Endocrine Disrupting Chemicals
Hazard pictograms

Physical Hazards

Health Hazards

Env. hazards
Endocrine disruptor

An exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones responsible for the maintenance of homeostasis and the regulation of developmental processes.

Kavlock et al., 1996
How do endocrine disruptors work?

When absorbed in the body, an endocrine disruptor can decrease or increase normal hormone levels (left), mimic the body's natural hormones (middle), or alter the natural production of hormones (right).
## Select human nuclear receptors and related functions

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Abbreviation</th>
<th>Physiological Function</th>
<th>Endogenous Ligand</th>
<th>Examples of Endocrine Disrupting Chemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen</td>
<td>AR</td>
<td>Male sexual development</td>
<td>Testosterone</td>
<td>Pesticides, Phthalates, Plasticisers, Polyhalogenated compounds</td>
</tr>
<tr>
<td>Estrogen</td>
<td>ER α, β</td>
<td>Female sexual development</td>
<td>Estradiol</td>
<td>Alklyphenols, BPA, Dioxins, Furans, Halogenated hydrocarbons, Heavy metals</td>
</tr>
<tr>
<td></td>
<td>GPR30 (non-nuclear)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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</thead>
<tbody>
<tr>
<td>Thyroid Hormone</td>
<td>TR α, β</td>
<td>Metabolism, Heart rate</td>
<td>Thyroid Hormone</td>
<td>BPA, Dioxins, Furans, PCDeS, PCBs, Perchlorates, Pesticides, Phalates, Phytoestrogens</td>
</tr>
<tr>
<td>Progesterone</td>
<td>PR</td>
<td>Female sexual development</td>
<td>Progesterone</td>
<td>BPA, Fungicides, Herbicides, Insecticides</td>
</tr>
</tbody>
</table>

## Select human nuclear receptors and related functions

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</thead>
<tbody>
<tr>
<td>Arylhydrocarbon</td>
<td>AhR</td>
<td>Circadian rhythm</td>
<td>Unknown</td>
<td>Dioxins, Flavonoids, Herbicides, Indoles, PCBs, Pesticides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Organ development</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stress response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peroxisome Proliferator-Activated</td>
<td>PPAR α, β, λ</td>
<td>Lipid homeostasis</td>
<td>Lipids/Fatty Acids</td>
<td>BPA, Organotins</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>GR α, β</td>
<td>Development</td>
<td>Cortisol</td>
<td>Arsenic, BPA, Phthalates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stress response</td>
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<td></td>
</tr>
</tbody>
</table>

Model of the endocrine systems targeted by EDCs
Variety of chemicals

- Pesticides
- Herbicides
- Fungicides
- Plasticizers
- Surfactants
- Organometals
- Halogenated polyaromatic hydrocarbons
- Phytoestrogens
di-n-pentyl phthalate (DnPeP)
di(2-ethylhexyl) phthalate (DEHP)
di-n-butyl phthalate (DnBP)
di-iso-butyl phthalate (DiBP)
butylbenzyl phthalate (BBzP)
Dicyclohexyl phthalate (DCHP)
Di-iso-nonyl phthalate (DiNP)

Gennings et al. (2014) *U.S. Consumer Product Safety Commission*
## Major phthalates and their uses (1)

<table>
<thead>
<tr>
<th>Common phthalates</th>
<th>Uses/Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenyl phthalate</td>
<td>Plasticizer in nitro- and ethylcellulose, polystyrene, phenol and vinyl resins</td>
</tr>
<tr>
<td>Dethyhexyl/ Dioctyl phthalate</td>
<td>In PVC, construction and automotive, flooring, medical and sanitary products (e.g., blood/dialysis bags, dialysis equipment, syringe, implants, catheters and tubings (intravenous, nasogastric transfusion, air tubes) floor tiles and furniture upholstery, wall coverings; toys; food packaging; wood coating to enhance the performance properties of the wood coatings formulations; hydraulic fluid dielectric fluids in capacitors; solvent in light sticks, plastic films, gloves, cable and wiring flooring, shower curtains; ethylcellulose resins (e.g., plastic film, imitation leather, electric wire, cable wearer, sheet, planet, mould plastic products and used in nitrocellulose paints, etc.</td>
</tr>
</tbody>
</table>
Major phthalates and their uses (2)

<table>
<thead>
<tr>
<th>Common phthalates</th>
<th>Uses/Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dibutyl phthalate</strong></td>
<td>Cellulose acetate plastics, personal care products (e.g., nail polish and solvents, cosmetics), lacquers, varnishes, coatings (e.g., pharmaceuticals); fragrance ingredients in many other cosmetics, etc.</td>
</tr>
<tr>
<td><strong>Benzylbutyl phthalate</strong></td>
<td>Plasticizer in PVC products such as vinyl floor tiles, adhesives and sealants, car-care products, toys, food packaging, synthetic leather, industrial solvents, personal care products.</td>
</tr>
</tbody>
</table>
Phthalate metabolism in humans

Phases:
- **Phase I**: De-esterification, followed by oxidation, hydroxylation, or carboxylation.
- **Phase II**: Glucuronide conjugation.
- **Phase III**: Excretion.

Chemical Reactions:
2. Metabolites → Glucuronyl transferase → Glucuronide conjugation; Urine, Sweat, Feces.
Exposure characteristics

• DEHP, DiNP are mainly used in polyvinyl chloride (PVC) plastics (electrical wires and cables, automotive parts, medical and sanitary products, in several categories of toys (plastic books, balls, dolls) etc.).

• DnBP, DiBP, BBzP, - in personal care products, textile industry (e.g., synthetic leather), pesticides, lubricants and adhesives.
Migration of phthalates into the environment from the embodiment of plastics

- pH, temperature, pressure, irradiation, solvents, chemical conductant, *etc.*

- Naked polymer

- Leachate

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## Research activities concerning phthalates in EU (example)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Available knowledge</th>
</tr>
</thead>
</table>
Knowledge gaps

- The available data allow assertions concerning **routes of exposure and exposition in some regions**, but no EU wide statement is possible
- Taking into account, that data representative for population only are available from Flanders and Germany
- There are **gaps in data on exposure for eastern Europe**,
- **Full time series** are available from Germany – more data on trends in exposure are needed
- More **studies on workers** are needed
There is a large literature on the toxicity of **bisphenol A** (BPA) including at low doses.

BPA elicits a variety of endocrine disrupting effects targeting steroid hormones as well as thyroid hormones.

Studies have indicated that it could be associated with increased risk for:

- Fetal development: miscarriages, decreased birth weight at term
- Reproductive and sexual dysfunctions
- Breast and prostate cancer or at least significant breast tissue remodelling
- Altered immune system activity
- Obesity and metabolic dysfunctions and diabetes in adults
- Cardiovascular disease in adults
- Cognitive and behavioural development in young children
Applicable Regulations (1)

4,4'-isopropylidenediphenol (bisphenolA, BPA)
(EC 201-245-8, CAS 80-05-7)
REACH Annex V; Annex XVII, Entry 66
PACT list entry 13/04/2017: Hazard assessment. Scope: ED.
OSH Legislation: Consumer uses, Article service life, Widespread uses by professional workers, Formulation or re-packing, Uses at industrial sites, Manufacture, Signs at work, CAD, Young workers, Pregnant or breastfeeding workers.
Applicable Regulations (2)

ECHA has recently classified BPA as an endocrine disruptor and a substance of high concern.

Commission Regulation (EU) 2016/2235 was published on the restriction of BPA in thermal paper based on the recommendation of the SEAC (*shall apply from 2 January 2020*).

Commission Directive (EU) 2017/164 revised the OEL (Occupational Exposure Limit values) for BPA of 2 mg/m³ TWA in occupational settings.
## Bisphenols time trend analysis

<table>
<thead>
<tr>
<th>Study name</th>
<th>German Environmental Specimen Bank (ESB)</th>
<th>Health Related Environmental Monitoring (HÄMI)</th>
<th>Male Reproductive Health Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Owner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Germany</td>
<td>Sweden</td>
<td>Denmark</td>
</tr>
<tr>
<td>Study population</td>
<td>Young students 20-29 years</td>
<td>Children 4-18 years</td>
<td>Young men 18-25 years</td>
</tr>
<tr>
<td>Frequency sampled</td>
<td>annually</td>
<td>2-4 years intervals</td>
<td>Annually</td>
</tr>
<tr>
<td>Number of samples</td>
<td>?</td>
<td>1400</td>
<td>~2000 (~300 pr year)</td>
</tr>
<tr>
<td>Regional/national</td>
<td>Regional (4 different locations)</td>
<td>Regional/national (?)</td>
<td>Regional (greater Copenhagen area)</td>
</tr>
<tr>
<td>Samples available</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Sample type</td>
<td>24 h sample</td>
<td>Spot urine (random and first morning)</td>
<td>Spot urine (random)</td>
</tr>
<tr>
<td>Bisphenol data available</td>
<td>No*#</td>
<td>No*#</td>
<td>BPA data available for samples collected September 2008 through June 2009 33 men with spot, morning and 24 h samples BPA data</td>
</tr>
<tr>
<td>Access to bisphenol data</td>
<td>Individual data - yes</td>
<td>Individual data - yes</td>
<td>Individual data- depending on use and collaboration - yes Aggregated data - yes</td>
</tr>
</tbody>
</table>
HBM4EU Policy-related Questions

1. What is the current exposure of the EU population to BPA?
2. Do different regulatory controls across the EU concerning in particular BPA lead to different exposures?
3. Are bisphenols exposure levels of concern for health?
4. Is occupational exposure of cashiers a health concern?
5. What is the toxicity of BPA substitutes?
6. Are health risks age and gender dependent? Can we find evidence for low-dose effects within mixtures?
7. How can this feed into assessment of the Tolerable Daily Intake (TDI) for BPA, as set by the European Food Safety Authority (EFSA)?
Why do we need HBM4EU?

- To better understand the consequences of **human exposure to various chemicals**, a key aspect of environmental health
- To bridge the gap between **science and policy making**
- To share **evidence of use** from national programmes
- **To share existing experience** in the EU and to share the burden
- To generate better evidence for **better regulation**
- To give better access by a new data-infrastructure - **IPChem**
- To **include aggregate exposure** in the health risk assessment
HBM4EU partners

22 EU Member States
3 Associated States
1 Partly Associated State

(3 candidates to join in later)

109 Partners
41 Participants

Financial volume: ~ 73 M €

Management Board Member

Horizon 2020 Programme
Contract No. 733032 HBM4EU
Endocrine Disrupting Chemicals and Disease Susceptibility

• Chemical exposures during development can alter disease susceptibility later in life.
• Endocrine disrupting chemicals (EDCs) can produce adverse developmental, reproductive, neurological, cardiovascular, metabolic and immune effects in humans.
• EDCs interfere with the synthesis, secretion, transport, activity, or elimination of natural hormones.