

Association des lactariums de France (ADLF)

Nantes, 20-21 mai 2011



Le lait maternel à l'interface environnement-santé

Jean-Philippe Antignac

P. Marchand, B. Veyrand, A. Venisseau, B. Le Bizec

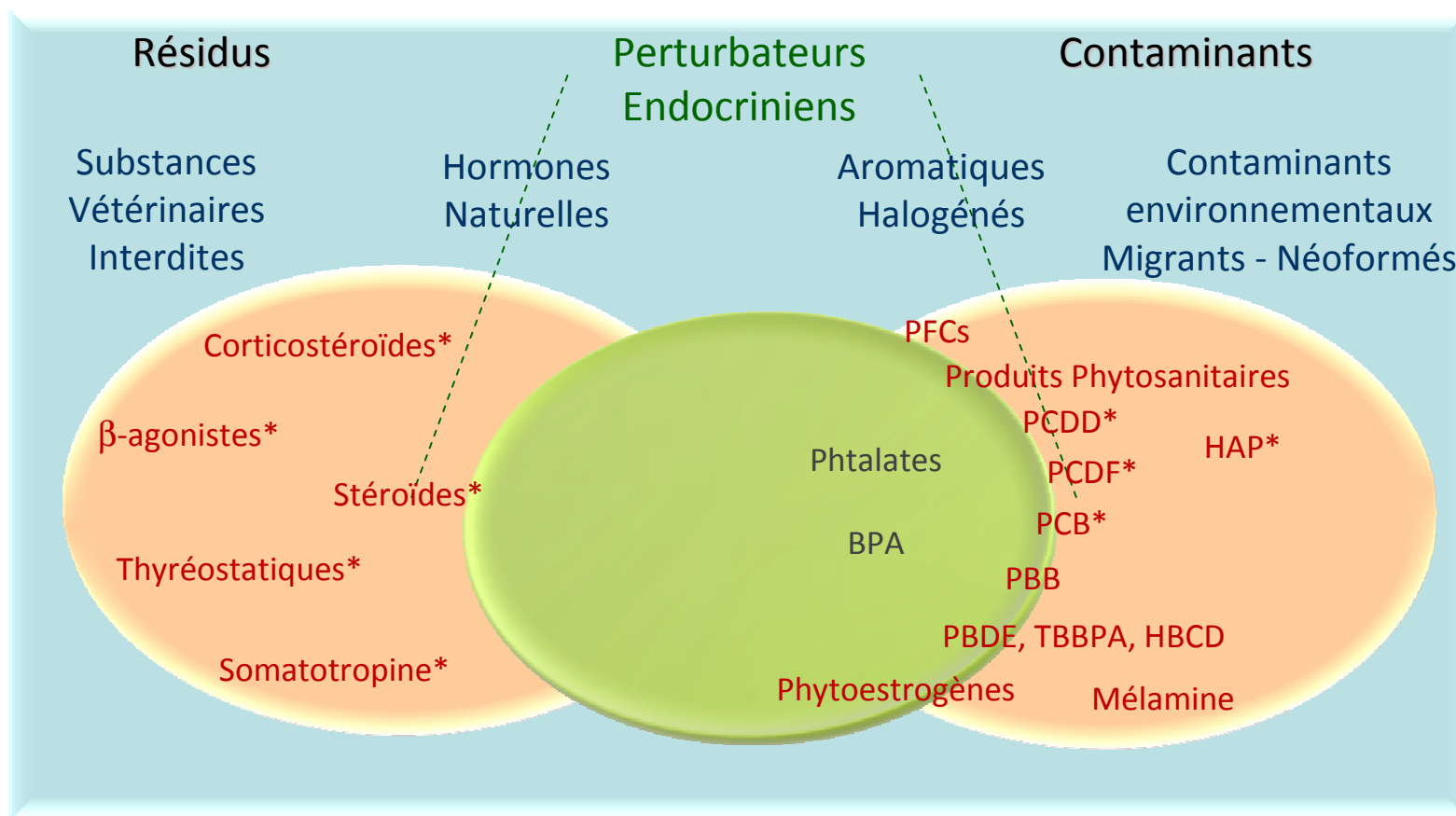


Laboratoire d'Etude des Résidus et Contaminants dans les Aliments
Ecole Nationale Vétérinaire, Agroalimentaire et de l'Alimentation Nantes
Atlantique www.laberca.org – www.saraf-educ.org

- Introduction
- Les principaux dangers chimiques
- Les challenges méthodologiques
- Les recherches en cours
- Conclusion

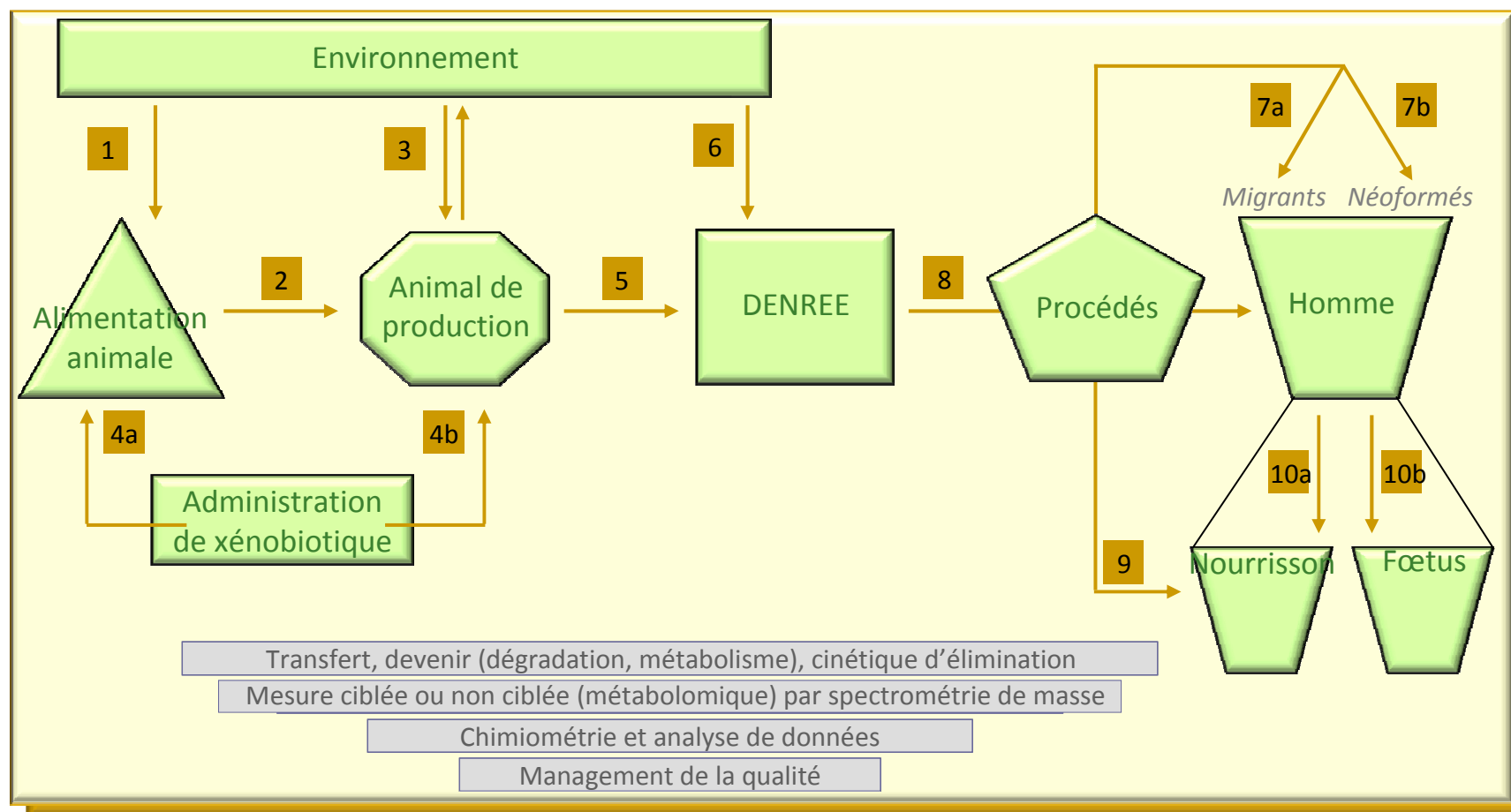


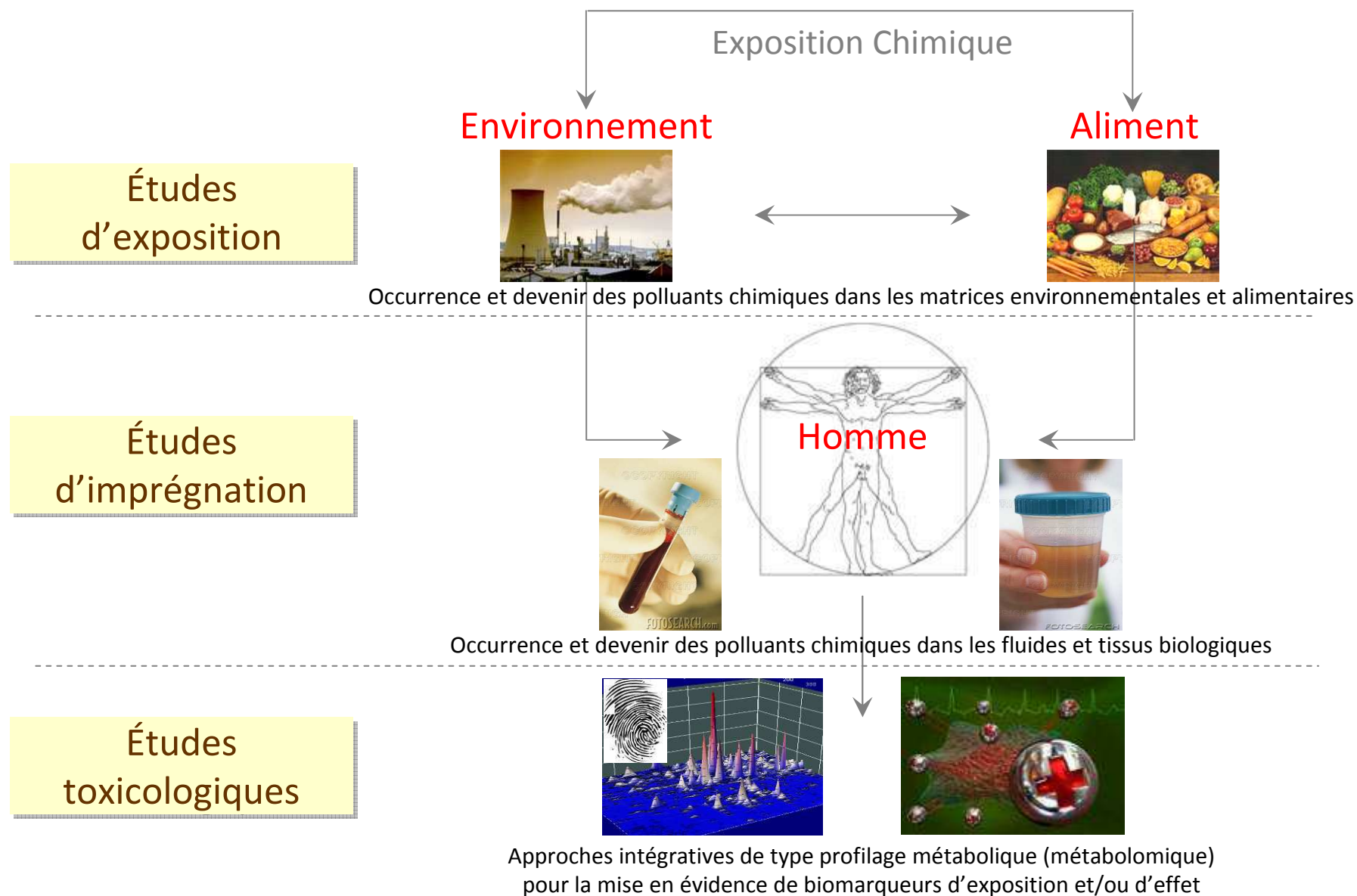
La sécurité chimique des aliments



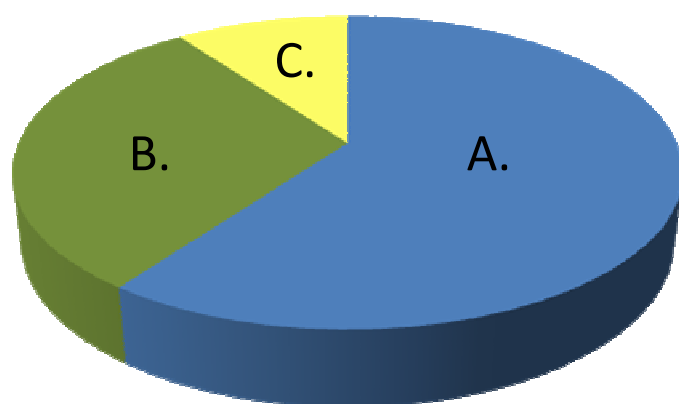
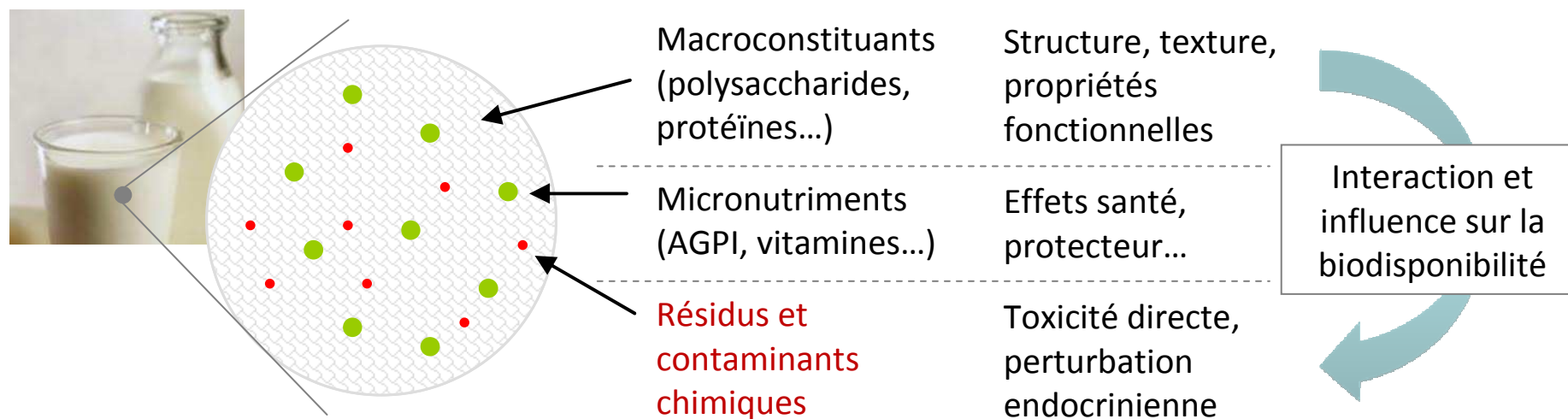
* Laboratoire National de Référence (LNR) pour la Direction Général de L'Alimentation (DGAL)

Les dangers chimiques dans l'alimentation : de leurs sources jusqu'à l'homme et sa descendance





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



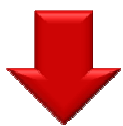
- A. Fraction aqueuse
Certaines hormones, **phytoestrogènes**, métabolites
- B. Fraction protéique
Contaminants perfluorés (PFCs)
- C. Fraction lipidique
Certaines hormones, **contaminants lipophiles** (POPs)

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

Parce que particulièrement exposées

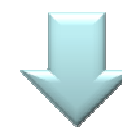


- De part une alimentation particulière
- Occupationnellement / professionnellement

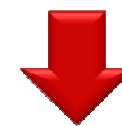


Lait Maternel

Parce que particulièrement vulnérables



- Stades critiques du développement :
- Puberté
 - Période périnatale
 - Période foétale

Vecteur d'exposition directe
du nourrisson allaité

+

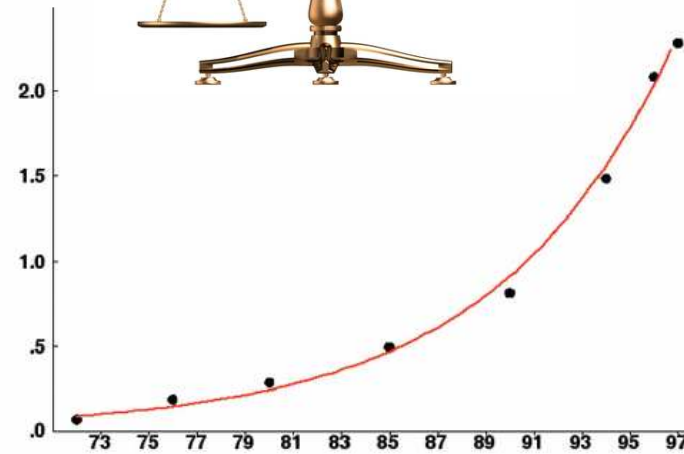
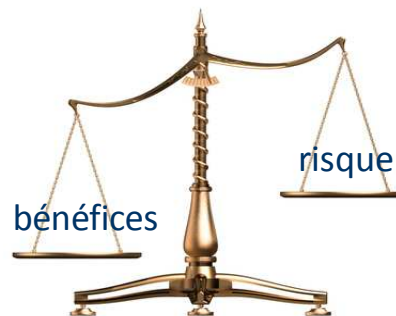
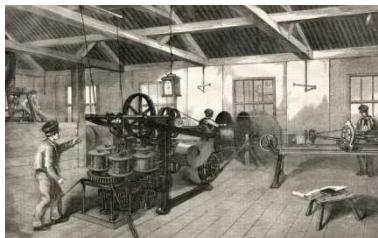
Indicateur de l'imprégnation
de la mère et donc du fœtus

Une question d'actualité aujourd'hui plus qu'hier

1900

2000

Relative constance des bénéfices individuels au plan nutritionnel, psychologique...



Annex I-Figure 21 - Time trend of BDE-47 concentrations (ng/g fat) in Swedish mothers' milk.



Accroissement du risque chimique global lié aux changements environnementaux

Plan

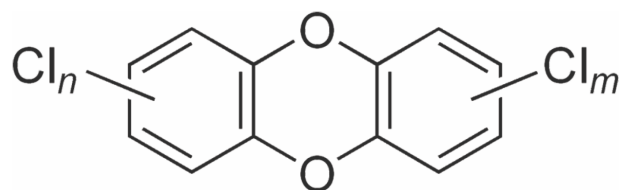
- Introduction
- Les principaux dangers chimiques
- Les challenges méthodologiques
- Les recherches en cours
- Conclusion



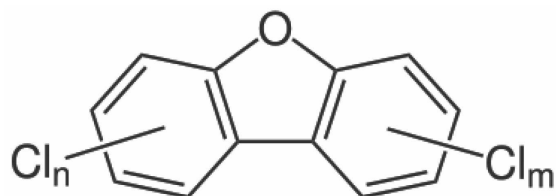
- Dioxines et PCBs



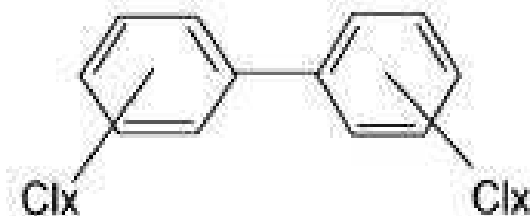
Polychlorinated dibenzo-*p*-dioxin (PCDDs)



Polychlorinated dibenzofurans (PCDFs)



Polychlorinated biphenyls (PCBs)



- Comment évaluer la toxicité d'un mélange de congénères?



Concepts de :

Toxic Equivalent Factors (TEF)
&
Toxic Equivalent Quotient (TEQ)

- Exprimé en équivalent 2,3,7,8-TCDD (pg TEQ/g de lipides)

The International Programme
on Chemical Safety (IPCS)



Compound	WHO 1998 TEF	WHO 2005 TEF*
<i>chlorinated dibenzo-p-dioxins</i>		
2,3,7,8-TCDD	1	1
1,2,3,7,8-PeCDD	1	1
1,2,3,4,7,8-HxCDD	0.1	0.1
1,2,3,6,7,8-HxCDD	0.1	0.1
1,2,3,7,8,9-HxCDD	0.1	0.1
1,2,3,4,6,7,8-HpCDD	0.01	0.01
OCDD	0.0001	0.0003
<i>chlorinated dibenzofurans</i>		
2,3,7,8-TCDF	0.1	0.1
1,2,3,7,8-PeCDF	0.05	0.03
2,3,4,7,8-PeCDF	0.5	0.3
1,2,3,4,7,8-HxCDF	0.1	0.1
1,2,3,6,7,8-HxCDF	0.1	0.1
1,2,3,7,8,9-HxCDF	0.1	0.1
2,3,4,6,7,8-HxCDF	0.1	0.1
1,2,3,4,6,7,8-HpCDF	0.01	0.01
1,2,3,6,7,8,9-HpCDF	0.01	0.01
OCDF	0.0001	0.0003

$$TEQ = \sum_{n_1} (PCDD_i \times TEF_i) + \sum_{n_2} (PCDDF_i \times TEF_i) + \sum_{n_3} (PCB_i \times TEF_i)$$

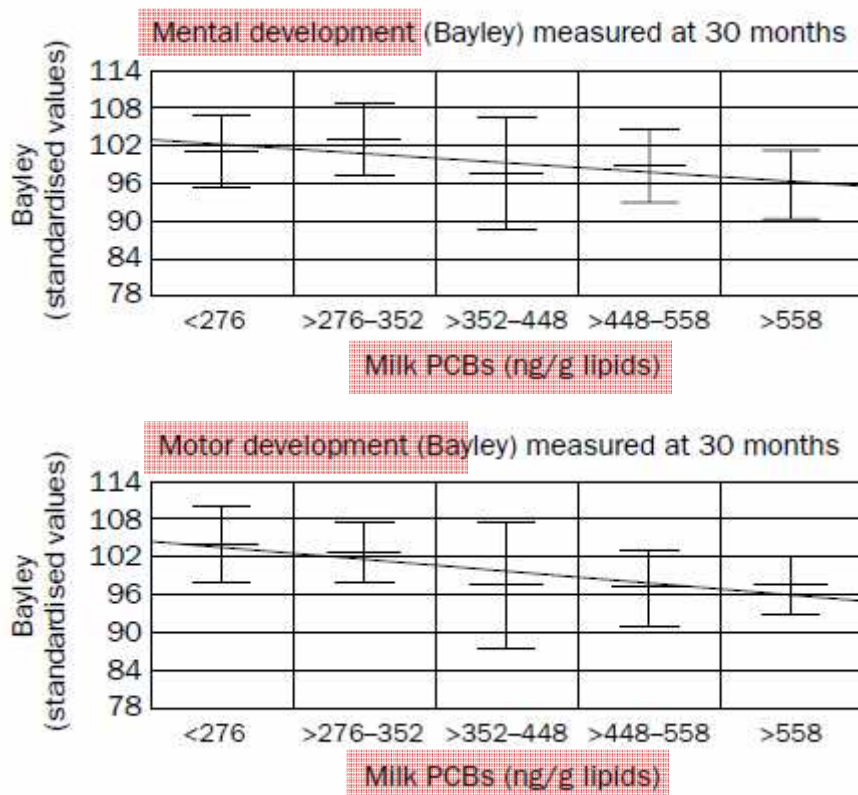
- Toft et al. Reproductive toxicol. 2004;19:5-26

« Review: epidemiological evidence on reproductive effects of persistent organochlorines in human. »

Epidemiological studies addressing effects of persistent organochlorines on birth weight

Reference and place	Exposure groups/compounds	Mean (median) or range of exposure	Mean, median, or midrange estimated as maternal serum PCB or DDE ^a	Birth weight
[78], Michigan, USA	Fish eaters – PCBs	2.5 ng/g PCB as Arochlor 1260 in cord serum; 5.5 ng/g in maternal serum	5.5 ng/g	↓
[70], New York State, USA	Working women exposed to PCB	9–33 ng/g Arochlor 1254 in serum, only measured on subset	21 ng/g	↓
[65], Wisconsin, USA	Fish eaters (PCBs)	0.6–5 ng/g estimated as sum of 13 congeners in maternal serum on subset	2.8 ng/g	↑
[68], Taiwan	PCB, PCDF maternal exposure	No exposure assessment	–	↓
[92], Sweden	Fishermen's wives east coast (high PCB) vs. west coast (lower PCB)	No exposure assessment	–	↓
[76], Sweden	East coast fishermen's wives high vs. low fish consumption, living in fishing village	No exposure assessment	–	↓
[79], The Netherlands	General population (PCBs)	0.80 ng/g, sum PCB-118, -138, -153, -180 in cord serum	1.6 ng/g	↓
[18], Sweden	East coast fishermen's wives CB-153 estimated in blood >300 ng/g lipid in plasma	0.9 ng/g, determined as CB-153 in plasma (lipid-adjusted 20–780 ng/g)	3.4 ng/g	↓
[80], Rural Finland	General population PCDDs + PCDF PCB	Sum of PCB 140–1624 ng/g fat in breast milk	5.9 ng/g	→
[71], USA	<i>p,p'</i> -DDE increasing concentrations	25 ng/g in serum	25 ng/g	↓
[81], Faroe Islands	Fishing community (PCB)	Sum of PCB measured in maternal serum 860 ng/g lipid	2.2 ng/g	→
[73], India	General population (<i>p,p'</i> -DDE) HCHs Other DDTs	7.6 ng/g in maternal blood	7.6 ng/g	↓ ↓ →
[75], Ukraine	General population (DDE, PCB)	DDE: 2457 ng/g milk fat Sum PCB 605 ng/g milk fat	16.4 ng/g DDE 4.0 ng/g PCB	→

- Walkowiak et al. Lancet 2001;358:1602-07
« Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psycho-development in early childhood. »



- Winneke et al. Toxicology Letters 1998;102/3:423-28
“Developmental neurotoxicity of polychlorinated bisphenyls: cognitive and psychomotor functions in 7-month old children.”

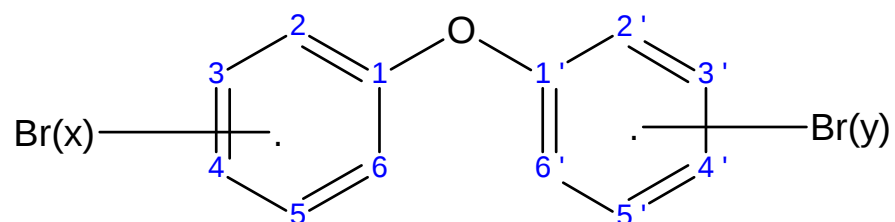
Variable	β^a	SE_{β}	t	P^b
Σ PCB (cord)				
Bayley MDI	-0.06	0.38	-0.17	0.43
Bayley PDI	0.009	0.63	0.01	-
Fagan-Test (Visual Recognition Memory)	0.93	1.13	0.82	-
Σ PCB (milk)				
Bayley MDI	-0.69	0.41	-1.67	0.048
Bayley PDI	-0.71	0.63	-1.12	0.13
Fagan-Test (Visual Recognition Memory)	-0.20	1.19	-0.17	0.43

^aFor confounders/covariates of this model, see Table 1.

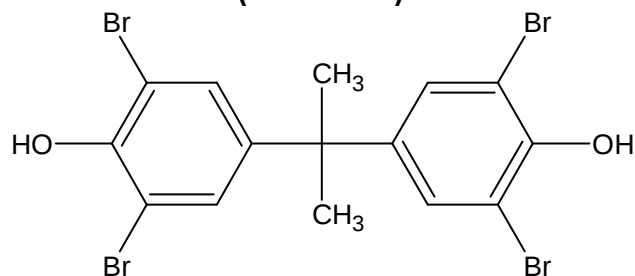
^bOne-tailed probabilities (directional hypothesis).

- Retardateurs de flamme Bromés (RFBs)

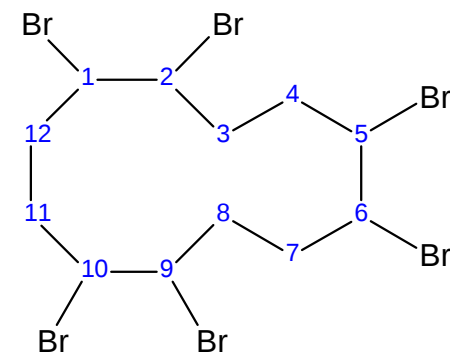
Polybrominated diphenylethers
(PBDE)



Tetrabromo-bisphenol-A
(TBBP-A)



Hexabromocyclododecane
(HBCD)



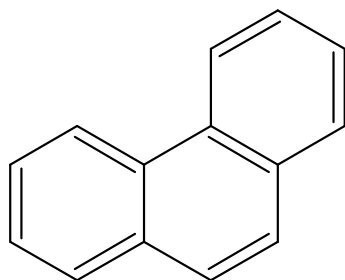
• Chao et al. Environment International 2007;33:239–245

«Levels of polybrominated diphenyl ethers (PBDEs) in breast milk from central Taiwan and their relation to infant birth outcome and maternal menstruation effects. »

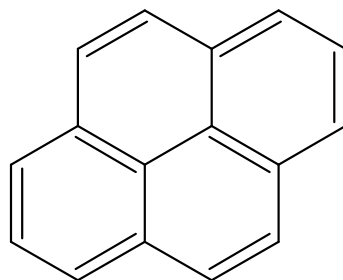
	BDE-47	BDE-85	BDE-99	BDE-100	BDE-153	BDE-209
Birth weight						
≤3.05 kg (n=7)	2.15 (1.57–2.95) ^a	0.034 (0.017–0.069)	0.727 (0.419–1.26)	0.451 (0.347–0.586)	0.948 (0.704–1.28)	0.346 (0.128–0.936)
>3.05 kg (n=13)	1.05 (0.837–1.32)	0.019 (0.012–0.032)	0.296 (0.211–0.422)	0.318 (0.283–0.357)	0.717 (0.527–0.976)	0.105 (0.062–0.178)
p value	0.001** ^b (0.001***)	0.151 (0.067)	0.004** (0.001**)	0.004** (0.007**)	0.207 (0.181)	0.015* (0.004**)
Birth length						
≤50.0 cm (n=8)	1.67 (0.988–2.81)	0.033 (0.021–0.051)	0.629 (0.383–1.03)	0.432 (0.330–0.563)	0.940 (0.696–1.27)	0.306 (0.137–0.683)
>50.0 cm (n=12)	1.18 (0.935–1.48)	0.019 (0.016–0.035)	0.303 (0.200–0.459)	0.318 (0.285–0.355)	0.705 (0.512–0.971)	0.103 (0.056–0.192)
p value	0.130 (0.148)	0.162 (0.198)	0.021* (0.040*)	0.012* (0.025*)	0.182 (0.276)	0.024* (0.033*)
Head circumference						
<33.0 cm (n=7)	1.68 (1.11–2.52)	0.025 (0.013–0.048)	0.454 (0.269–0.768)	0.391 (0.311–0.492)	0.838 (0.577–1.33)	0.185 (0.058–0.592)
≥33.0 cm (n=13)	1.20 (0.886–1.63)	0.023 (0.013–0.040)	0.382 (0.235–0.618)	0.343 (0.287–0.410)	0.766 (0.580–1.01)	0.147 (0.079–0.275)
p value	0.163 (0.274)	0.791 (0.576)	0.616 (0.521)	0.334 (0.433)	0.690 (0.697)	0.671 (0.401)
Breast circumference						
≤32.5 cm (n=7)	1.95 (1.37–2.76)	0.032 (0.015–0.068)	0.686 (0.371–1.27)	0.455 (0.351–0.590)	0.901 (0.658–1.23)	0.343 (0.126–0.933)
>32.5 cm (n=13)	1.11 (0.845–1.46)	0.020 (0.012–0.033)	0.306 (0.215–0.435)	0.316 (0.283–0.354)	0.737 (0.539–1.01)	0.105 (0.062–0.179)
p value	0.012* (0.015*)	0.241 (0.126)	0.011* (0.05*)	0.002** (0.003**)	0.369 (0.266)	0.016* (0.003**)
Quetelet's index						
≤11.8 kg/m ² (n=10)	1.75 (1.30–2.37)	0.033 (0.021–0.054)	0.605 (0.387–0.948)	0.416 (0.336–0.514)	0.894 (0.622–1.28)	0.259 (0.126–0.532)
>11.8 kg/m ² (n=10)	1.04 (0.756–1.44)	0.017 (0.009–0.031)	0.272 (0.180–0.410)	0.311 (0.274–0.351)	0.700 (0.522–0.937)	0.098 (0.049–0.198)
p value	0.015* (0.024*)	0.060 (0.043*)	0.008* (0.009*)	0.015* (0.031*)	0.249 (0.307)	0.043* (0.019*)

- Hydrocarbures aromatiques polycycliques

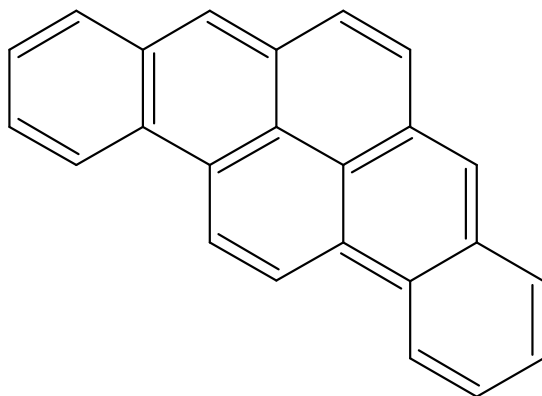
Phenanthrene



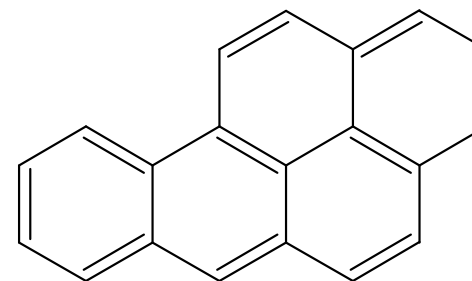
Pyrene



Dibenzo[a,i]pyrene



Benzo[a]pyrene



- Polanska et al. Int J of Occupl Med Environ Health 2010;23(4):339 – 346
« Exposure to polycyclic aromatic hydrocarbons and newborn biometric indicators »

Table 3. Association between 1-HP in urine and child parameters at birth

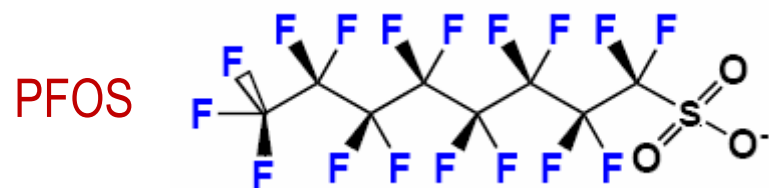
Outcome	Adjusted*			Adjusted**			Adjusted ***		
	coef.	se	p	coef.	se	p	coef.	se	p
Birth weight (g)	-245.60	64.50	< 0.001	-158.30	64.600	0.01	-105.400	66.100	0.10
Child length (cm)	-1.20	0.40	0.001	-0.70	0.400	0.05	-0.400	0.400	0.30
Head circumference (cm)	-0.70	0.20	0.006	-0.50	0.300	0.05	-0.300	0.300	0.20
Chest circumference (cm)	-0.80	0.30	0.001	-0.70	0.009	0.02	-0.400	0.300	0.07
Ponderal index (g/cm ³)	-0.02	0.03	0.500	-0.02	0.030	0.60	-0.003	0.003	0.40
Cephalisation index (cm/g)	6.30	1.70	< 0.001	4.20	1.700	0.01	3.000	1.700	0.09

* For gestational age, gender of the newborn.

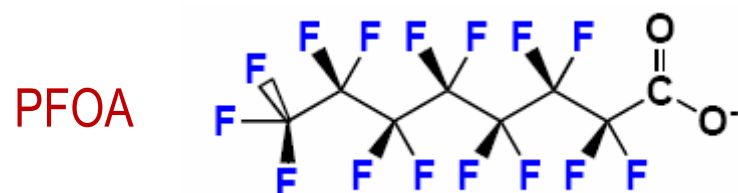
** For gestational age, gender, marital status, educational level, season of LMP, prepregnancy BMI, weight gain in pregnancy.

*** For gestational age, gender, marital status, educational level, season of LMP, prepregnancy BMI, weight gain in pregnancy and cotinine level in saliva.

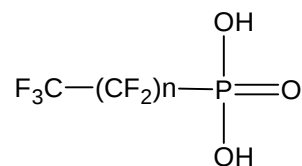
- PerfluoroalkylSulfonic acids



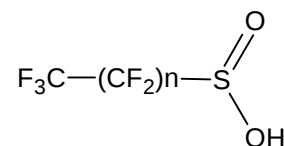
- PerfluoroalkylCarboxylic acids



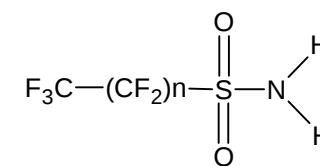
- PerFluoroalkylPhosphonic acids



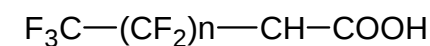
- PerfluoroalkylSulfinate



- PerFluoroalkylSulfonAmides



- Saturated Carboxylic acid Fluorotelomer



• Apelberg et al. (2007) Environmental Health Perspectives 115 : 1670-1676

“Cord serum concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in relation to weight and size at birth.”

Table 3. Estimated change in mean gestational age, birth weight, and birth size parameters with a change in PFOS or PFOA concentrations equal to one ln-unit or from the 25th to 75th percentile.

Model	n=293	PFOS	PFOA		
		Change in end point (95% CI) per ln-unit ^a	Per increase from the 25th to 75th percentile (IQR) ^b	Change in end point (95% CI) per ln-unit ^a	Per increase from the 25th to 75th percentile (IQR) ^b
Gestational age (days)					
Univariate		2.0 (−0.4 to 4.4)	1.7 (−0.3 to 3.7)	2.4 (−0.8 to 5.7)	1.4 (−0.4 to 3.2)
Adjusted ^c		1.1 (−1.2 to 3.4)	0.9 (−1.1 to 2.9)	1.9 (−1.3 to 5.0)	1.0 (−0.7 to 2.8)
Birth weight (g)					
Univariate		−37 (−139 to 64)	−31 (−117 to 54)	−97 (−234 to 40)	−54 (−131 to 23)
Adjusted for GA		−89 (−170 to −8)*	−75 (−143 to −7)*	−161 (−270 to −52)*	−90 (−151 to −29)*
Fully adjusted ^d		−69 (−149 to 10)	−58 (−125 to 9)	−104 (−213 to 5)	−58 (−119 to 3)
Head circumference (cm)					
Univariate		−0.22 (−0.52 to 0.07)	−0.19 (−0.44 to 0.06)	−0.46 (−0.87 to −0.06)*	−0.26 (−0.48 to −0.03)*
Adjusted for GA		−0.34 (−0.59 to −0.08)*	−0.28 (−0.50 to −0.07)*	−0.54 (−0.89 to −0.19)*	−0.30 (−0.50 to −0.10)*
Fully adjusted ^d		−0.32 (−0.56 to −0.07)*	−0.27 (−0.48 to −0.06)*	−0.41 (−0.76 to −0.07)*	−0.23 (−0.42 to −0.04)*
Length (cm)					
Univariate		0.25 (−0.21 to 0.72)	0.21 (−0.18 to 0.6)	−0.06 (−0.69 to 0.57)	−0.03 (−0.39 to 0.32)
Adjusted for GA		0.05 (−0.33 to 0.44)	0.05 (−0.28 to 0.37)	−0.30 (−0.82 to 0.22)	−0.17 (−0.46 to 0.12)
Fully adjusted ^d		0.13 (−0.26 to 0.52)	0.11 (−0.22 to 0.44)	−0.10 (−0.64 to 0.44)	−0.06 (−0.36 to 0.24)
Ponderal index (g/cm ³ × 100)					
Univariate		−0.070 (−0.119 to −0.021)*	−0.059 (−0.101 to −0.018)*	−0.074 (−0.140 to −0.007)*	−0.041 (−0.078 to −0.004)*
Adjusted for GA		−0.080 (−0.127 to −0.033)*	−0.067 (−0.107 to −0.028)*	−0.085 (−0.150 to −0.020)*	−0.048 (−0.084 to −0.011)*
Fully adjusted ^d		−0.074 (−0.123 to −0.025)*	−0.062 (−0.104 to −0.021)*	−0.070 (−0.138 to −0.001)*	−0.039 (−0.077 to −0.001)*

Abbreviations: GA, gestational age; IQR, interquartile range; ln-unit = natural log unit.

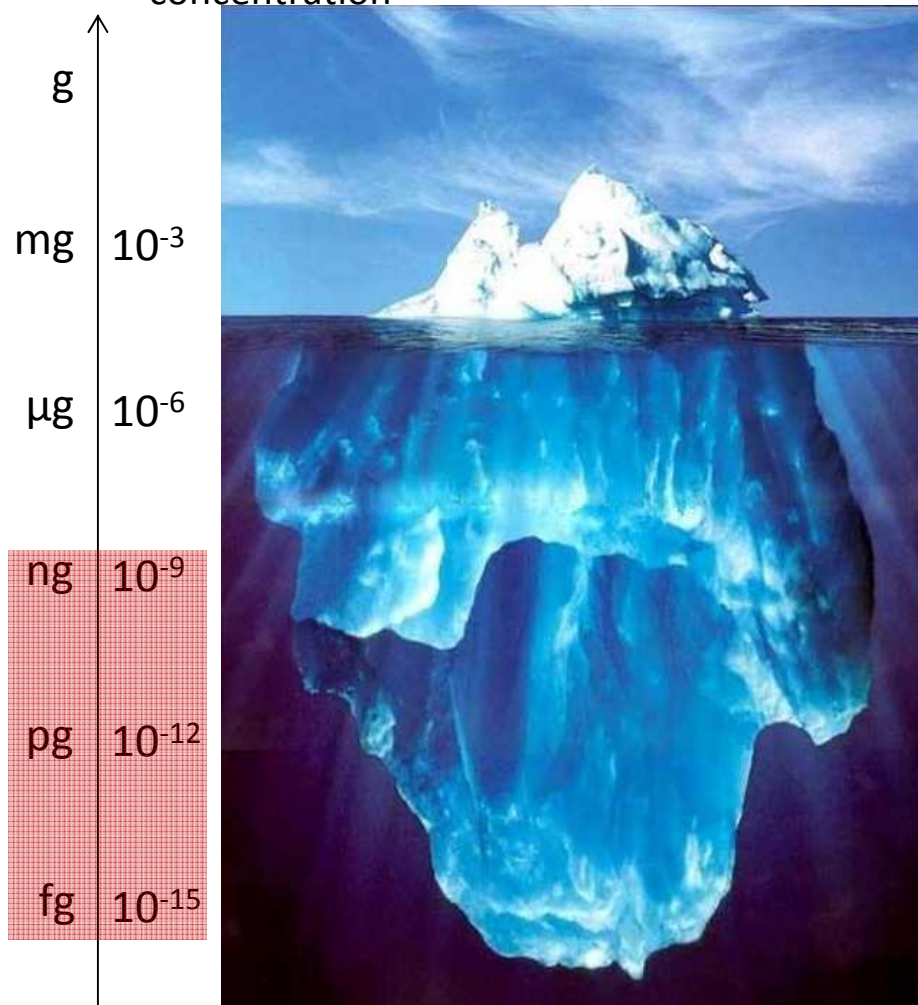
^aRepresents the change in the end point associated with a unit increase in ln(PFOS) or ln(PFOA), which is equivalent to a 2.7-fold increase in PFOS or PFOA. ^bInterquartile range is 3.4–7.9 ng/mL for PFOS and 1.2–2.1 ng/mL for PFOA. ^cAdjusted for maternal age, BMI, race, previous preterm birth, smoking, diabetes, and hypertension. ^dAdjusted for gestational age, maternal age, BMI, race, parity, smoking, baby sex, height, net weight gain, diabetes, and hypertension. For head circumference, adjusted model also includes delivery mode (C-section/vaginal). *Statistically significant ($p < 0.05$).

Plan

- Introduction
- Les principaux dangers chimiques
- Les challenges méthodologiques
- Les recherches en cours
- Conclusion



- Très faibles niveaux de concentration



- Matrices biologiques complexes



- Besoin d'identification non ambiguë et de quantification juste et précise



Exemple des Polluants Organiques Persistants (POPs type dioxines, PCB, PBDE)



A.S.E.



Récupération et transfert



Colonne Silice



Evaporation



Transfert en vial



Evaporation



Colonne Charbon



Colonne Florisil

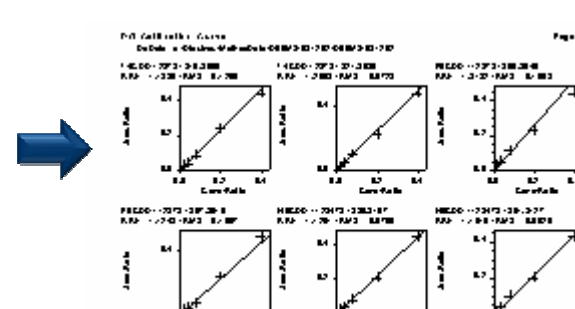
Exemple des Polluants Organiques Persistants (POPs type dioxines, PCB, PBDE)



Mesure



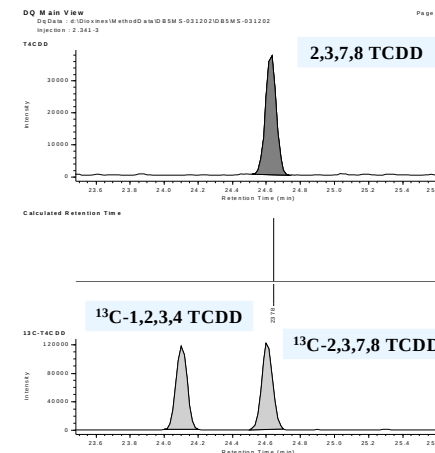
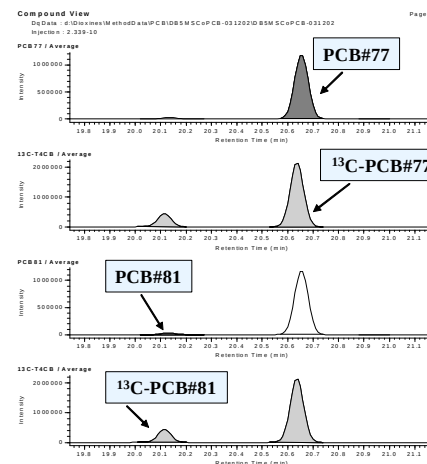
Retraitement



Courbes d'étalonnage et dilution isotopique

Analyse des Polychlorodibenzodioxines et Polychlorodibenzofuranes				
Echantillon n°:	2.282-9			
Matière: poisson	Méthode: LABERCA/01D-ts.1	Date de fin d'analyse:	31/10/2002	
Masse du pool avant lyophilisation:	179,64 g			
Masse du pool après lyophilisation:	62,60 g			
Pourcentage de matière sèche:	34,85			
Masse de la prise d'essai après lyophilisation:	16,60 g			
Equivalent poids frais:	47,64 g			
Masse de la matière grasse (MG):	6,77 g			
Pourcentage de matière grasse:	14,21			
	Rendement d'extraction %	Concentration en pg/g de MG	Concentration en pg/g de poids frais	TEF
2,3,7,8 - TCDD	101,4	0,06	0,0062	1
1,2,3,7,8 - PeCDD	83,2	0,27	0,0388	1
1,2,3,4,7,8 - HxCDD	90,2	0,02	0,0031	0,1
1,2,3,6,7,8 - HxCDD	97,0	0,13	0,0181	0,1
1,2,3,7,8,9 - HxCDD	98,0	0,02	0,0034	0,1
1,2,3,4,6,7,8 - HxCDD	89,5	0,13	0,0191	0,01
OCDD	77,4	0,16	0,0220	0,0001
Somme des PCDDs	-	0,79	0,1127	-
2,3,7,8 - TCDF	99,0	1,61	0,2288	0,1
1,2,3,7,8 - PeCDF	109,2	0,19	0,0271	0,05
2,3,4,7,8 - PeCDF	110,9	0,80	0,1131	0,5
1,2,3,4,7,8 - HxCDF	93,3	0,02	0,0028	0,1
1,2,3,6,7,8 - HxCDF	106,8	0,03	0,0038	0,1
1,2,3,7,8,9 - HxCDF	87,7	0,02	0,0028	0,1
2,3,4,6,7,8 - HxCDF	90,8	0,04	0,0055	0,1
1,2,3,4,6,7,8 - HxCDF	88,7	0,03	0,0040	0,01
1,2,3,4,7,8,9 - HpCDF	81,4	0,02	0,0028	0,01
OCDF	72,3	0,02	0,0028	0,0001
Somme des PCDFs	-	2,77	0,3936	-
RESULTAT FINAL: (en TCDD - Equivalent)				
I-TEQ	0,93	pg/g de MG		
I-TEQ	0,13	pg/g de poids frais		

Exemple de feuille de retraitement



Exemples de chromatogrammes diagnostiques

Plan

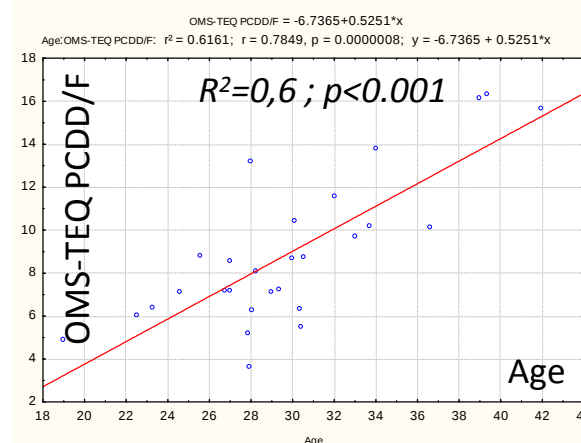
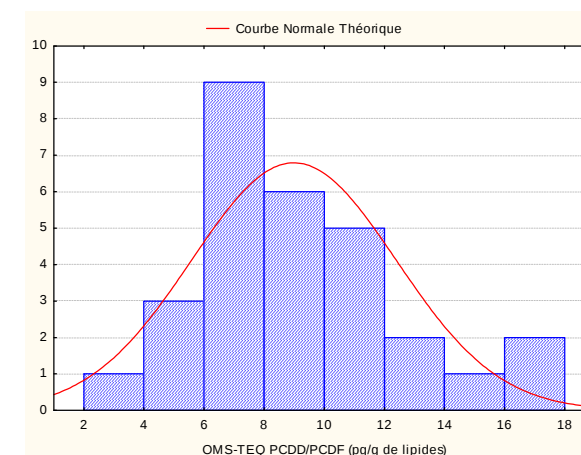
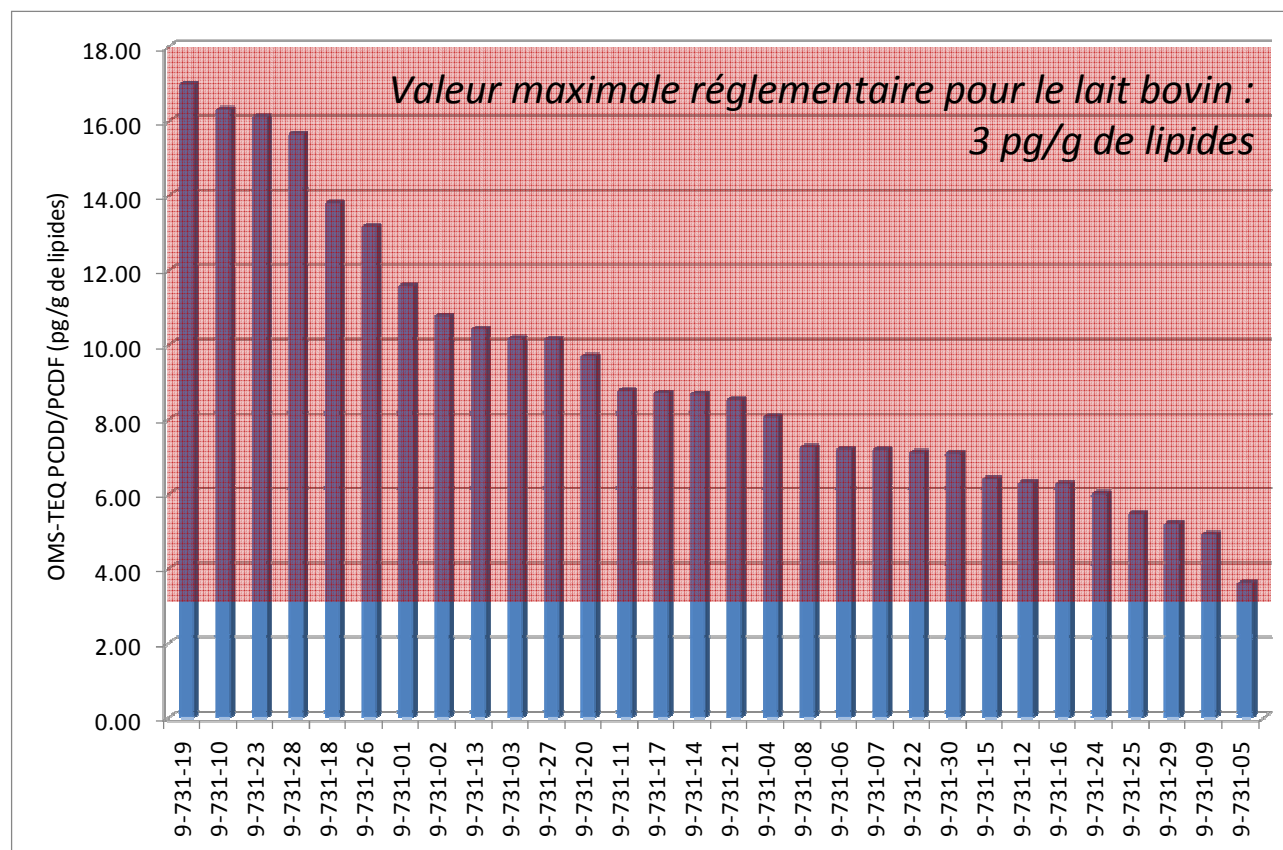
- Introduction
- Les principaux dangers chimiques
- Les challenges méthodologiques
- Les recherches en cours
- Conclusion



- Le projet NUPEM
(Nutrition Périnatale et Empreintes Métaboliques)



Dioxines (PCDD/PCDF)

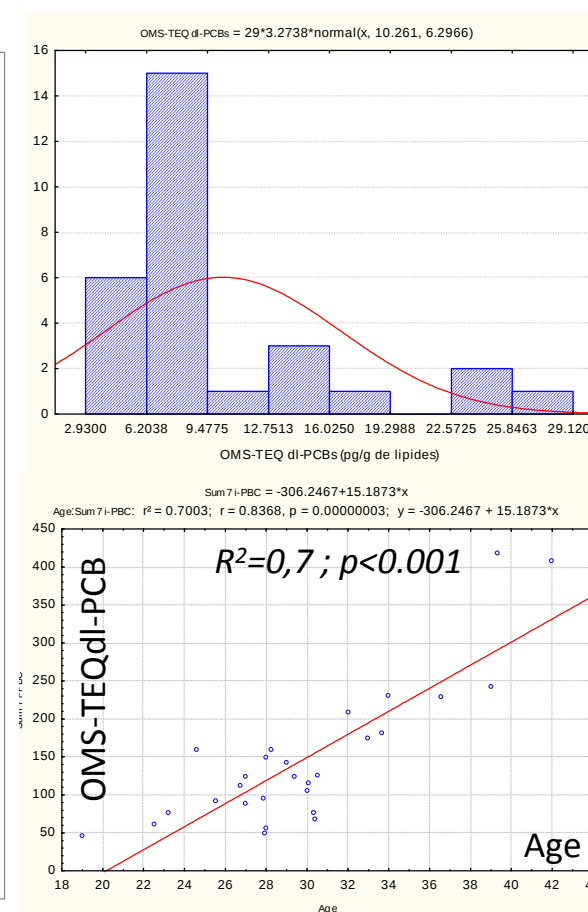
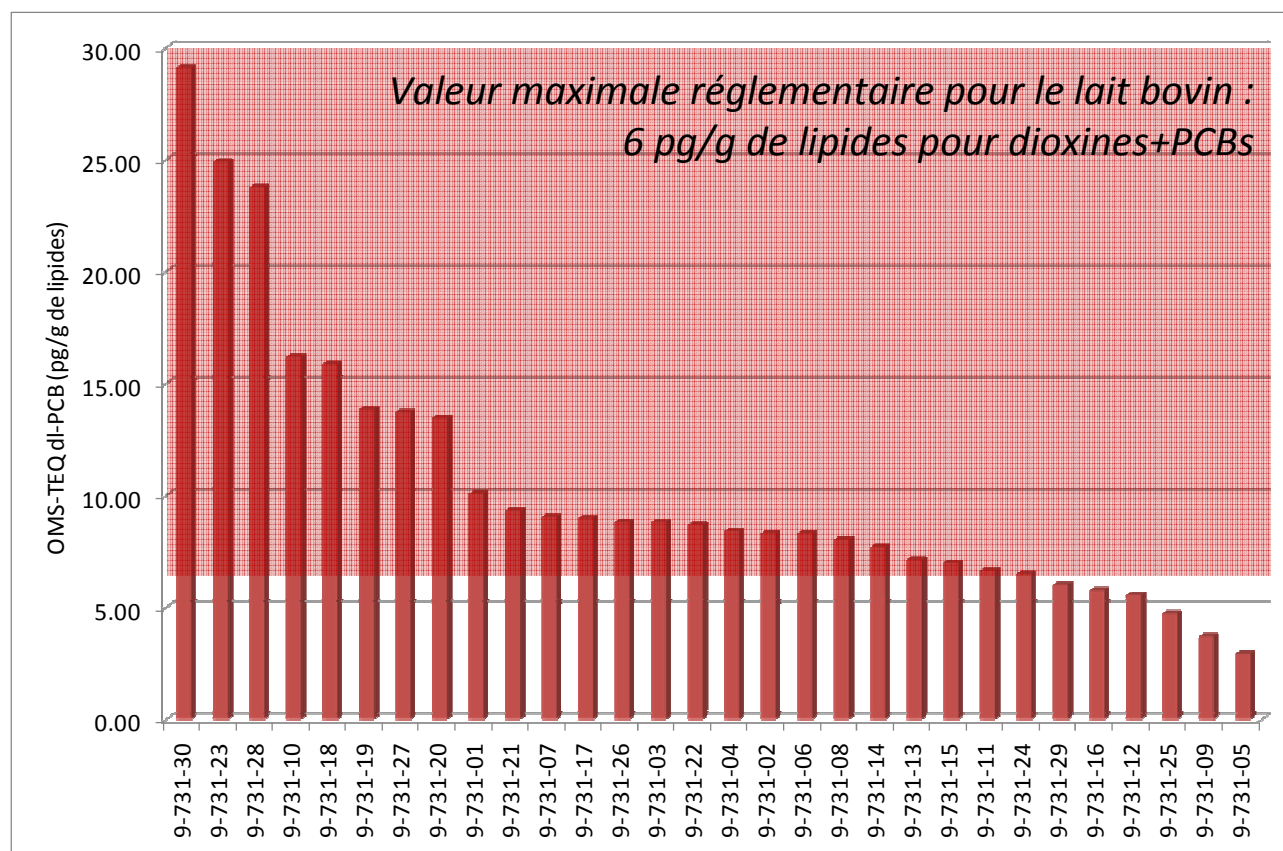


Niveaux de concentration en dioxines (PCDD/F) dans 30 prélèvements de lait maternel

- Le projet NUPEM
(Nutrition Périnatale et Empreintes Métaboliques)



Polychlorobiphenyls (PCB)

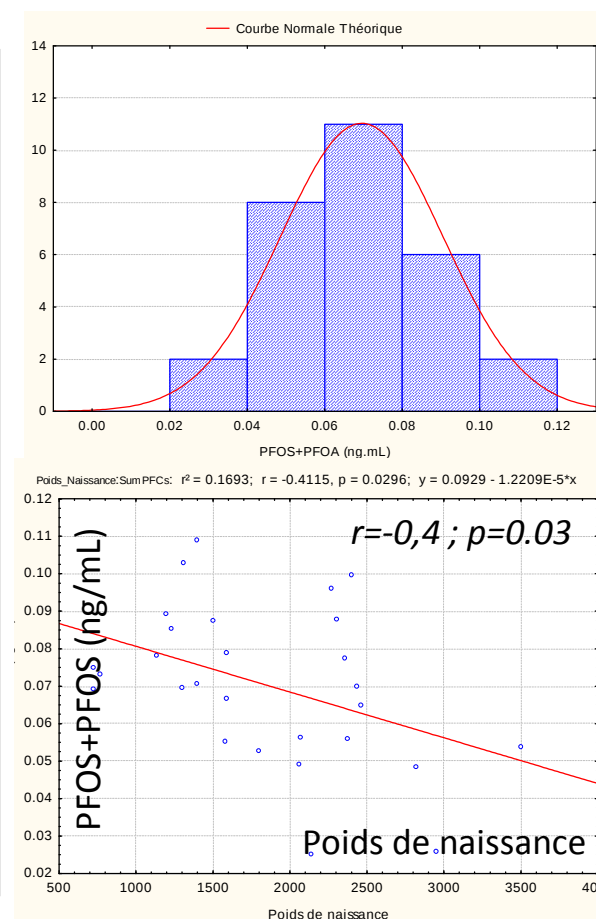
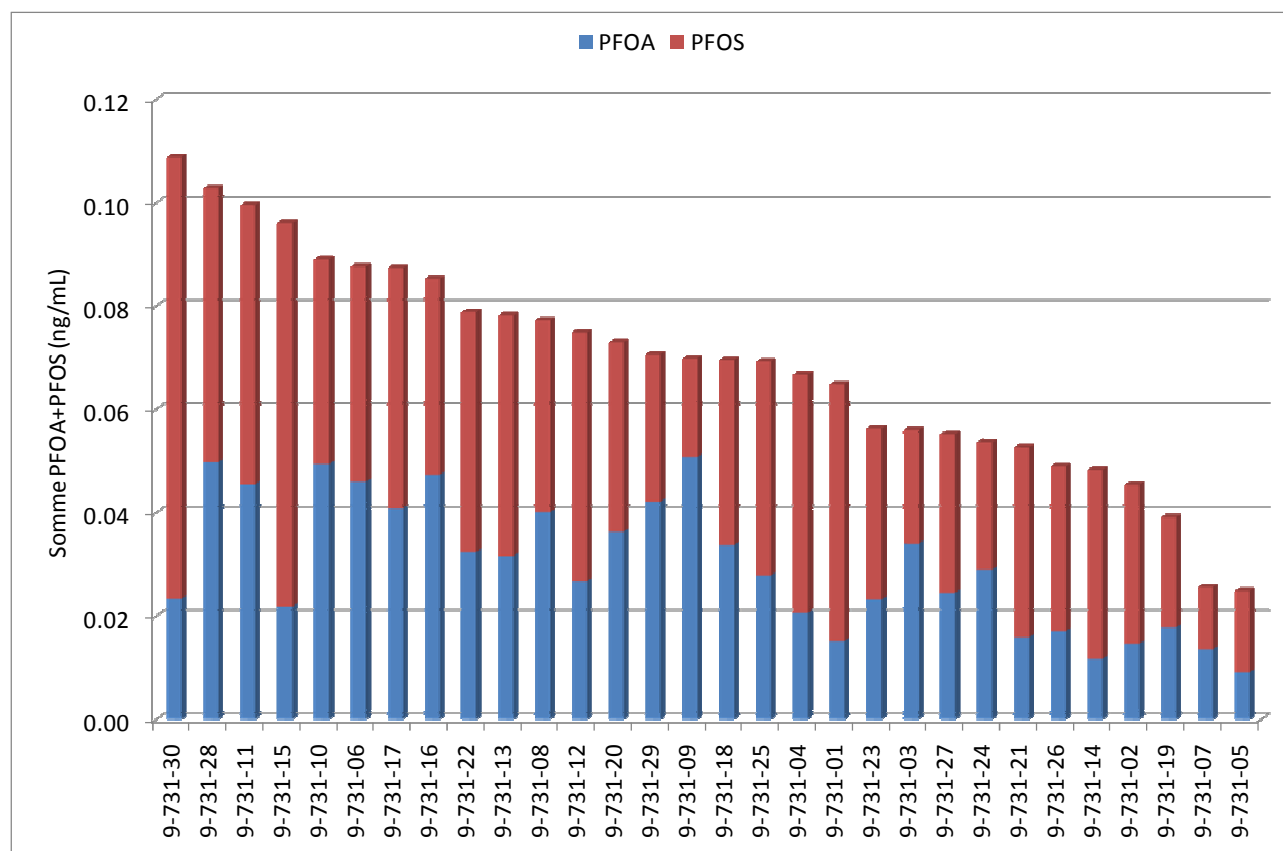


Niveaux de concentration en polychlorobiphenyls(PCB) dans 30 prélèvements de lait maternel

- Le projet NUPEM
(Nutrition Périnatale et Empreintes Métaboliques)



Contaminants perfluorés (PFC)

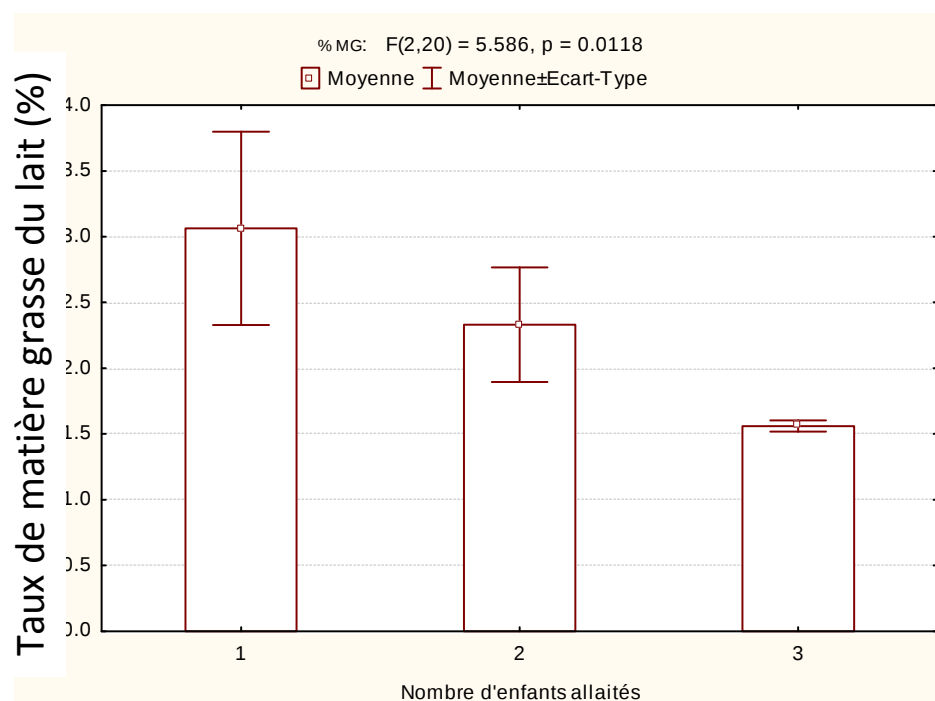


Niveaux de concentration en contaminants perfluorés (PFC) dans 30 prélèvements de lait maternel

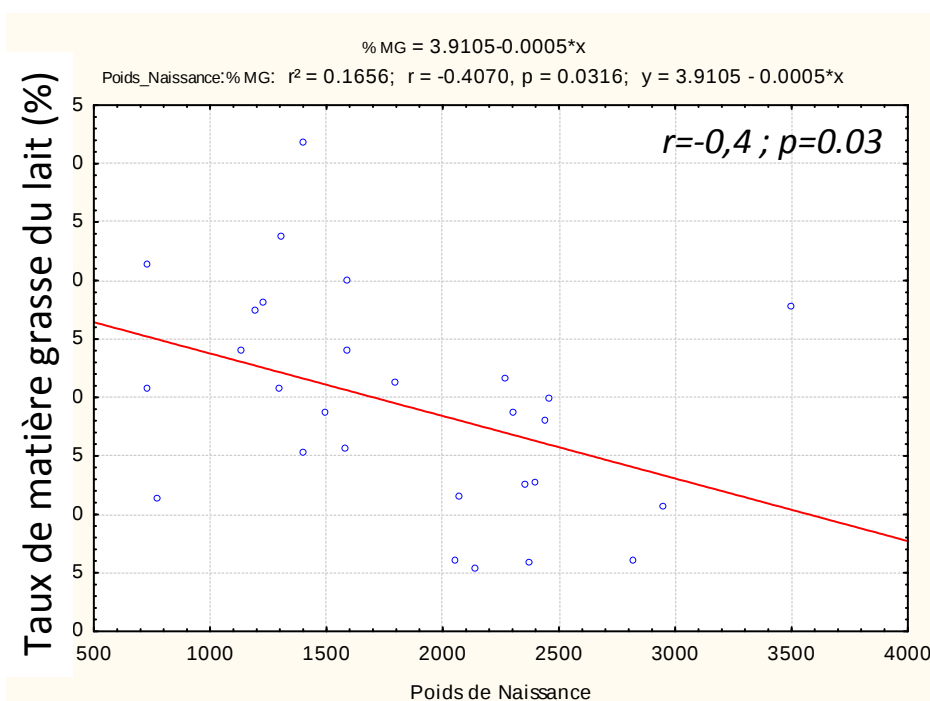
- Le projet NUPEM
(Nutrition Périnatale et Empreintes Métaboliques)



La fraction lipidique du lait maternel

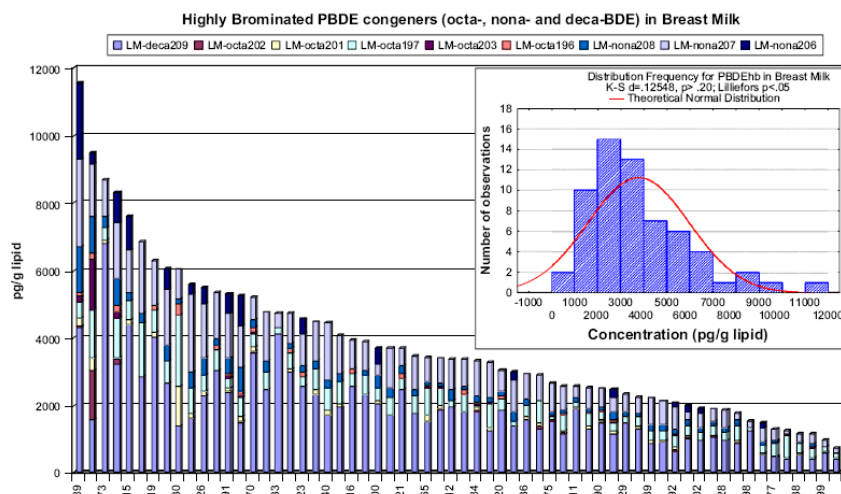


Nombres d'enfants allaités

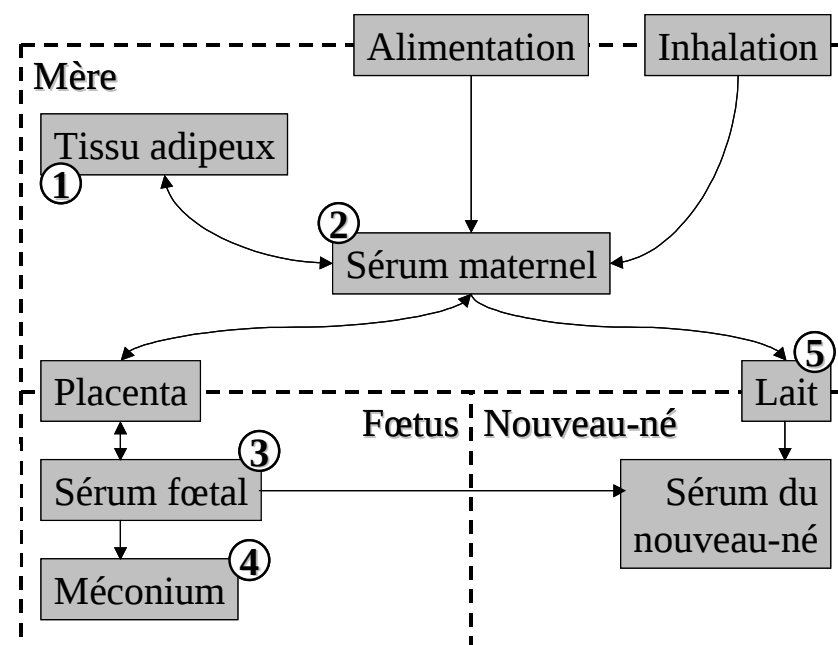
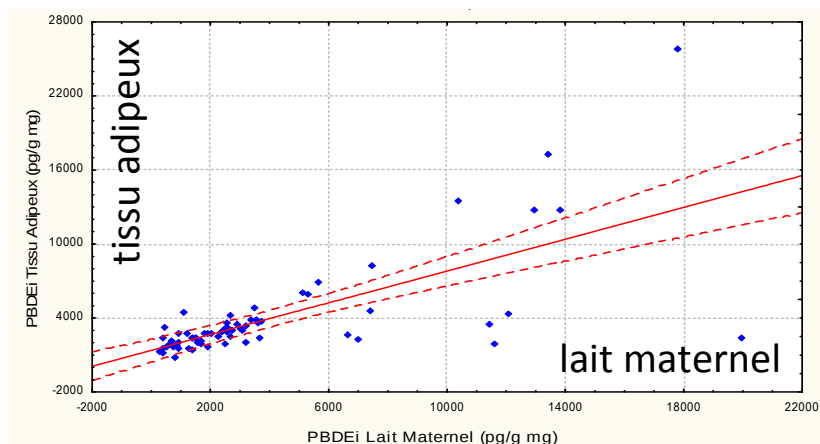


Poids de naissance

• Le projet BED - « Brominated Endocrine Disruptors » (Exposition du nouveau-né/foetus aux RFBs)

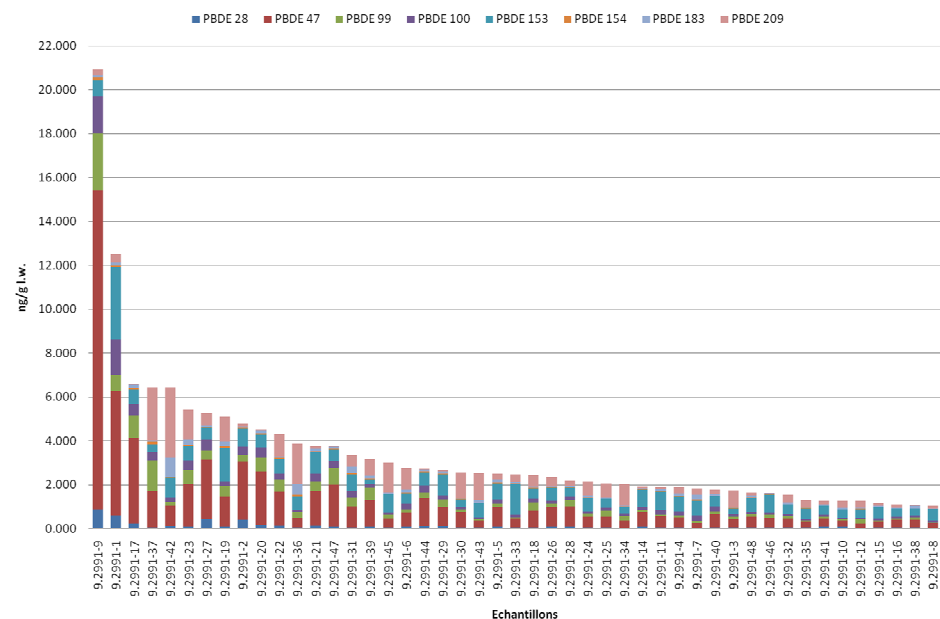
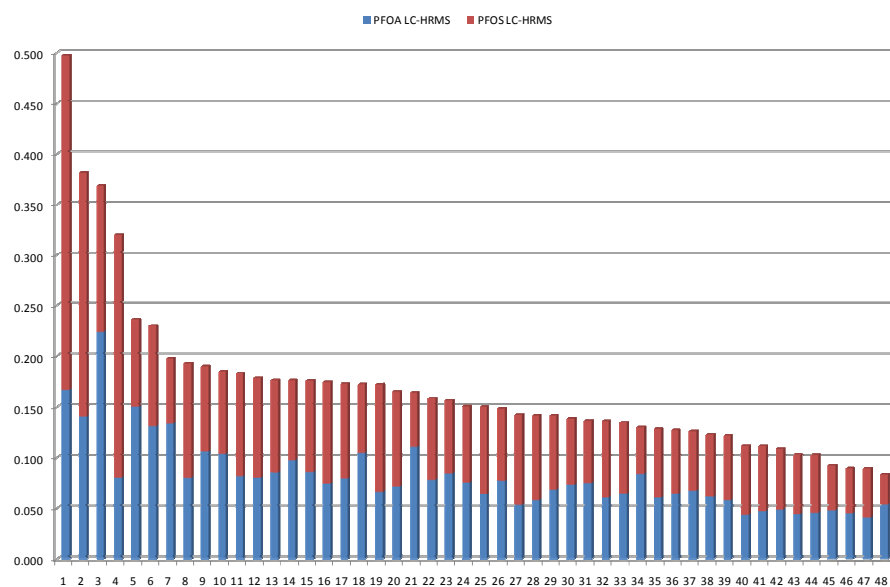


Niveaux de concentration en polybromodiphényléthers (PBDE) dans 100 prélèvements de lait maternel



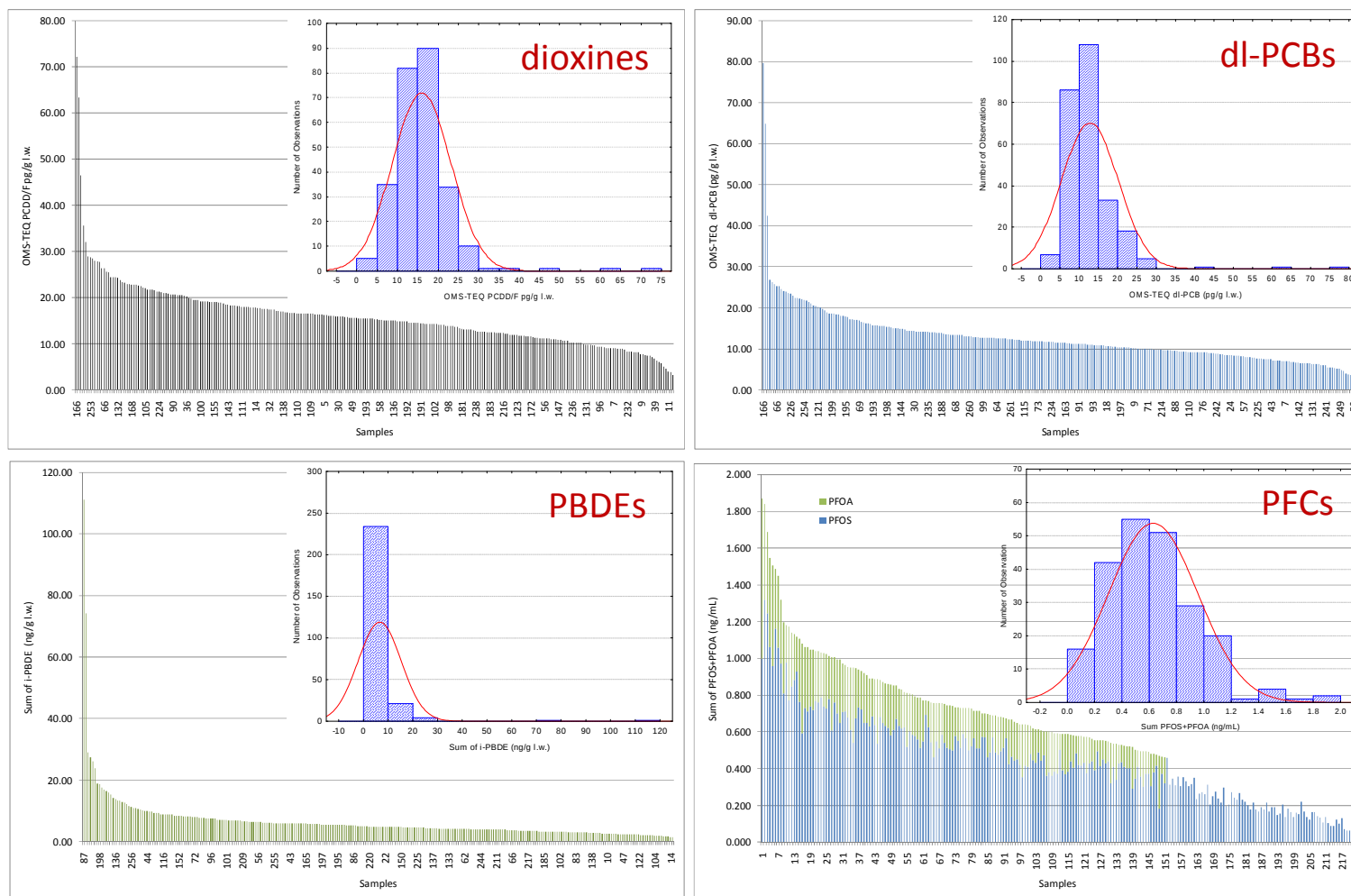
	PBDE	TBBP-A	α-HBCD
1 – Tissu adipeux maternel	++	Ø	++
2 – Sérum maternel	++	+	?
3 – Sérum fœtal	+	+	?
4 – Méconium	+	?	?
5 – Lait maternel	+++	+	+++

- Le projet ELFE - « Etude longitudinale française depuis l'enfance » (Etude pilote 2009-2010)



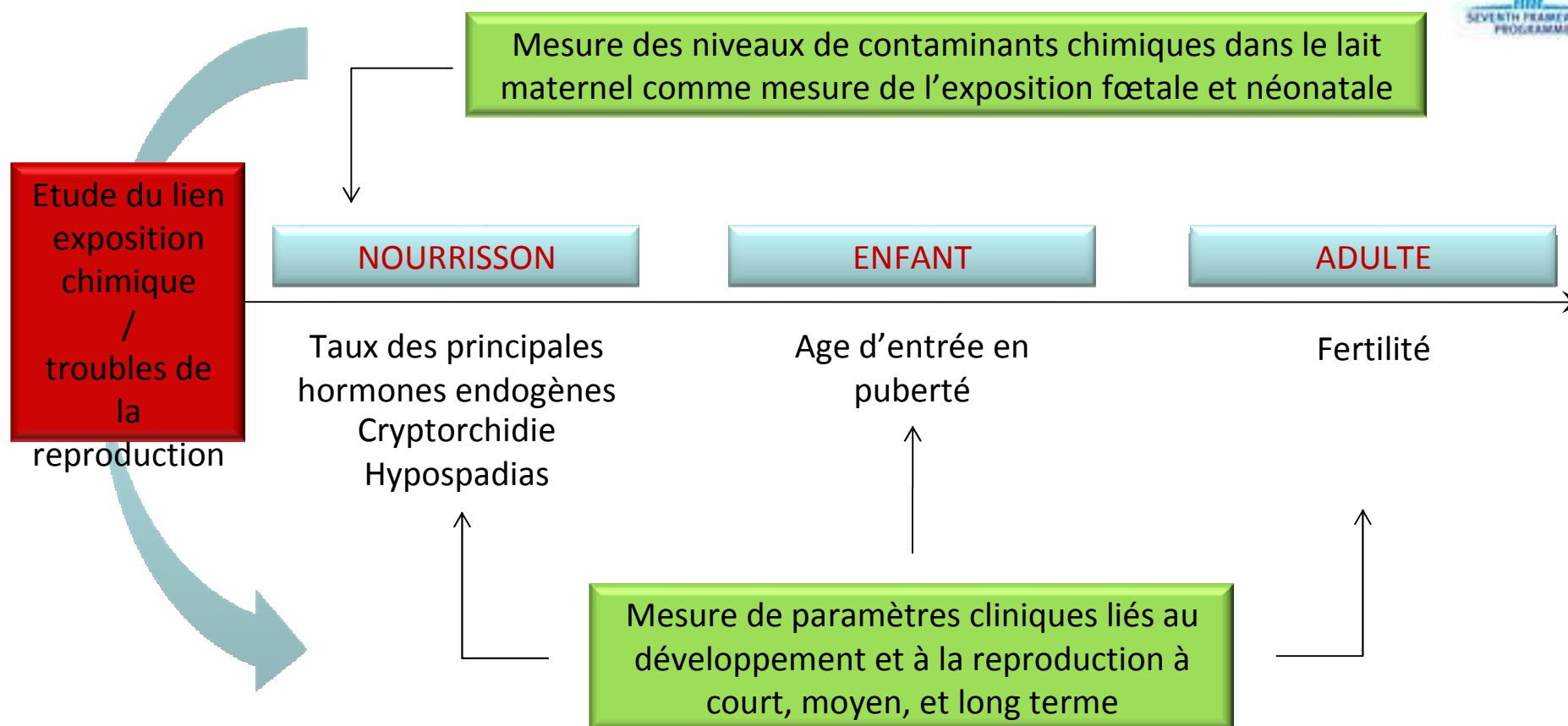
Niveaux de concentration en contaminants perfluorés (PFC) et retardateurs de flamme bromés dans 50 prélèvements de lait maternel

• Le projet DEER « Developmental effects of environment on reproduction



Niveaux de concentration en polluants organiques persistants (POPs)
dans 260 prélèvements de lait maternel (dioxines, PCB, PBDE, PFC)

- Le projet DEER « Developmental effects of environment on reproduction »



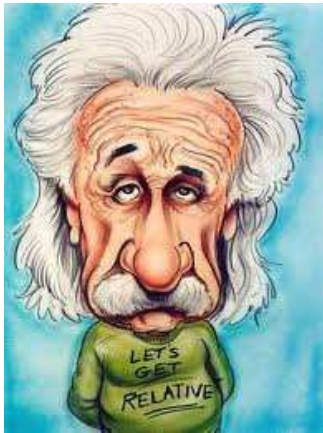
Plan

- Introduction
- Les principaux dangers chimiques
- Les challenges méthodologiques
- Les recherches en cours
- Conclusion



Conclusion

« Take home messages »



- Les bénéfices attribués au lait maternel ne sont pas occultés
- Le risque chimique lié au lait maternel reste un sujet discuté
- Sensibiliser n'est pas alarmer



- Certains faits et observations supportent cette problématique montante
- Une appréciation ouverte de type bénéfice-risque est à encourager
- Vers l'introduction de nouveaux critères de « qualité/sécurité » ?

Remerciements



- CHU/CRNH/PHAN
(Projet NUPEM)
Arnaud Legrand
Cécile Boscher
Clair-Yves Boquien
Martine Champ
Jean-Christophe Rozé

- InVS
(Projet ELFE)
Stéphanie Vandertorren

- Righospitalet (Copenhague, DK)
(Projet DEER)
NielsE Skakkebeack
Katharina Main

<http://www.laberca.org>
<http://www.saraf-educ.org>

Et vous pour
votre attention !