

Endocrine disruptors

Anses risk assessment activities

EU-OSHA workshop
Workplace risks to reproductivity : from knowledge to action
16 January 2014

Background history and context

In 2009, Anses was asked by French ministries to:

- **Identify products and/or articles** containing potential endocrine disruptors (ex. Bisphenol A, Phtalates, Perfluorinated compounds...)
- **Estimate human exposures** to these EDs in particular pregnant women and/or newborns or infants
- **Conduct a Human health risk assessment :**
 - **Reproductive effects:** fertility or developmental abnormalities on the reproductive development (eg. cryptorchy, hypospadias...) and/or
 - **Endocrine effects** (specifically for reproductive endocrine disruption).
- **For BPA to conduct a complete Human health risk assessment** including effects on the thyroid organ, the immune system, neuro-development, diabetes, obesity...).
- **General population and occupational setting**

<http://www.anses.fr/en/content/bisphenol-anses-demonstrates-potential-health-risks-and-confirms-need-reduce-exposure>

- Risk assessment of Bisphenol A (BPA) on human health
- Other Bisphenols (S, F, M, B, AP, AF, BADGE)
- BPA substitutes overview : hazards and uses
- Social representations: an analysis of uncertainties and their interpretations on Endocrine disruptors definition and criteria

ED Risk assessment reports under completion

- **5 substances in consumer goods :**

Chemical compounds	Production and uses
•N hexane	Glues, paint, varnish, lubricants, etc. : out and indoor air
toluene	Glue, degreasing agents, car air fresheners, etc.: out and indoor air
MTBE	Motor fuel : out and indoor air
Quaternium 15(Q15)	Mosquito repellents, detergents, adhesives, etc.: Out and indoor air
o-phenylphenol (OPP)	Air freshener, sanitizers and cleaning agents, etc. : out and indoor air

Pending ED reports (2014)

- **6 substances for which toxicological profiles and exposure data are being assembled : the relevance of performing RA will depend on the identification of exposure situations**

Chemical compounds

- 4-nitrophenol

4-tert-octylphénol

DEGME

4-tertButylPhénol

4-nonylphénol

Chlorocrésol

- **Occupational exposure limits**
- **BPA 2014**
- **BBP** under review
- **DEHP and DBP** adopted, to be submitted to public consultation soon in 2014

EDs under prioritization for RA

•PHTHALATES

- Di-n-butylphtalate : DBP
- Diisobutylphtalate : DIBP
- Butylbenzylphtalate : BBP
- Diethylhexylphtalate : DEHP,
- Diisononylphtalate : DINP
- Diisodecylphtalate : DIDP
- Diisopentylphtalate :DIIP
- Dipropylphtalate
- Mono-n-butylphtalate
- Di-n-hexylphtalate
- Di-2propyl-heptylphtalate : DPHP
- Diisoundecylphtalate : DIUP
- Dicyclohexylphtalate :
- Diisooctylphtalate : DIOP
- Ditridecylphtalate : DTDP

•Perfluorinated :

- PFOA
- PFOS

•Polybrominated :

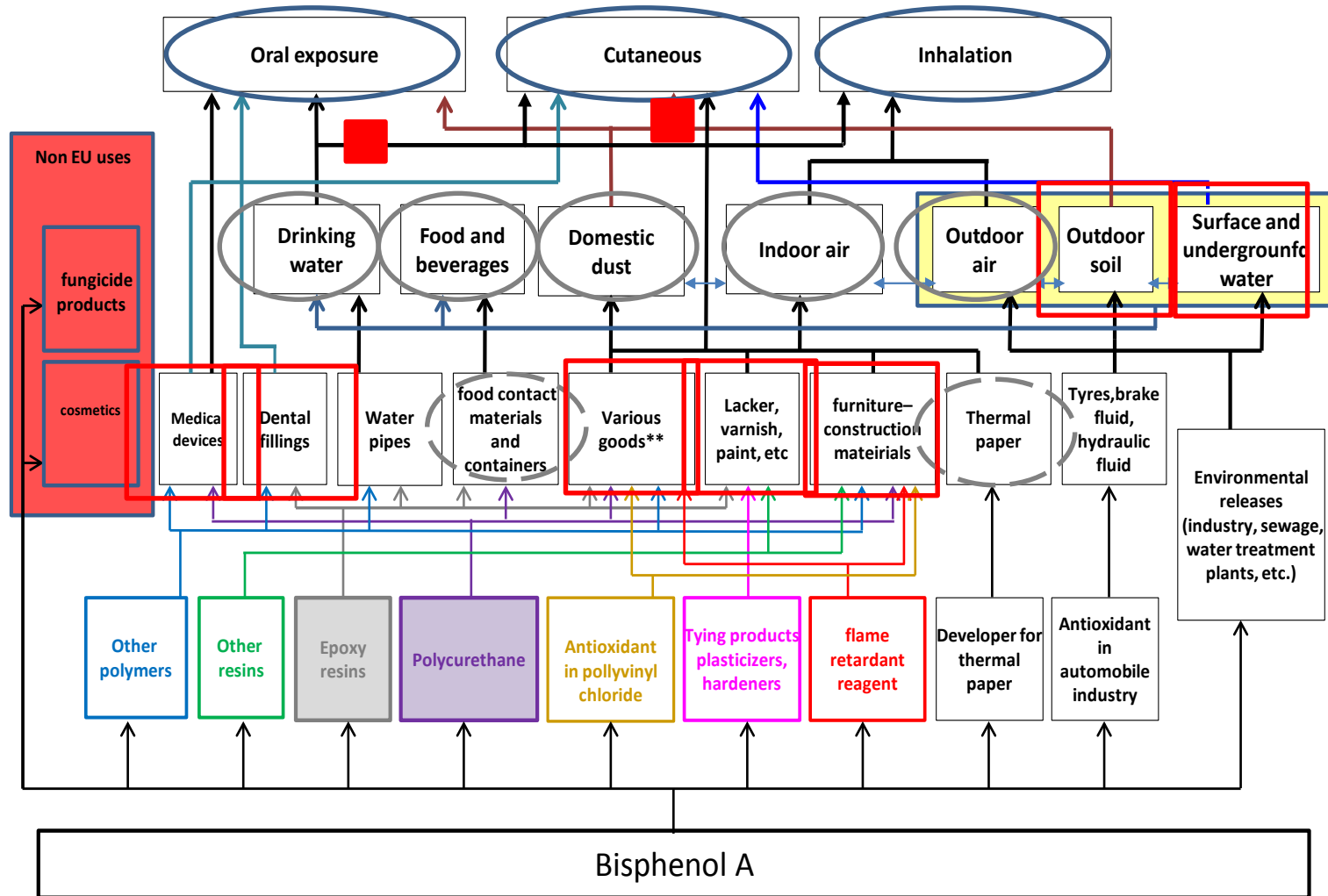
- 2,2',4,4'-tetrabrominated diphenylether (2,2',4,4'-tetraBDE)
- Decabrominated diphenylether (DecaBDE)

BPA Effects and associated Toxicological Value selected for the RA

Critical effects	Study reference	Route of exposure	LOAEL	NOAEL*	Internal NOAEL by application of a bioavailability factor of 3%	Internal TV by application of a Margin of Safety (MOS) of 300 on the internal NOAEL
			(µg/kg/d)	(µg/kg/d)	(µg/kg/d)	(µg/kg/d)
Brain and behaviour	Xu <i>et al.</i> , 2010c	oral	/	50	1.5	0.005
Female reproductive system	Rubin <i>et al.</i> , 2001	oral	/	100	3	0.01
Metabolism and obesity	Miyawaki <i>et al.</i> , 2007	oral	260	87	2.6	0.009
Mammary gland	Moral <i>et al.</i> , 2008	oral	/	25	0.75	0.0025

Conceptual diagram for BPA exposure assessment

→ On the basis of BPA uses report (Anses, 2011)



** : CD, DVD, computers, screens, household electric appliances, small electric equipment, cell phones, optical equipment, sportswear, etc.

Exposure assessment methodology

- Identification of sources, compartments and routes of exposure literature, inventory of uses based on a survey of industries that targeted French companies;
- BPA contamination data literature, specific French surveys commissioned by the Anses in order to document BPA concentration in indoor air, settled dust, drinking water, food and thermal receipts;
- Development of exposure scenarios
- Several studies document levels of BPA in thermal receipts (Biedermann *et al.* 2011, EWG 2010, Mendum *et al.* 2010, etc.). However none of them relate to thermal receipts distributed in France
- Anses coordinated a study : 50 receipts (sept.-oct. 2011)

BPA contamination data : thermal receipts

	SCL, 2011	Biedermann <i>et al.</i> , 2010	EWG, 2010	Danish EPA, 2011	Östberg et Noaksson, 2010 cité dans Danish EPA, 2011	Mendum <i>et al.</i> , 2010	Schreder, 2010	Liao and Kannan, 2011b	Geens <i>et al.</i> , 2012
Country	France	Switzerland	USA et Japan	Danmark	Sweden	USA	USA	USA, Japan, Korea Vietnam	Belgium
Sampling places	Supermarkets, shops, stations-service, banks	Chromatograms shops, cinemas...	Shops, supermarkets, public institutions	Supermarkets, shops, banks	Récolte par 4 familles suédoises	Not precised	Shops and restaurants	Supermarkets, shops, banks, stations service, restaurants, fast-food	Banks, shops, restaurant, parkings...
Number of receipts tested	50	13	36	12	16	10 (tickets non imprimés)	22	103	44
Number of receipts with BPA	36 (soit 72 %)	11 (soit 85 %)	16 (soit 44 %)	9 (soit 75 %)	100 %	8 (soit 80 %)	11 (soit 50 %)	97 (soit 94 %)	44 (soit 100 %)
BPA concentration in receipts (% m/m)									
Moyenne	1,33 %	1,33 %	1,9 %	1,14 %	1,58 %	1,24 %	1,70 %	0,0211 %2	1,46 %
Min – Max	0,8–1,9 %	0,8–1,7 %	0,8–2,8 %	0,87-1,70 %	0,58-3,2 %	0,3–1,5 %	0,9–2,2 %	<10-7–1,4 %	0,9-2,1 %
LD / LQ	LD : 0,01% LQ : 0,02%	LQ : 0,00005%	non précisé	LD = 0,00005%	LD = 0,00005%	LD : 0,09% LQ : 0,26%	LD : 0,005%	LQ : 10-7%	LQ = 0,000001%
Analytical method	LC-MS/MS	HPLC/fluo	HPLC/ CoulArray	HPLC/GC/MS	-	GC/FID	GC/MS	LC/MS-MS	GC-ECNI/MS
Other bisphenols searched	BPS	-	BPB, BPS, BPF	BPS	-	-	-	-	-

Handling of thermal receipts Cashier scenario – Pregnant women



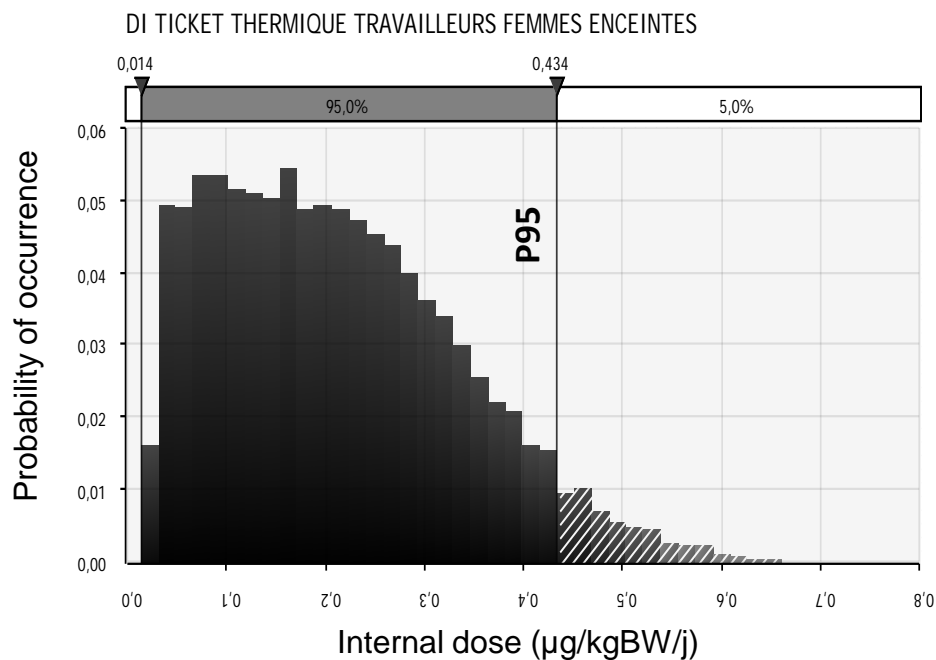
F =Percutaneous absorption flow, D= duration of exposure, S= surface in contact with the paper,
BW=body weight

$$\text{Internal dose } (\mu\text{g.kgBW}^{-1}.\text{d}^{-1}) = \frac{F (\mu\text{g.cm}^{-2}.\text{h}^{-1}) \times D (\text{h.d}^{-1}) \times S (\text{cm}^2)}{\text{BW (kg)}}$$



Internal Dose ($\mu\text{g/kgBW/d}$)

Minimum	0.01
P5	0.05
P25	0.11
P50	0.20
P75	0.29
P90	0.38
P95	0.43
Maximum	0.71
Mean	0.21



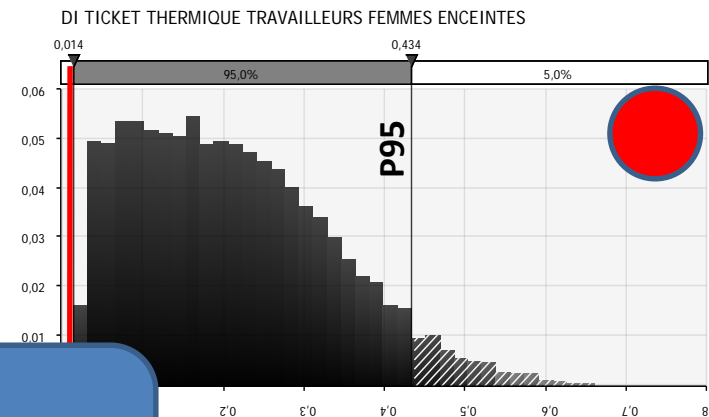
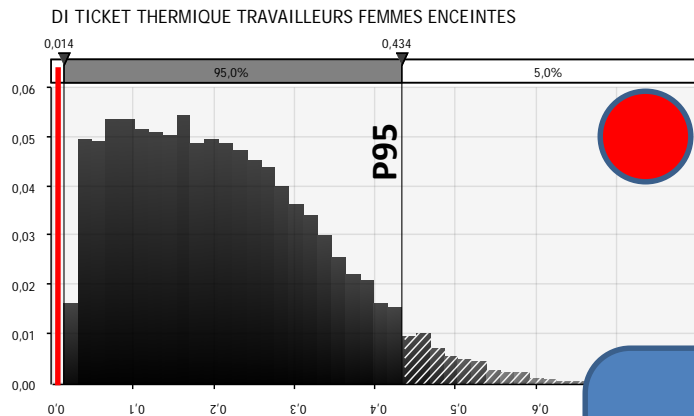
Effect on brain and behaviour

ITV = 0.005 $\mu\text{g}/\text{kg}/\text{j}$



Effect on the femal reproductive system

ITV = 0.01 $\mu\text{g}/\text{kg}/\text{j}$



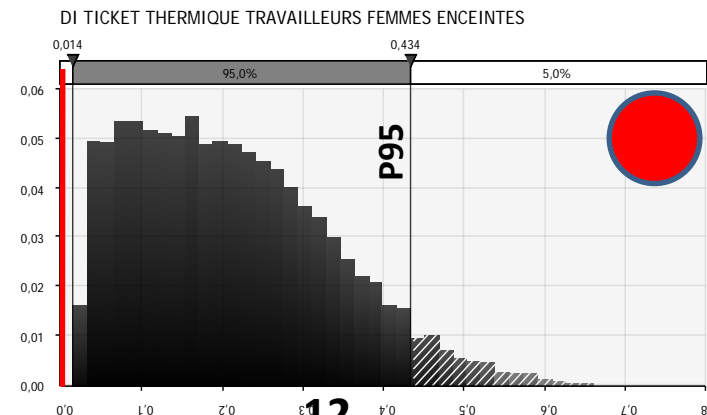
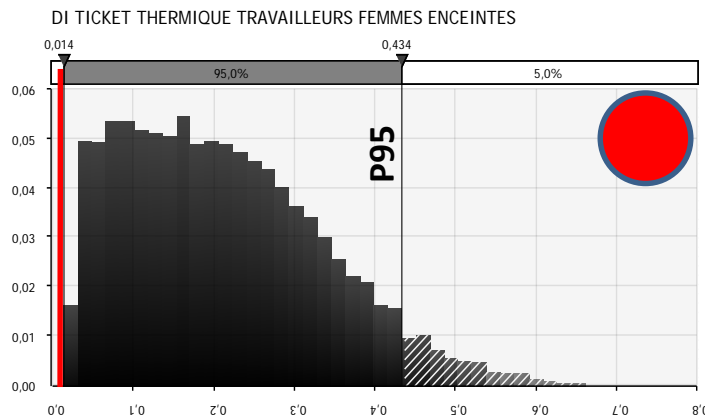
Level of confidence : limited

Effect on metabolism and obesity

ITV = 0.009 $\mu\text{g}/\text{kg}/\text{j}$

Effect on mammary gland

ITV = 0.0025 $\mu\text{g}/\text{kg}/\text{j}$



Conclusions

There are **risk situations for the unborn child associated with exposure to BPA during pregnancy**. Risks relate to the mammary gland and may be characterized by an increase in the number of undifferentiated epithelial structures associated with an increased susceptibility of the mammary gland to tumour transformation. The risks potentially affect children of both sexes.

- Given the uncertainties associated with the RA, the **confidence level has been described as moderate** by the experts.
- The aggregate assessment taking into account the different exposures showed the **predominance of dietary exposure compared to other routes**. Nevertheless the study of particular exposure scenarios during pregnancy identified **specific risk situations associated with the handling of thermal paper** and also with the drinking of water from refillable polycarbonate containers

Conclusions

The scenario relating to the handling of thermal paper thus revealed, in addition to the effect on the mammary gland, risk situations involving other effects for the **unborn child**. These may affect the brain and behaviour, metabolism and obesity or the female reproductive system. Given the many uncertainties associated with the RA the confidence level was described by the experts as limited.

- To date, the available data are insufficient to conduct a RA for other target groups (infants, adolescents, etc.)
- Besides the legislative measures already taken in France, Anses issued a number of recommendations seeking mainly to reduce the risks associated with exposure to BPA during pregnancy as well as to increase the confidence level in the results of RA. These recommendations will help *iso facto* reduce the exposure of the population to BPA as previously recommended by the agency.

Recommendations

- **to eliminate or reduce the risks associated with exposure to BPA**
 - by dietary exposure
 - by handling thermal paper
- **to acquire knowledge on the toxicity** of BPA relevant to RA
- **to support studies aimed at better characterizing exposures** to BPA relevant to RAs:
 - In terms of external exposure *via* food and *via* other sources of exposure
 - In terms of internal exposure
- **to improve RA methodology:** to develop procedures to take NMDR in RA, to review the relevance of using one or more Tox.ref. value or Total diet intakes for substances for which NMDR relationships are observed and for which the periods of vulnerability are not always known
- **to perform a specific biomonitoring study in the workplace** to confirm the estimated internal doses (INRS)

Thank you for your attention