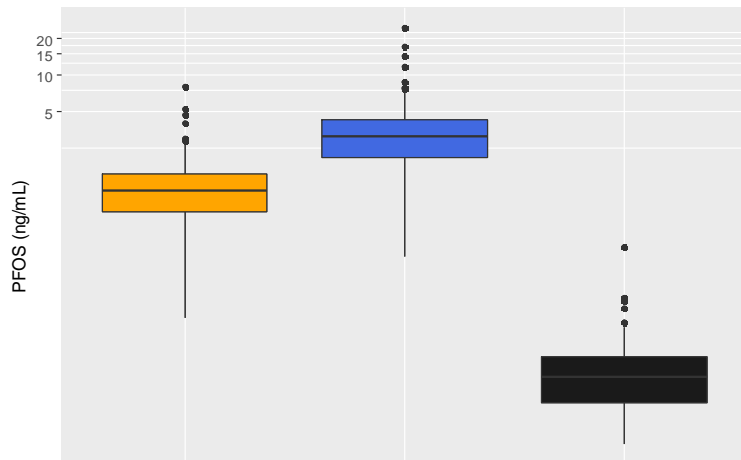


Perfluorooctanesulfonic acid

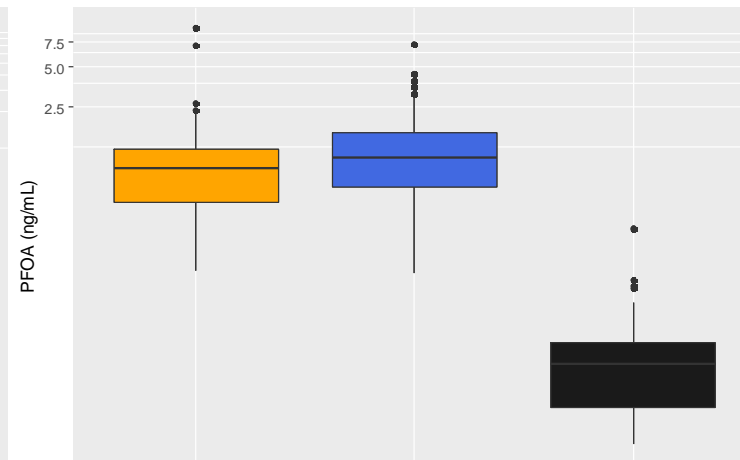
PFOA



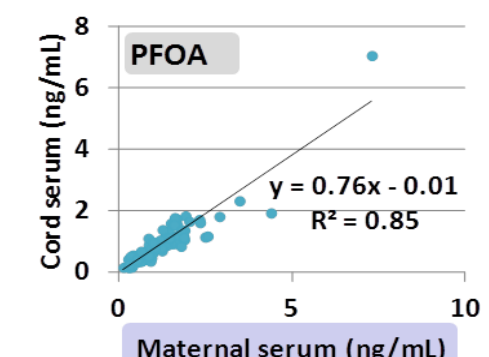
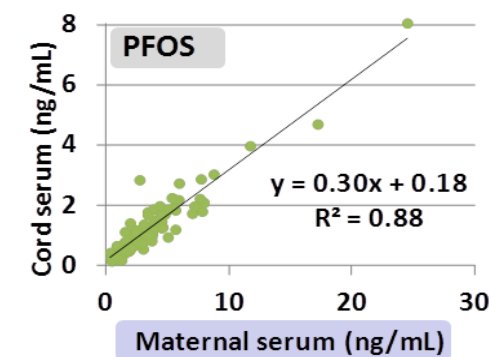
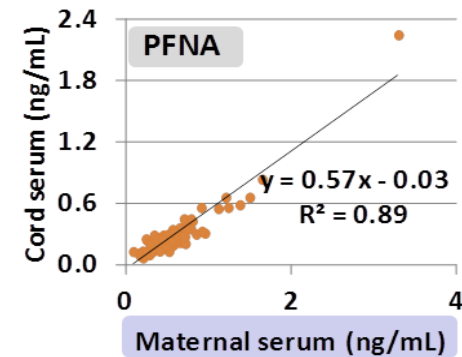
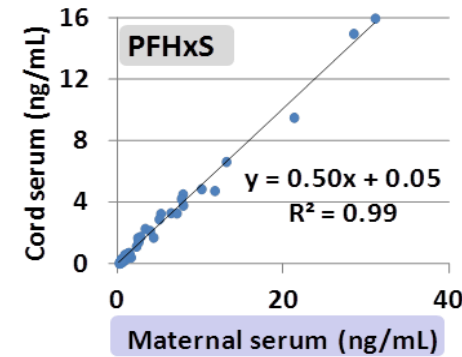
Perfluorooctanoic Acid



Cord serum Mat. serum Milk

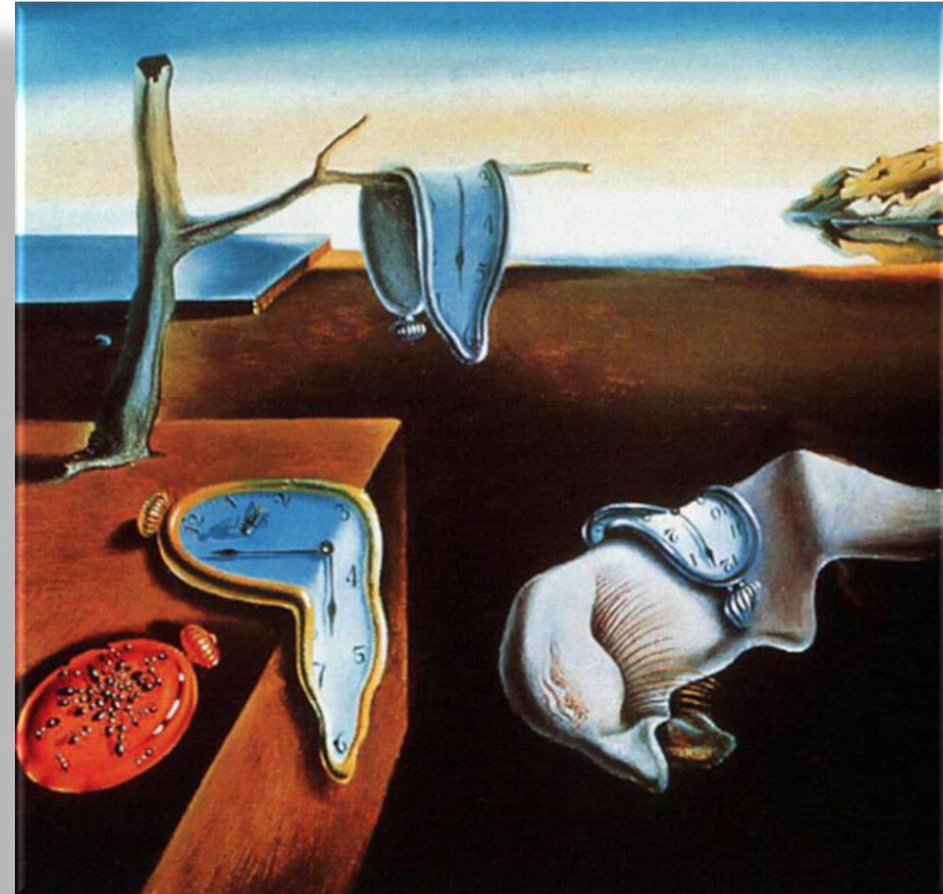


Cord serum Mat. serum Milk



Cariou et al, *Env. Int.*
2015;84:71–81.

- Introduction
- What measuring ?
- How measuring ?
- Where measuring ?
- Real case studies
- Conclusion

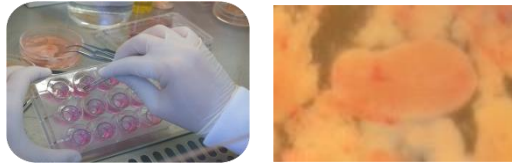




IMPACTESTIS project - "Impact des analgésiques sur le testicule humain fœtal et adulte." - AAP-2012-037
Collab. INSERM 1097 IRSET (Bernard Jegou, Severine Mazaud-Guittot, Millissia Ben Maamar)

Coord. INSERM 1087 IRSET

Human Testis explants exposed to EDCs (Ibuprofen, paracetamol, bisphenols, phtalates...)



Intra or extra cellular content

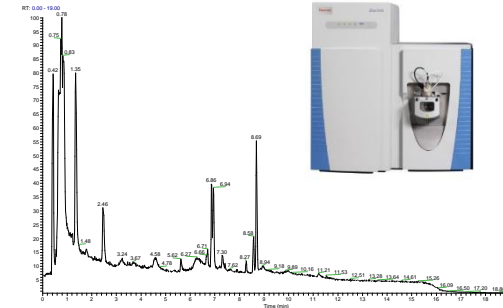
Endo-metabolome

Exo-metabolome

3 complementary levels of characterization

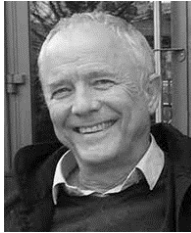


Metabolomics
Lipidomics
Stereoidomics



ML
030814
TCT F750
JL71-105574
JL
05.00-1000.00
MS
20141114-011

Pr. B. Jegou
INSERM 1087 IRSET



Check for updates

Ibuprofen alters human testicular physiology to produce a state of compensated hypogonadism

David Møbjerg Kristensen^{a,b,c,1,2}, Christèle Desdoits-Lethimonier^{b,1}, Abigail L. Mackey^{d,e}, Marlene Danner Dalgaard^f, Federico De Masi^f, Cecilie Hurup Munkbøl^g, Bjarne Styrihave^g, Jean-Philippe Antignac^h, Bruno Le Bizec^h, Christian Platelⁱ, Anders Hay-Schmidt^j, Tina Kold Jensen^k, Laurianne Lesné^b, Séverine Mazaud-Guittot^b, Karsten Kristiansen^{l,m}, Søren Brunak^{a,c}, Michael Kjaer^{d,e}, Anders Juul^{n,o}, and Bernard Jégou^{b,2}

^aDanish Headache Center, Department of Neurology, Rigshospitalet, University of Copenhagen, 1165 Copenhagen, Denmark; ^bUniversité de Rennes I, Inserm, EHESP-School of Public Health, Irset (Institut de Recherche en Santé, Environnement et Travail) - UMR_S 1085, F-35000 Rennes, France; ^cNovo Nordisk Foundation Center for Protein Research Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3A, 2200 Copenhagen, Denmark;

RESEARCH ARTICLE

An Investigation of the Endocrine-Disruptive Effects of Bisphenol A in Human and Rat Fetal Testes

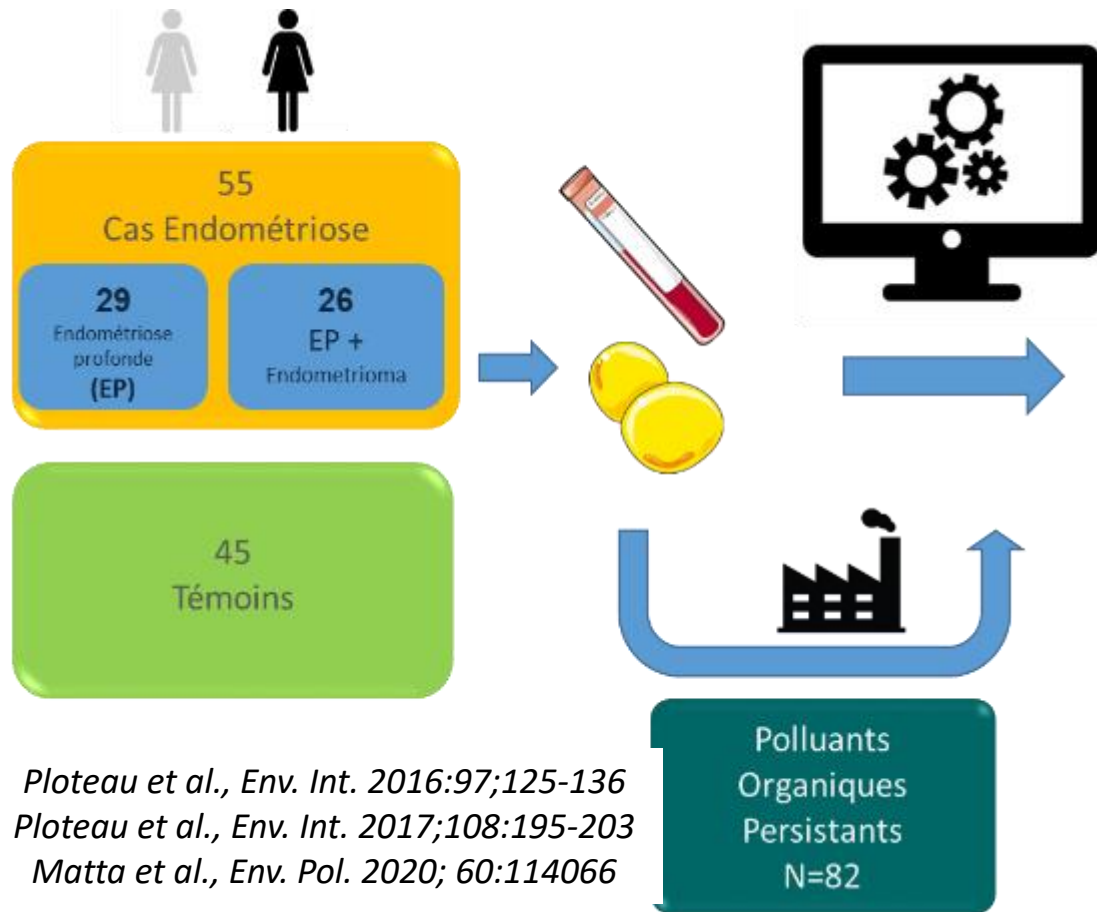
Millissia Ben Maamar^{1,2,†}, Laurianne Lesné^{1,2,†}, Christèle Desdoits-Lethimonier^{1,2,†}, Isabelle Coiffec^{1,2}, Julie Lassarguère^{1,2}, Vincent Lavoué³, Yoann Deceuninck⁴, Jean-Philippe Antignac⁴, Bruno Le Bizec⁴, Elisabeth Perdu⁵, Daniel Zalko⁵, Charles Pineau^{1,2}, Cécile Chevrier^{1,2}, Nathalie Dejuçq-Rainsford^{1,2}, Séverine Mazaud-Guittot^{1,2,†}, Bernard Jégou^{1,2,6,*†}

Etude ENDOMET (2013-2016) – Première étude Française du lien POP-endométriose

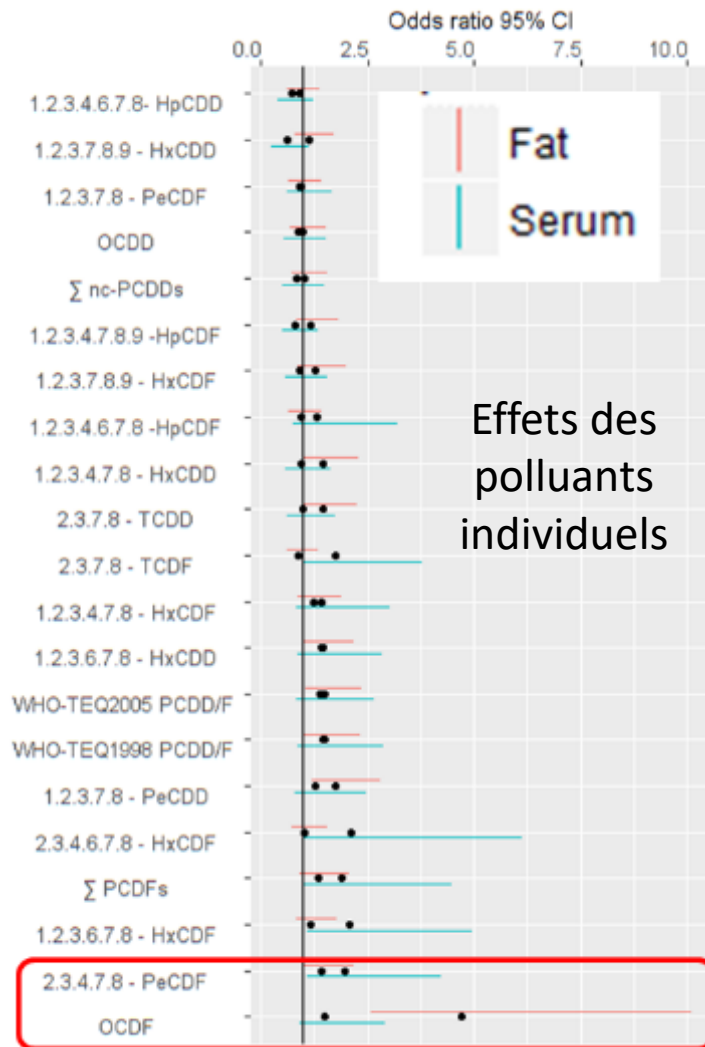
1. Génération de nouvelles données d'exposition



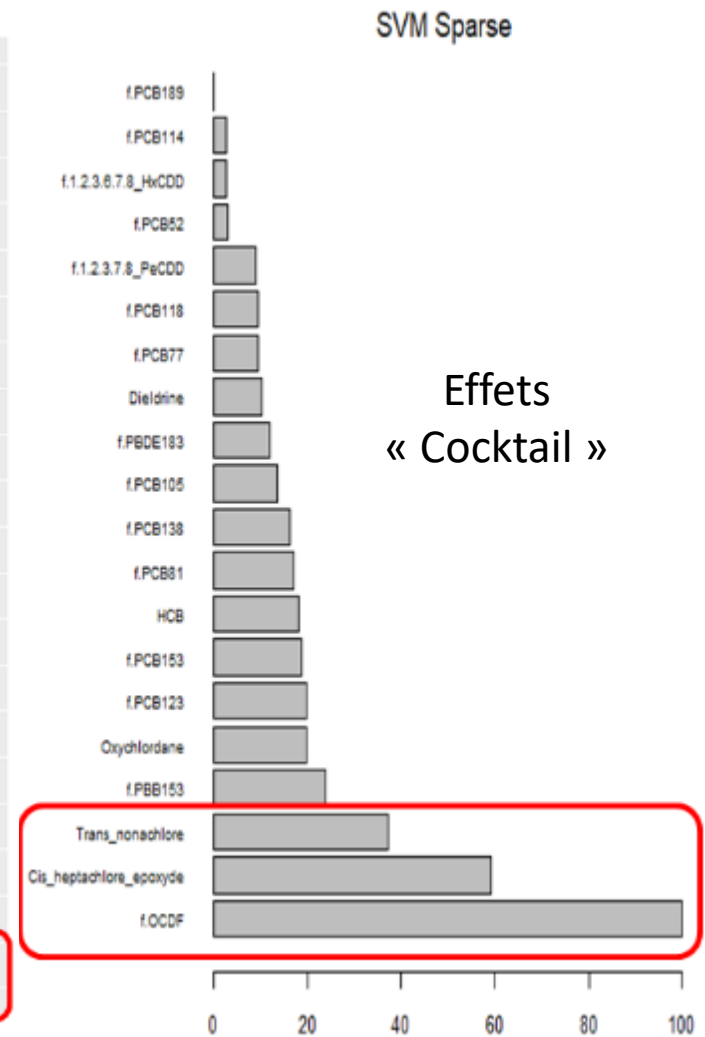
PhD
Pr. S. Ploteau
LABERCA / CHU Nantes



Ploteau et al., *Env. Int.* 2016;97:125-136
Ploteau et al., *Env. Int.* 2017;108:195-203
Matta et al., *Env. Pol.* 2020; 60:114066



Effets des polluants individuels



Effets « Cocktail »



Etude ENDOMET (2013-2016) – Première étude Française du lien POP-endométriose

2. Revue systématique des études épidémiologiques



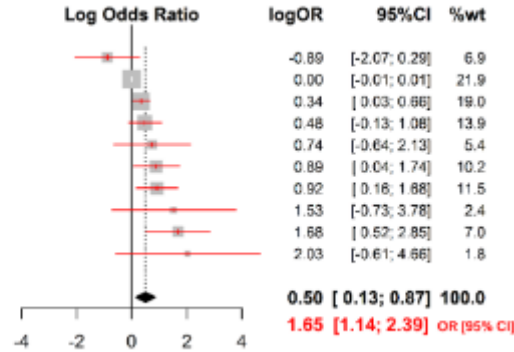
Dr. G. Cano-Sancho
LABERCA

PCDD/Fs

Reference	Chemical	Matrix	OR	LB	UB
Taukino et al. 2005	TEQ-Total DLC	SER	0.41	0.12	1.27
Niskar et al. 2009	TEQ- PCDD/Fs	SER	1	0.99	1.01
Martinez-Zamora et al. 2015	TCDD	AT	1.41	1.12	2.1
Ploteau et al. 2017	TEQ- PCDD/Fs	AT	1.61	0.9	3.01
Eskenazi et al. 2002	TCDD	SER	2.1	0.5	8
Simsa et al. 2010	TEQ-Total DLC	PLA	2.44	1.04	5.7
Cai et al. 2011	TEQ- PCDD/Fs	PEF	2.5	1.17	5.34
Pauwels et al. 2001	TEQ-Total DLC	SER	4.6	0.48	43.62
Heller et al. 2005	TEQ-Total DLC	SER	5.39	1.68	17.3
Mayani et al. 1997	TCDD	SER	7.6	0.87	169.7

Random effects model

Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0.1646$, $p < 0.01$

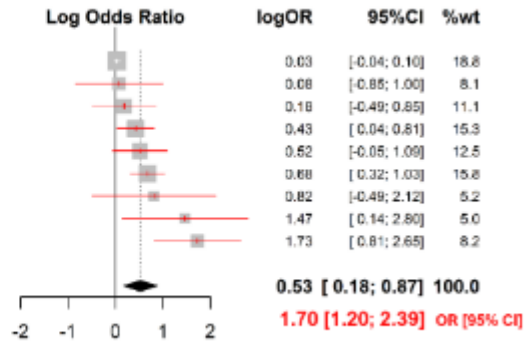


PCBs

Reference	Chemical	Matrix	OR	LB	UB
Buck Louis et al 2012	c-PCBs	AT	1.03	0.98	1.1
Niskar et al. 2009	PCBs	SER	1.08	0.43	2.73
Trabert et al. 2010	ndl-PCBs	SER	1.2	0.6	2.3
Ploteau et al. 2017	PCBs	AT	1.53	1.04	2.26
Hoffman et al. 2007	Aroclor	SER	1.68	0.95	2.98
Martinez-Zamora et al. 2015	PCBs	AT	1.97	1.36	2.77
Louis et al. 2005	PCBs	SER	2.26	0.81	8.34
Heller et al. 2005	d-PCBs	SER	4.34	1.15	16.39
Porpora et al. 2009	PCBs	SER	5.63	2.25	14.1

Random effects model

Heterogeneity: $I^2 = 78\%$, $\tau^2 = 0.1671$, $p < 0.01$

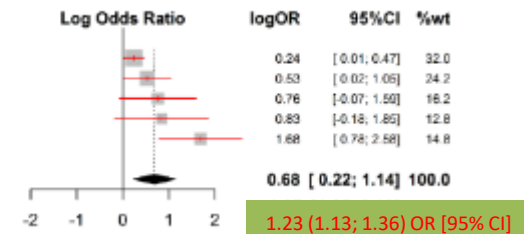


Pesticides

Reference	Chemical	Matrix	OR	LB	UB
Buck Louis et al 2012	v-HCH	AT	1.27	1.01	1.59
Upson et al. 2013	β-HCH	Serum	1.7	1	2.8
Porpora et al. 2010	p,p'-DDE	Serum	2.14	0.93	4.93
Cooney et al. 2010	l-nanochlor	Serum	2.3	0.8	6.1
Ploteau et al. 2017	Cis-heptachlore epoxyde	AT	5.36	2.44	14.84

Random effects model

Heterogeneity: $I^2 = 65\%$, $\tau^2 = 0.1576$, $p = 0.02$



Human epidemiological studies

- Overall positive associations
- Heterogeneous study designs, populations, clinical procedures and analytical methods for exposure biomarkers

Environment International 123 (2019) 209–223



Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint



Review article

Human epidemiological evidence about the associations between exposure to organochlorine chemicals and endometriosis: Systematic review and meta-analysis

German Cano-Sancho^{a,*}, Stéphane Ploteau^b, Komodo Matta^a, Evdochia Adoamnei^c, Germaine Buck Louis^d, Jaime Mendiola^c, Emile Darai^{e,f}, Jean Squifflet^g, Bruno Le Bizec^a, Jean-Philippe Antignac^a

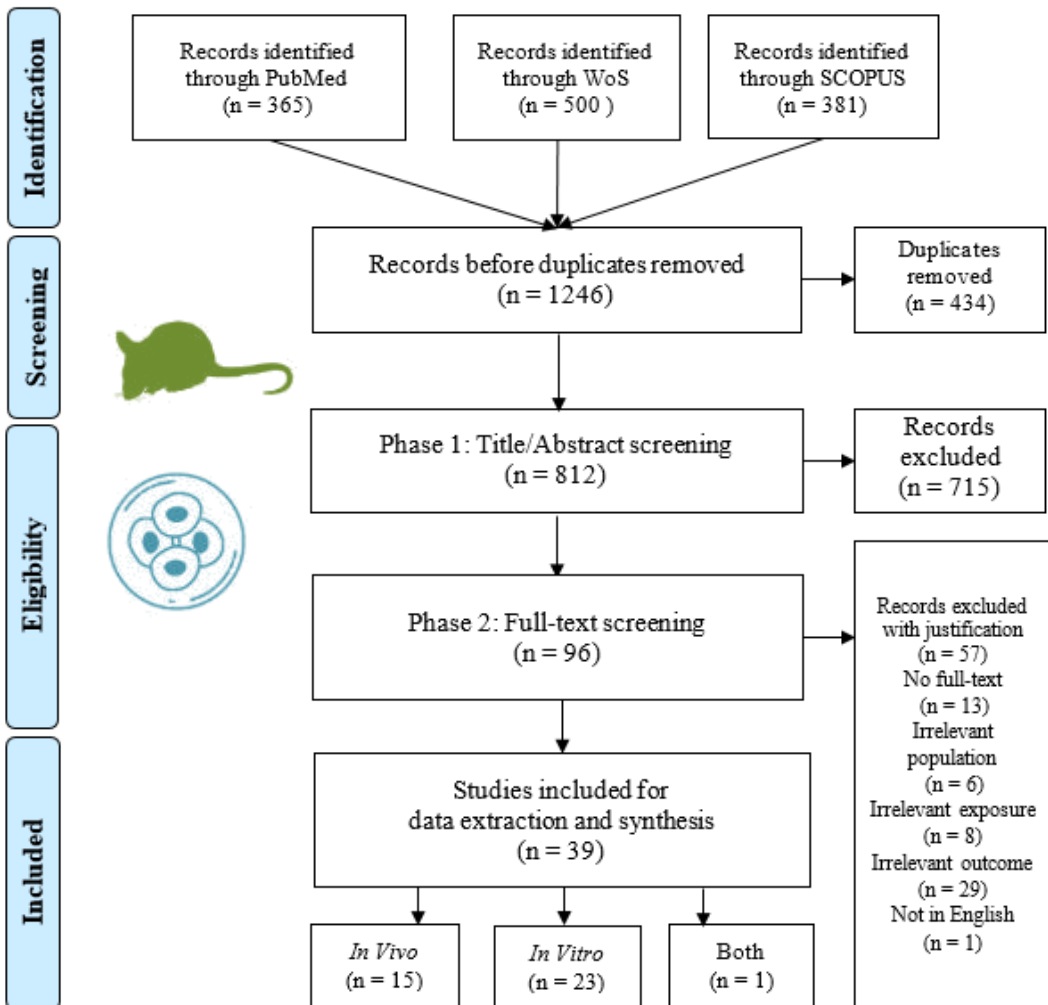


Cano-Sancho et al, Env. Int. 2019,123:209-223.



Etude ENDOXOMICS (2018-2022) – Etude approfondie du lien POP-endométriose

1. Revue systématique des études expérimentales



- **39 total studies included**

- 15 *in vivo*, 23 *in vitro*, 1 both

- **3 animal models**

- Rat (autologous implant)
- Mouse (autologous implant and nude)
- Monkey (autologous implant and spontaneous onset)

- **Various cell models**

- Endometrial Stromal Cells (ESCs), ESC co-cultures, Endometrial Epithelial Cells, Endometrial Endothelial Cells, Endometrial Explants, Uterine Fibroblasts, Granulosa Cells

- **14 Chemicals**

2,3,7,8-TCDD	PCB 126	HCB
1,3,6,8-TCDD	PCB 153	4-CDE
4-PeCDF	p,p'-DDT	ATR
PCB 77	p,p'-DDE	MXC
PCB 104	o,p'-DDT	



Dr. G. Cano-Sancho
LABERCA



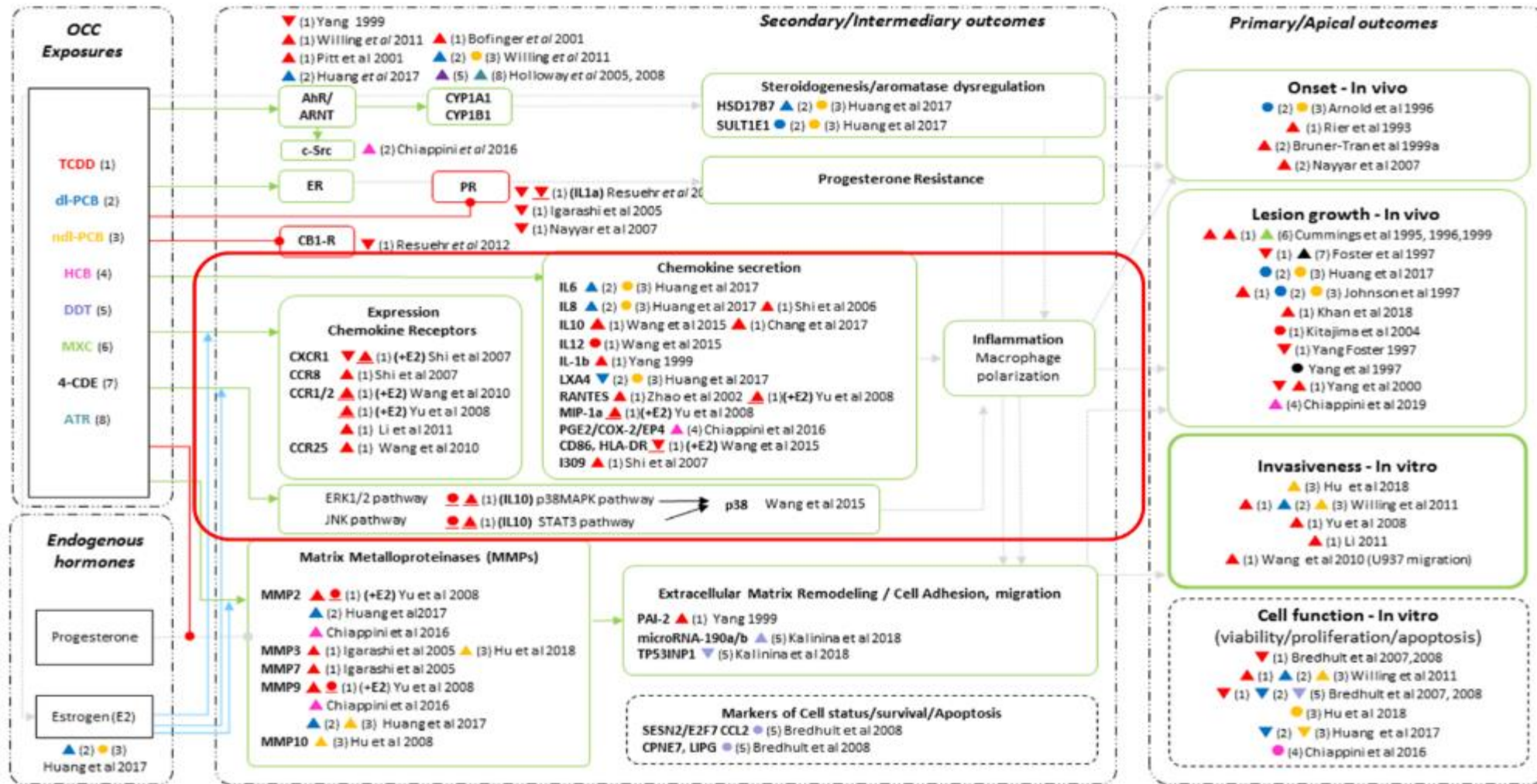
PhD
Dr. K. Matta

Matta et al, *Env. Int.*
2019;124:400-407.

Matta et al, *EHP*
2021;129(7):076003

Etude ENDOXOMICS (2018-2022) – Etude approfondie du lien POP-endométriose

2. Identification des Adverse Outcome Pathways (AOP) fonctionnels sous-jacents



Dr. G. Cano-Sancho
LABERCA



PhD
Dr. K. Matta

Matta et al, EHP
2021;129(7):076003

Role in endometriosis ↓	Name of the Endocrine disruptor →	PCB	TCDD	BPA	Phthalate
i) Chronic Inflammation (Proinflammatory Cytokines)		IL-6, IL-8 ↑	IL-8, COX-2, PGE2 ↑	p-AKT, p-ERK, p-JNK, MAPK, TNF-α, IL-6, IL-1β ↑	MAPK, ERK1/2, IKB, NF-κB, COX-2 ↑
ii) Cell migration/ Invasion (Remodeling Enzymes/ Matrix metalloproteinases)		MMP-3 & MMP-10 ↑	MMP-3 & MMP-7 ↑	1) MMP-2 & MMP-9 ↑ 2) TIMPs ↓	1) MMP-2 & MMP-9 ↑ 2) TIMPs ↓
iii) Growth Factor Signaling / Cellular Proliferation		Epidermal Growth Factor signaling ↑	TGF-β ↓	Epidermal Growth Factor signaling ↑	Ki-67, Pak4 ↑
iv) Estrogen Signaling		E ₂ ↑	Steroid Enzymes (P-450 aromatase) ↑	ER-α ↑	ER-α ↑
v) Anti-inflammatory		Lipoxin A4 (LX4) ↓	—	—	—
vi) Progesterone Resistance		Caused due to dysregulation of thyroid transcripts ↑	i) Caused due to dysregulation of thyroid transcripts ↑ ii) PR-B ↓	Caused due to dysregulation of thyroid transcripts ↑	Caused due to dysregulation of thyroid transcripts ↑
vii) Developmental Genes		—	—	HOX- A10 ↑	—
viii) Oxidative Stress		↑ Reactive Oxygen Species (ROS)	↑ Reactive Oxygen Species (ROS)	1) ↑ Reactive Oxygen Species (ROS) 2) Antioxidant enzymes: Superoxide Dismutase (SOD), Catalase (CAT), Heme oxygenase (HO) ↓	1) ↑ Reactive Oxygen Species (ROS) 2) Antioxidant enzymes: Superoxide Dismutase (SOD), Catalase (CAT), Heme oxygenase (HO) ↓

Dutta et al,
Reprod Toxicol.
2023;115:56-73

Etude ENDOXOMICS (2018-2022) – Etude approfondie du lien POP-endométriose



3. Extension au lien exposition-endométriose-infertilité

Clinical recruitment n=437

Exposome-metabolome profiling

Data Analysis



Dr. G. Cano-Sancho
LABERCA



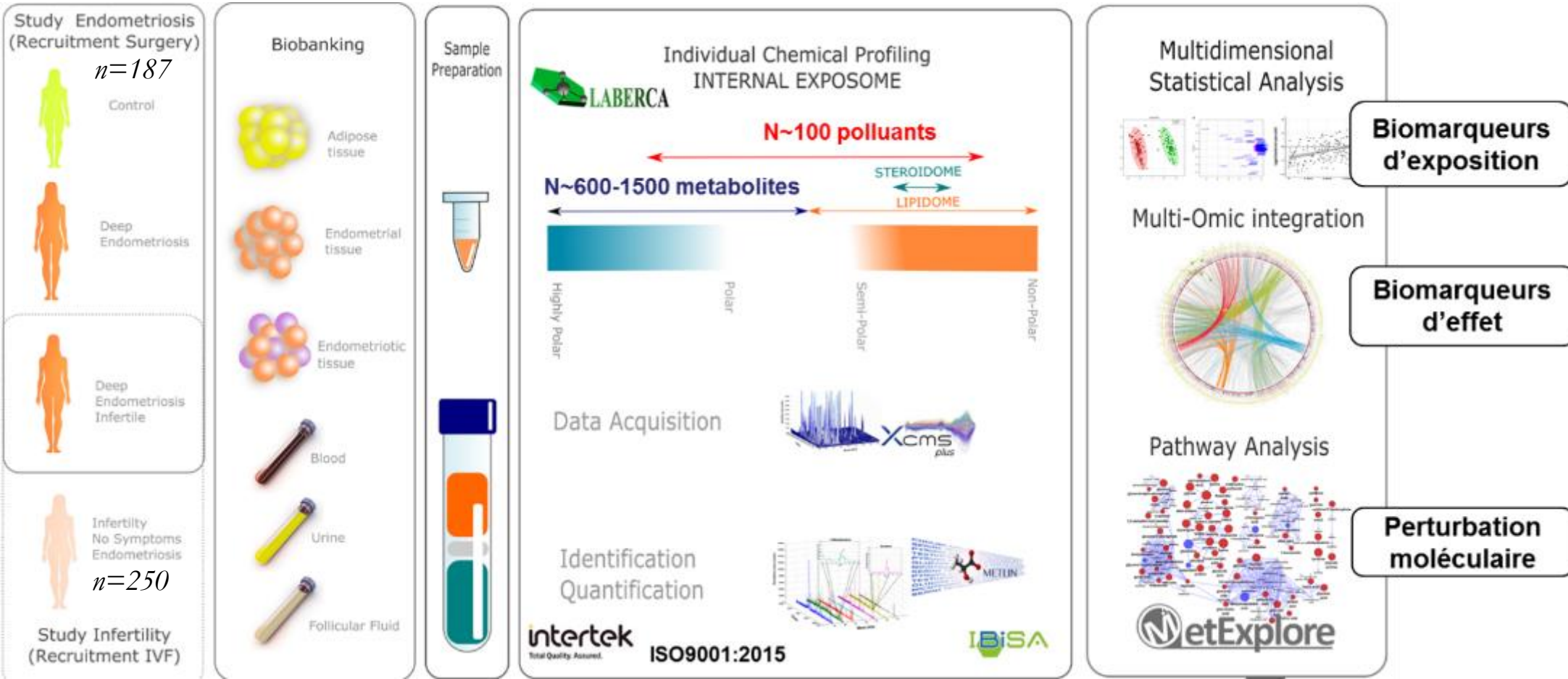
PhD T. Lefebvre
CHU Nantes



Pr. T. Freour
CHU Nantes



Pr. S. Ploteau
CHU Nantes



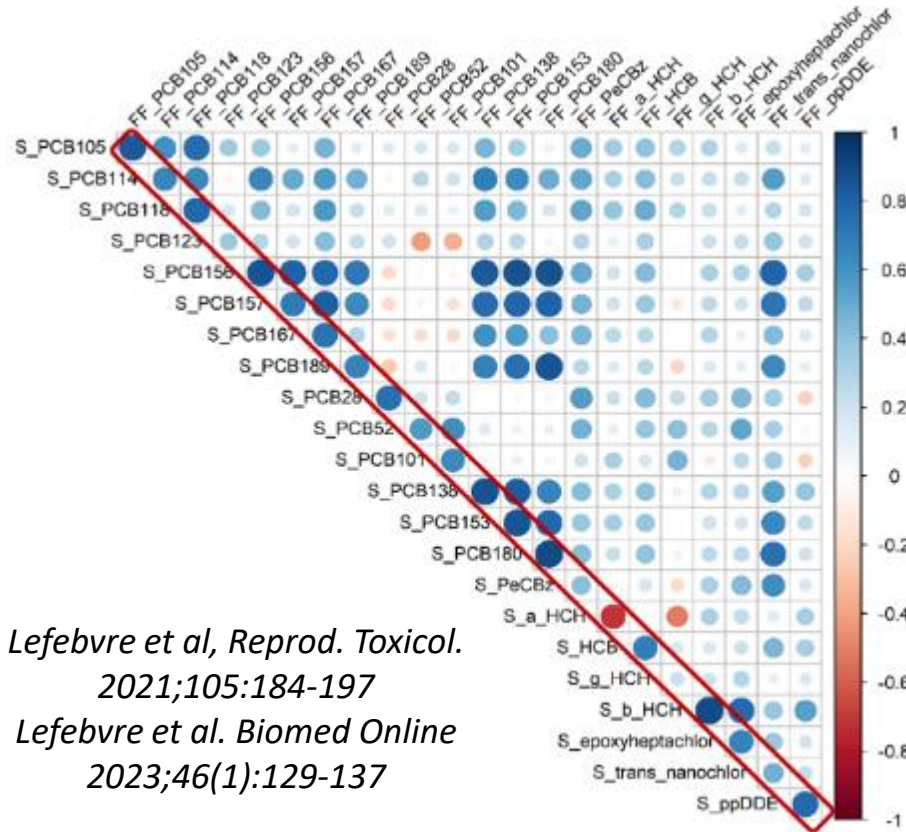
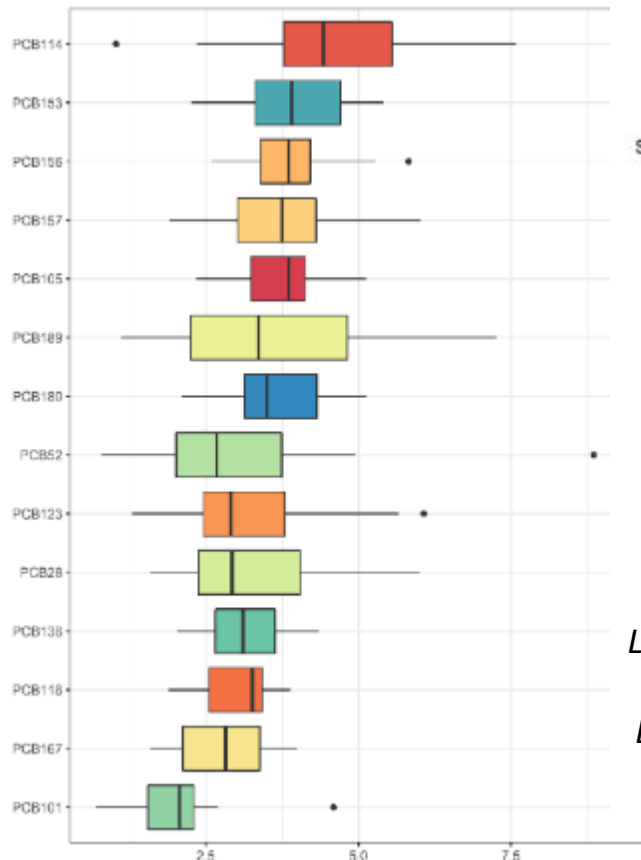
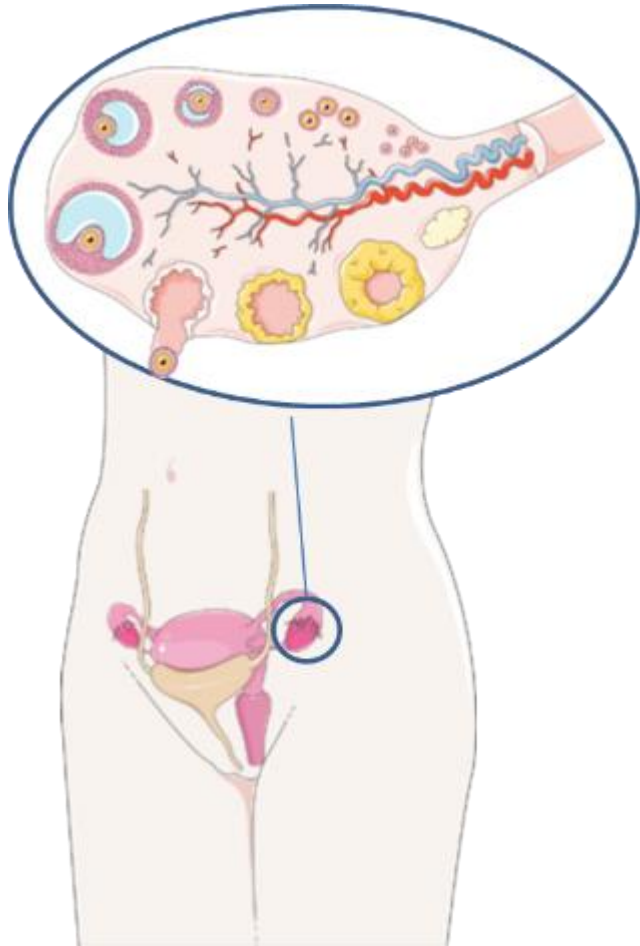
Etude ENDOXOMICS (2018-2022) – Etude approfondie du lien POP-endométriose



3. Extension au lien exposition-endométriose-infertilité

POPs présents dans le liquide folliculaire et corrélés avec niveaux sériques

Boxplot of ratios (A) and correlation (B) of POPs between serum and follicular fluid (FF)



Lefebvre et al, *Reprod. Toxicol.* 2021;105:184-197
 Lefebvre et al. *Biomed Online* 2023;46(1):129-137



Dr. G. Cano-Sancho
LABERCA



PhD T. Lefebvre
CHU Nantes



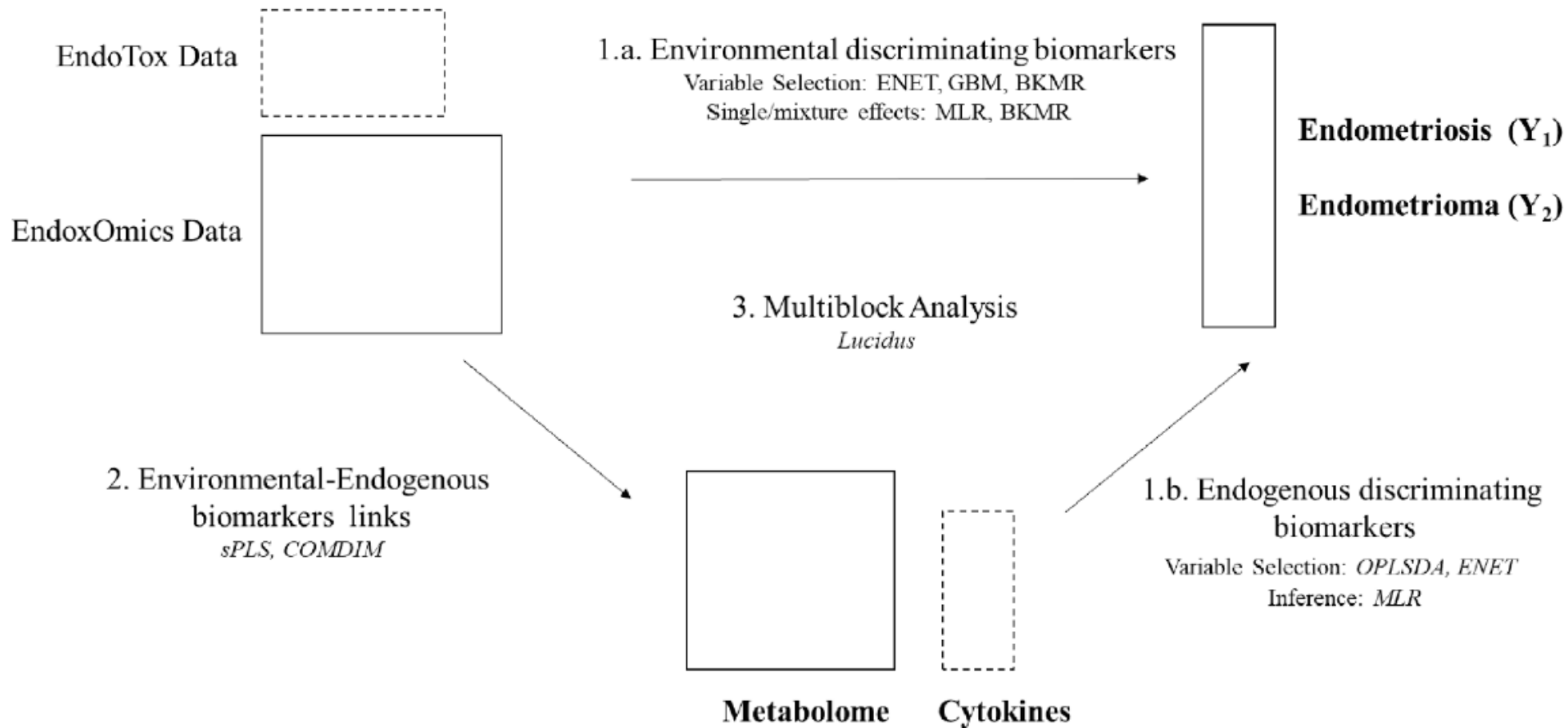
Pr. T. Freour
CHU Nantes



Pr. S. Ploteau
CHU Nantes

Etude ENDOXOMICS (2018-2022) – Etude approfondie du lien POP-endométriose
 4. Intégration multibloc (exposition – perturbation métabolique – issue de santé)

Chemical Exposures (POPs)



Dr. G. Cano-Sancho
LABERCA



Dr. P. De Tullio
Univ. Liège

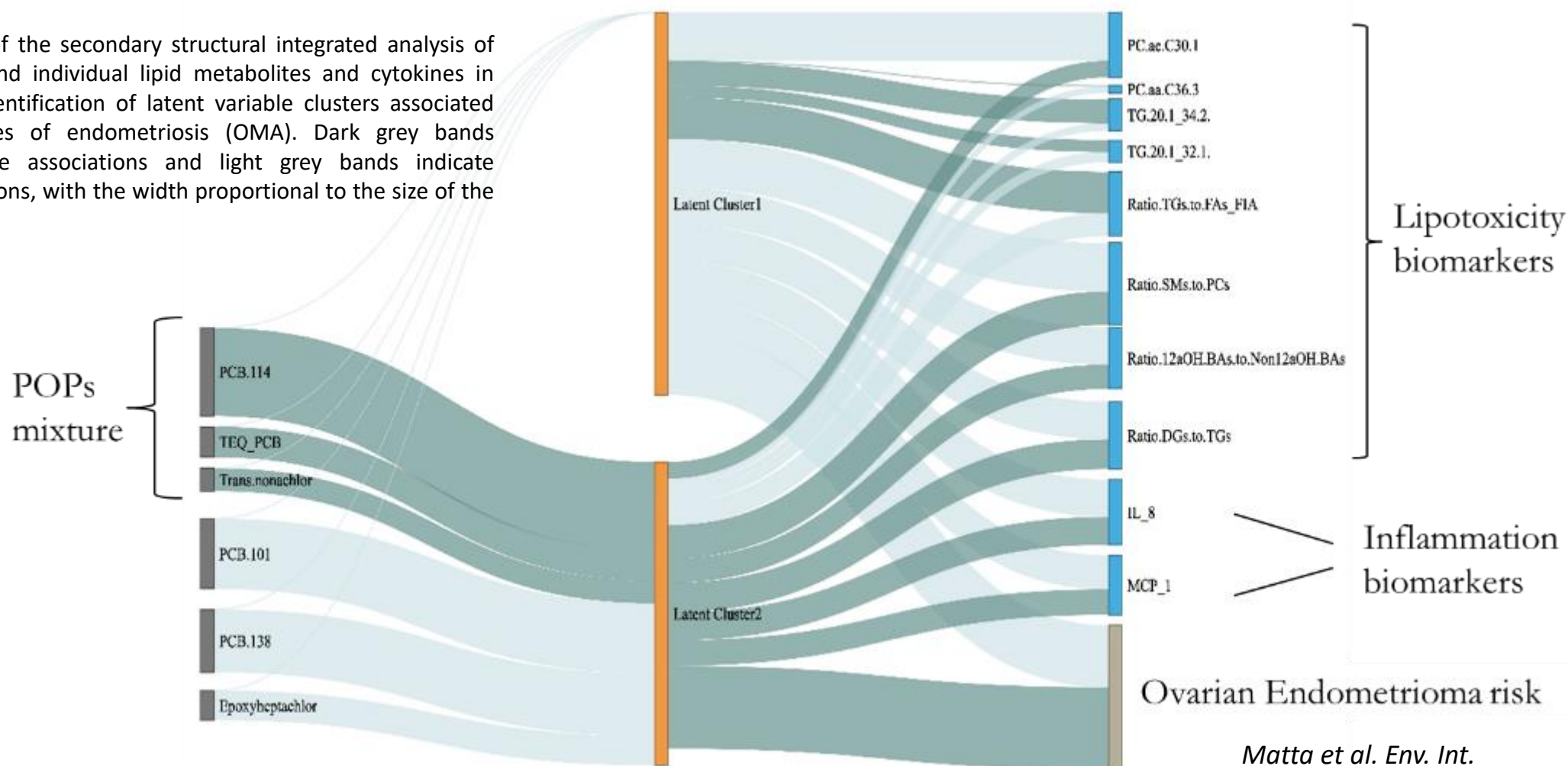


Pr. E. Vigneau
Oniris

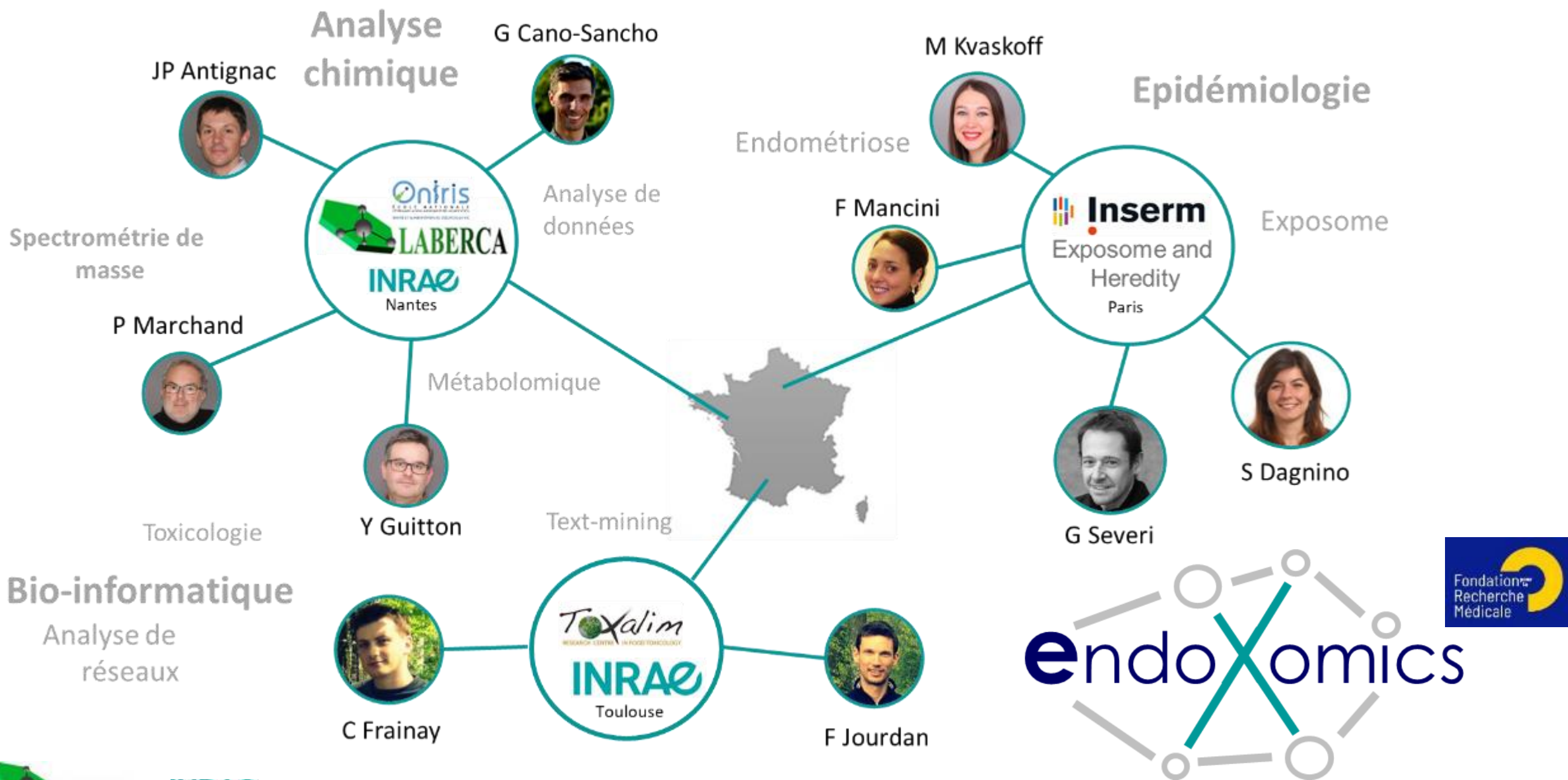
Etude ENDOXOMICS (2018-2022) – Etude approfondie du lien POP-endométriose

4. Intégration multibloc (exposition – perturbation métabolique – issue de santé)

Sankey diagram of the secondary structural integrated analysis of POPs exposure and individual lipid metabolites and cytokines in serum for the identification of latent variable clusters associated with severe cases of endometriosis (OMA). Dark grey bands represent positive associations and light grey bands indicate negative associations, with the width proportional to the size of the association.



Matta et al. *Env. Int.*
2022;158:106926



Etude Cas-Cohorte E3N

Analyse chimique intégrative

Résultats attendus



Bio-collection

Habitudes alimentaires

Mode de vie

Marqueurs d'exposition
Polluants organiques persistants



Analyse statistique et
bio-informatique



Facteurs de risque
environnementaux

Stratégies de prévention

Liens fonctionnels

Connaissance fondamentale

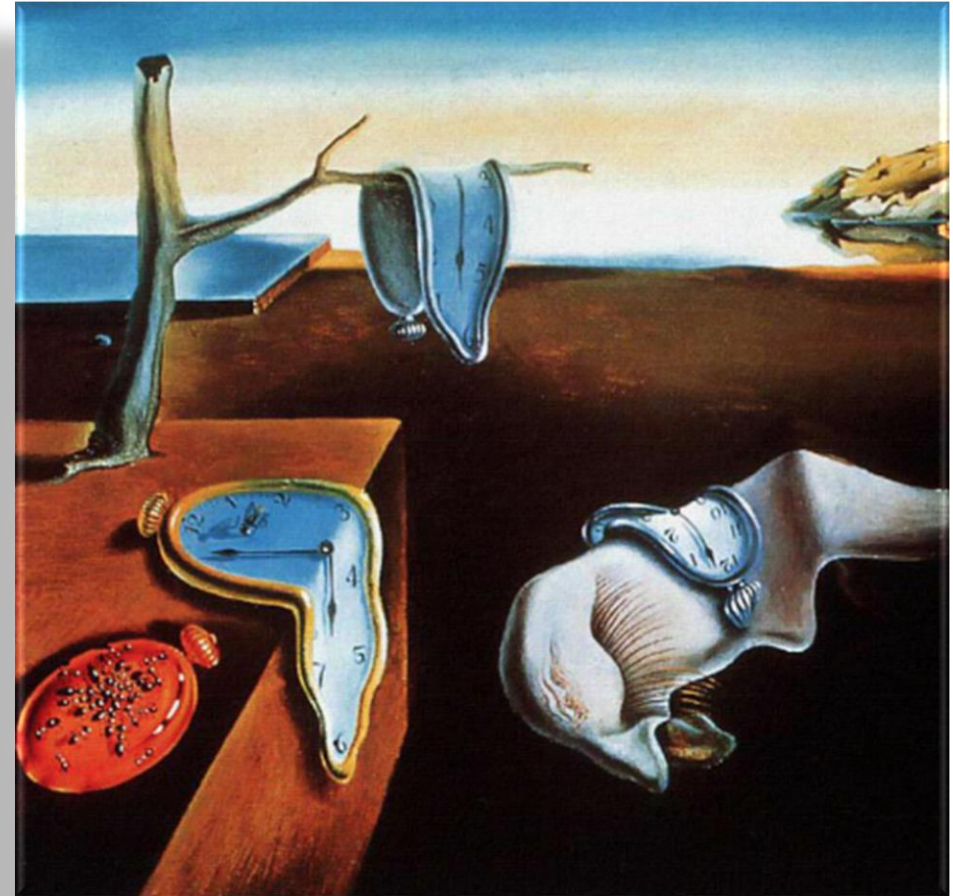
Biomarqueurs
prédictifs

Outils de diagnostic précoce

625 femmes
125 cas endométriose

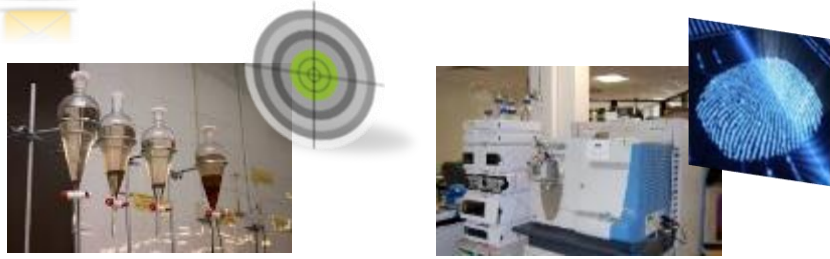


- Introduction
- What measuring ?
- How measuring ?
- Where measuring ?
- Real case studies
- Conclusion



Conclusions

How measuring?



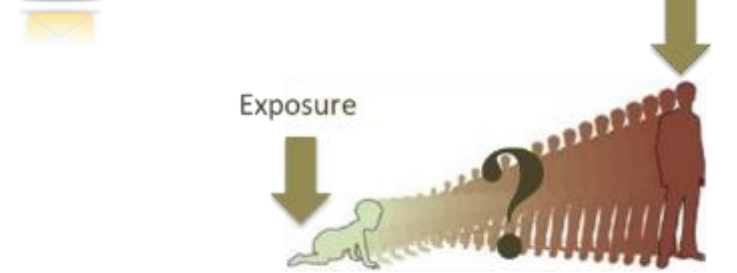
- Sample preparation remains a corner stone
- Targeted quantitative methods still needed
- Untargeted profiling methods now the trend

Where measuring?



- Need for more multi-compartment studies
- Stored vs. circulating ratio as integrative marker
- Non identical strategies for HBM / health studies

When measuring?



- Need for longitudinal data and PBPK modeling
- Need for better experimental models
- MS profiling in personalized medicine

What measuring?



- Need for more extended characterizations...
- ... Following the exposome and mixture issues
- Need for integrating exposure / effect markers

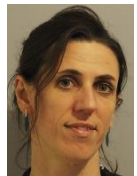
Remerciements



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Dr. Matta



Dr. Lefebvre



Dr. P. Marchand



Dr. Y. Guitton



Pr. B Le Bizec



Pr. S. Ploteau



Pr. T. Freour



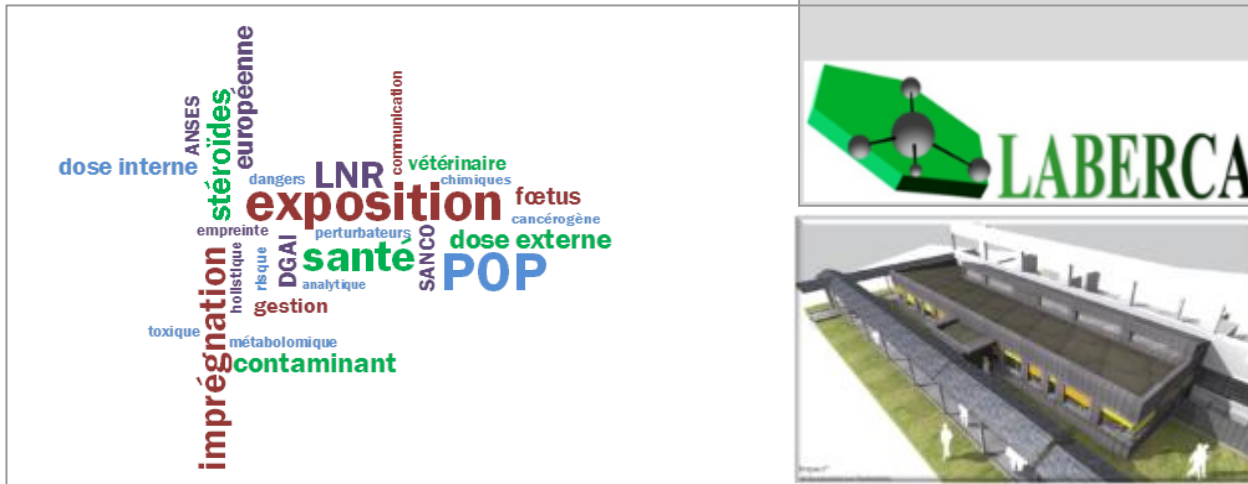
Dr. De Tullio et M. Campas





ÉTUDIER LE LIEN ENTRE EXPOSITION CHIMIQUE ENVIRONNEMENTALE ET TROUBLES DE LA REPRODUCTION : APPROCHES ET DÉFIS

Jean-Philippe ANTIGNAC



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