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, Phthalates, 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, hypospadia...) 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, diabetis, obesity...).

- 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
5 substances in consumer goods:

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

- **PHTALATES**
  - Di-n-butylphthalate : DBP
  - Diisobutylphthalate : DIBP
  - Butylbenzylphthalate : BBP
  - Diethylhexylphthalate : DEHP
  - Diisononylphthalate : DINP
  - Diisodecylphthalate : DIDP
  - Diisopentylphthalate : DIIP
  - Dipropylphthalate
  - Mono-n-butylphthalate
  - Di-n-hexylphthalate
  - Di-2propyl-heptylphthalate : DPHP
  - Diisoundecylphthalate : DIUP
  - Dicyclohexylphthalate
  - Diisooctylphthalate : DIOP
  - Ditridecylphthalate : DTDP

- **Perfluorinated :**
  - PFOA
  - PFOS

- **Polybrominated :**
  - 2,2′,4,4′-tetrabrominated diphenylether (2,2′,4,4′-tetraBDE)
  - Decabrominated diphenylether (DecaBDE)
<table>
<thead>
<tr>
<th>Critical effects</th>
<th>Study reference</th>
<th>Route of exposure</th>
<th>LOAEL (µg/kg/d)</th>
<th>NOAEL* (µg/kg/d)</th>
<th>Internal NOAEL by application of a bioavailability factor of 3% (µg/kg/d)</th>
<th>Internal TV by application of a Margin of Safety (MOS) of 300 on the internal NOAEL (µg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain and behaviour</td>
<td>Xu et al., 2010c</td>
<td>oral</td>
<td>/</td>
<td>50</td>
<td>1.5</td>
<td>0.005</td>
</tr>
<tr>
<td>Female reproductive system</td>
<td>Rubin et al., 2001</td>
<td>oral</td>
<td>/</td>
<td>100</td>
<td>3</td>
<td>0.01</td>
</tr>
<tr>
<td>Metabolism and obesity</td>
<td>Miyawaki et al., 2007</td>
<td>oral</td>
<td>260</td>
<td>87</td>
<td>2.6</td>
<td>0.009</td>
</tr>
<tr>
<td>Mammary gland</td>
<td>Moral et al., 2008</td>
<td>oral</td>
<td>/</td>
<td>25</td>
<td>0.75</td>
<td>0.0025</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Country</th>
<th>France</th>
<th>Switzerland</th>
<th>USA et Japan</th>
<th>Danmark</th>
<th>Sweden</th>
<th>USA</th>
<th>USA, Japan, Korea</th>
<th>Vietnam</th>
<th>Belgium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampling places</td>
<td>Supermarkets, shops, stations-service, banks</td>
<td>Chromatograms shops, cinemas...</td>
<td>Shops, supermarkets, public institutions</td>
<td>Supermarkets, shops, banks</td>
<td>Récolte par 4 familles suédoises</td>
<td>Not precised</td>
<td>Shops and restaurants</td>
<td>Supermarkets, shops, banks, stations service, restaurants, fast-food</td>
<td>Banks, shops, restaurant, parkings...</td>
</tr>
<tr>
<td>Number of receipts tested</td>
<td>50</td>
<td>13</td>
<td>36</td>
<td>12</td>
<td>16</td>
<td>10 (tickets non imprimés)</td>
<td>22</td>
<td>103</td>
<td>44</td>
</tr>
<tr>
<td>Number of receipts with BPA</td>
<td>36 (soit 72 %)</td>
<td>11 (soit 85 %)</td>
<td>16 (soit 44 %)</td>
<td>12 (soit 75 %)</td>
<td>16 (soit 100 %)</td>
<td>8 (soit 80 %)</td>
<td>11 (soit 50 %)</td>
<td>97 (soit 94 %)</td>
<td>44 (soit 100 %)</td>
</tr>
<tr>
<td>BPA concentration in receipts (% m/m)</td>
<td>Moyenne</td>
<td>1,33 %</td>
<td>1,33 %</td>
<td>1,9 %</td>
<td>1,14 %</td>
<td>1,58 %</td>
<td>1,24 %</td>
<td>1,70 %</td>
<td>0,021 %</td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>0,8–1,9 %</td>
<td>0,8–1,7 %</td>
<td>0,8–2,8 %</td>
<td>0,87–1,70 %</td>
<td>0,58–3,2 %</td>
<td>0,3–1,5 %</td>
<td>0,9–2,2 %</td>
<td>&lt;10–7–1,4 %</td>
</tr>
<tr>
<td></td>
<td>LD / LQ</td>
<td>LD : 0,01%</td>
<td>LQ : 0,00005%</td>
<td>non précisé</td>
<td>LD = 0,00005%</td>
<td>LD = 0,00005%</td>
<td>LD : 0,09%</td>
<td>LD : 0,005%</td>
<td>LQ : 10-7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LQ : 0,02%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analytical method</td>
<td>LC-MS/MS</td>
<td>HPLC/fluo</td>
<td>HPLC/ CoulArray</td>
<td>HPLC/GC/MS</td>
<td>-</td>
<td>GC/FID</td>
<td>GC/MS</td>
<td>LC/MS-MS</td>
<td>GC-ECNI/MS</td>
</tr>
<tr>
<td>Other bisphenols searched</td>
<td>BPS</td>
<td>-</td>
<td>BPB, BPS, BPF</td>
<td>BPS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Handling of thermal receipts
Cashier scenario – Pregnant women

\[ F = \text{Percutaneous absorption flow}, \ D = \text{duration of exposure}, \ S = \text{surface in contact with the paper}, \ BW = \text{body weight} \]

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

<table>
<thead>
<tr>
<th>Probability of occurrence</th>
<th>5.0%</th>
<th>95.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal dose ((\mu g/\text{kgBW/j}))</td>
<td>0.014</td>
<td>0.434</td>
</tr>
</tbody>
</table>

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

DI TICKET THERMIQUE TRAVAILLEURS FEMMES ENCEINTES
Effect on brain and behaviour

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

Effect on the female reproductive system

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

Effect on metabolism and obesity

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

Effect on mammary gland

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

Level of confidence: limited
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 mammay 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