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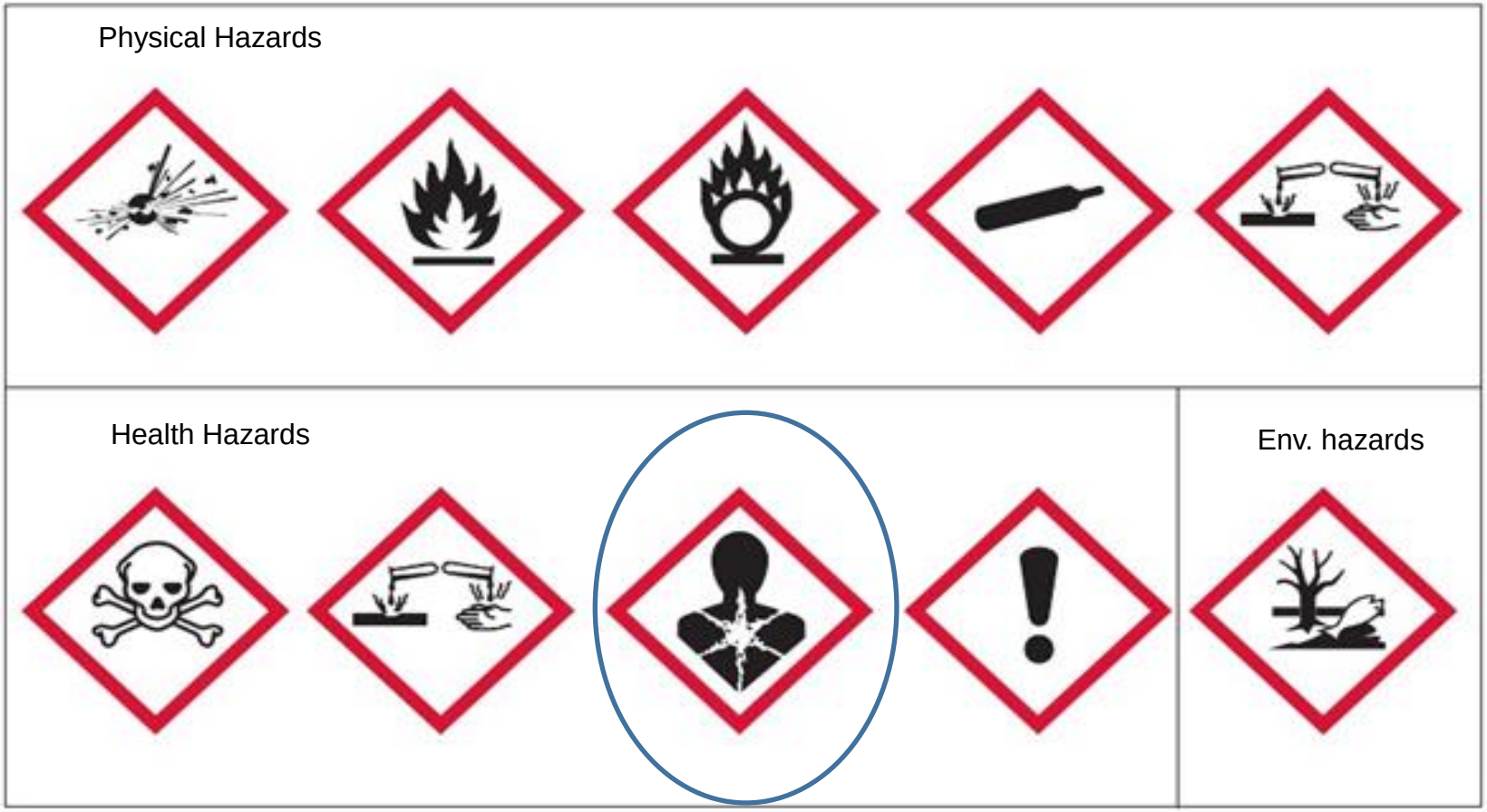
Endocrine Disrupting Chemicals

Inese Mārtiņsone, Dr. med.
RSU Institute of Occupational Safety and Environmental Health
inese.martinsone@rsu.lv

Hazard pictograms

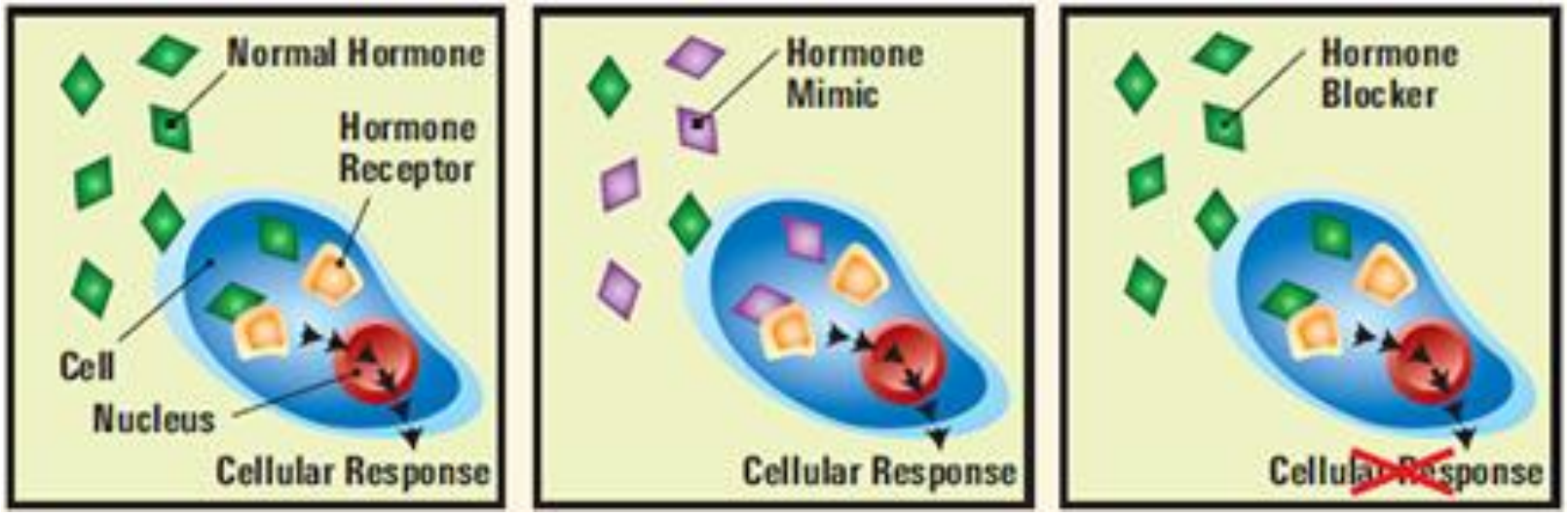


Endocrine disruptor

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

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

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Thaddeus T. Schug *et al*. J Steroid Biochem Mol Biol. 2011 Nov; 127(3-5): 204–215.

Select human nuclear receptors and related functions

Receptor	Abbreviation	Physiological Function	Endogenous Ligand	Examples of Endocrine Disrupting Chemicals
Thyroid Hormone	TR α, β	Metabolism Heart rate	Thyroid Hormone	BPA Dioxins Furans PBDEs PCBs Perchlorates Pesticides Phalates Phytoestrogens
Progesterone	PR	Female sexual development	Progesterone	BPA Fungicides Herbicides Insecticides

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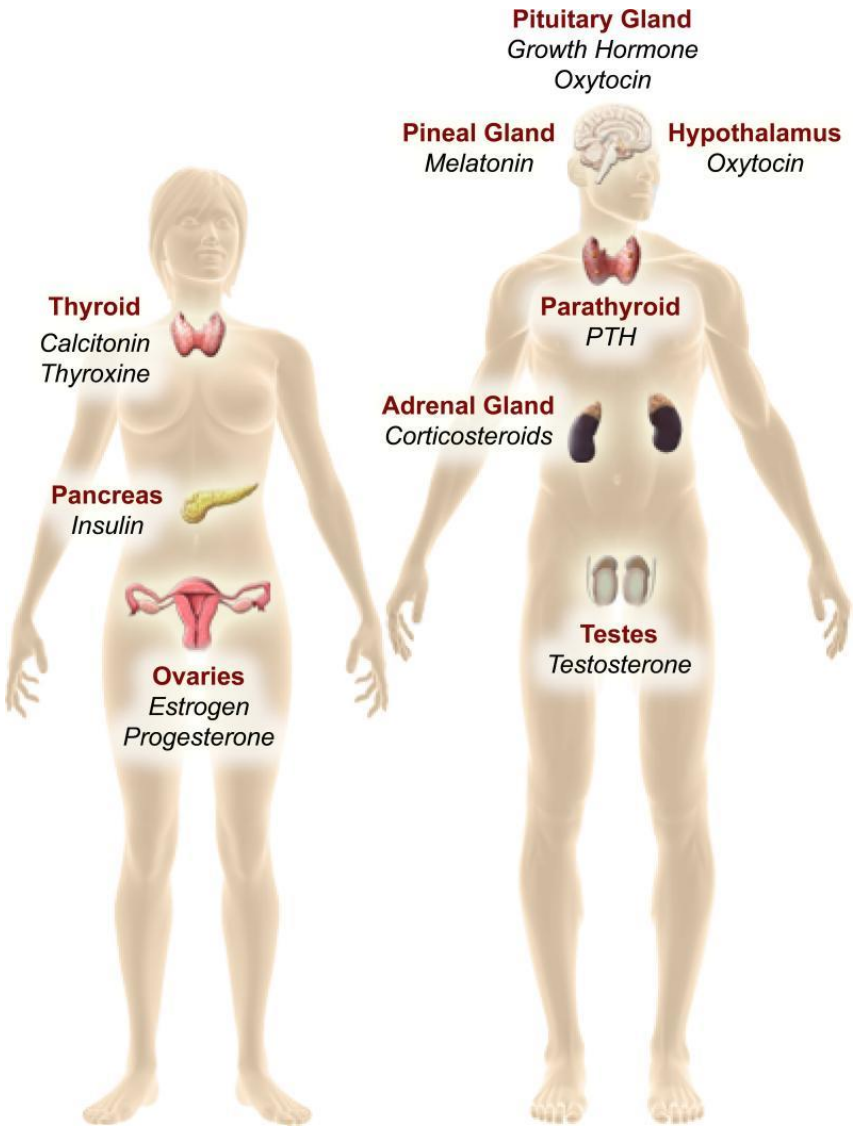
Select human nuclear receptors and related functions

Receptor	Abbreviation	Physiological Function	Endogenous Ligand	Examples of Endocrine Disrupting Chemicals
Arylhydrocarbon	AhR	Circadian rhythm Metabolism Neurogenesis Organ development Stress response	Unknown	Dioxins Flavonoids Herbicides Indoles PCBs Pesticides
Peroxisome Proliferator-Activated	PPAR α, β, λ	Lipid homeostasis	Lipids/Fatty Acids	BPA Organotins
Glucocordicoid	GR α, β	Development Metabolism Stress response	Cortisol	Arsenic BPA Phthalates

Thaddeus T. Schug *et al*. J Steroid Biochem Mol Biol. 2011 Nov; 127(3-5): 204–215.

Model of the endocrine systems targeted by EDCs



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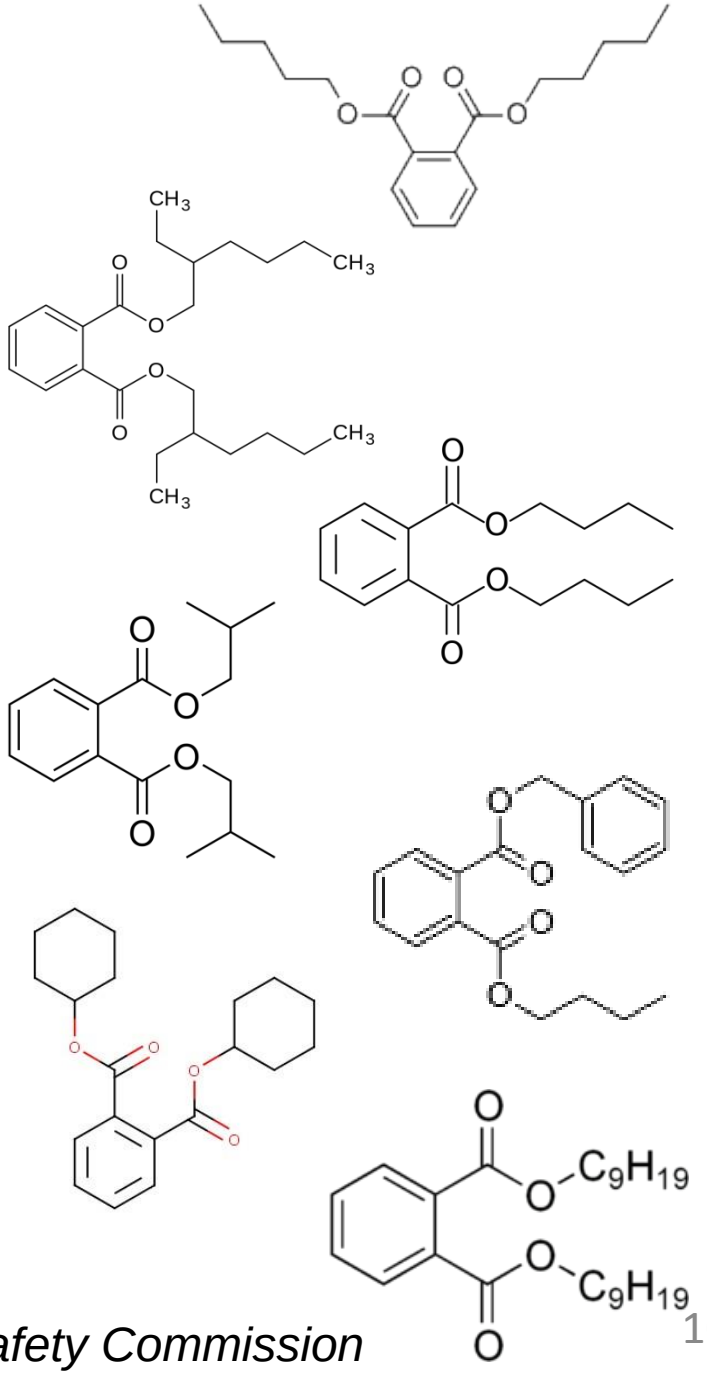
Variety of chemicals

- 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*

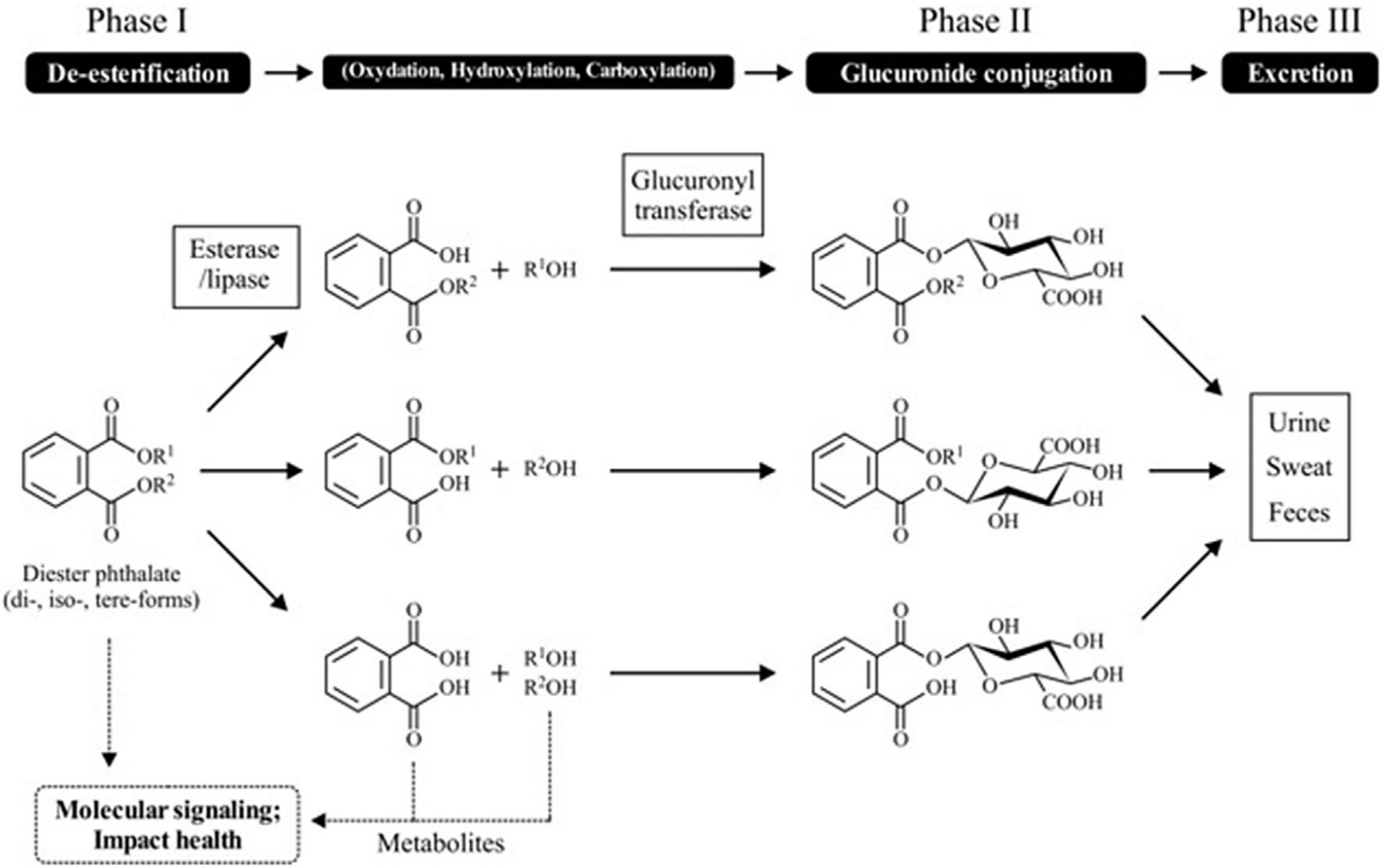
Major phthalates and their uses (1)

Common phthalates	Uses/Applications
Diphenyl phthalate	Plasticizer in nitro- and ethylcellulose, polystyrene, phenol and vinyl resins
Dethylhexyl/ Dioctyl phthalate	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.

Major phthalates and their uses (2)

Common phthalates	Uses/Applications
Dibutyl phthalate	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.
Benzylbutyl phthalate	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.

Phthalate metabolism in humans

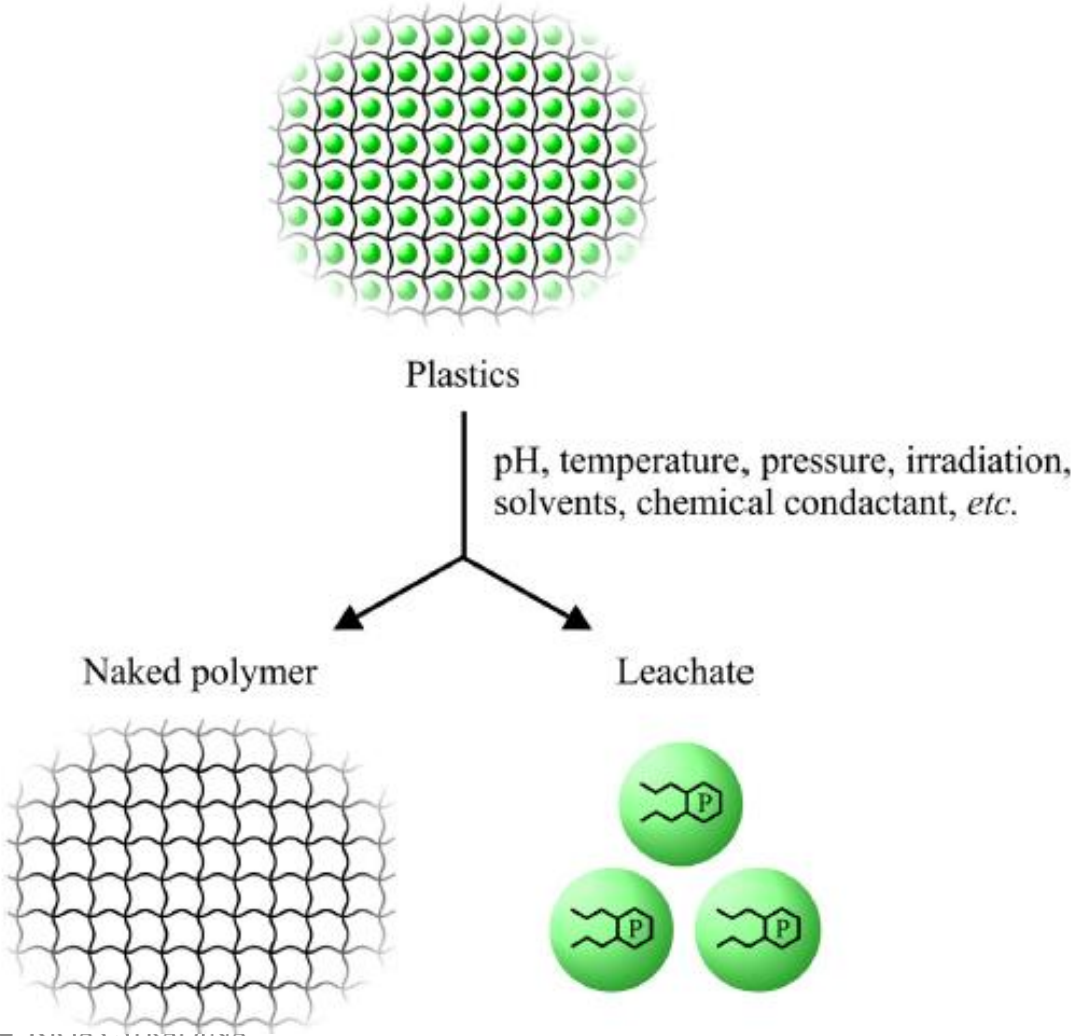


Benjamin S., *et all.* Journal of Hazardous Materials 340 (2017) 360–383

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) ect.).
- DnBP, DiBP, BBzP, - in personal care products, textile industry (e.g., synthetic leather), pesticides, lubricants and adhesives.

Migration of phthalates in to the environment from the embodiment of plastics



S. Benjamin et al. / Journal of Hazardous Materials 340 (2017) 360–383

Research activities concerning phthalates in EU (example)

Substance	Available knowledge
DEHP	**Flanders 2007/08, 2013/14 (13-17 yr.):** (Geens et al. 2014, Schoeters et al. 2017) *(rp)*; **Germany 2003-06 (3-14 yr.):** (Becker et al. 2009) *(rp)* **& 1988-2015 (20-29 yr**.): (Wittassek et al. 2007, Goen et al. 2011, Koch et al. 2016); **workers 2012:** (Koch et al. 2012); **Austria 2010-12 (6-15, 18-64, 65-81 yr.):** (Hartmann et al. 2015); **Denmark 2006-12 (4-9, 5-20 yr., young men, pregnant women):** (Frederiksen et al. 2014); **France 2011 (pregnant women):** (Dereumeaux et al. 2016); **Greece 2007/08 (new-borns):** (Myridakis et al. 2015);

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

Overview: BPA Toxicity

- 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:
  - ✓ Fetaldevelopment: 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.
Environmental legislation: Classified Seveso, Waste Directive Annex III
Professional and consumer legislation: Cosmetics (EC) No 1223/2009 Annex II; Toy safety Directive Appendix C

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/m^3 TWA** in occupational settings.

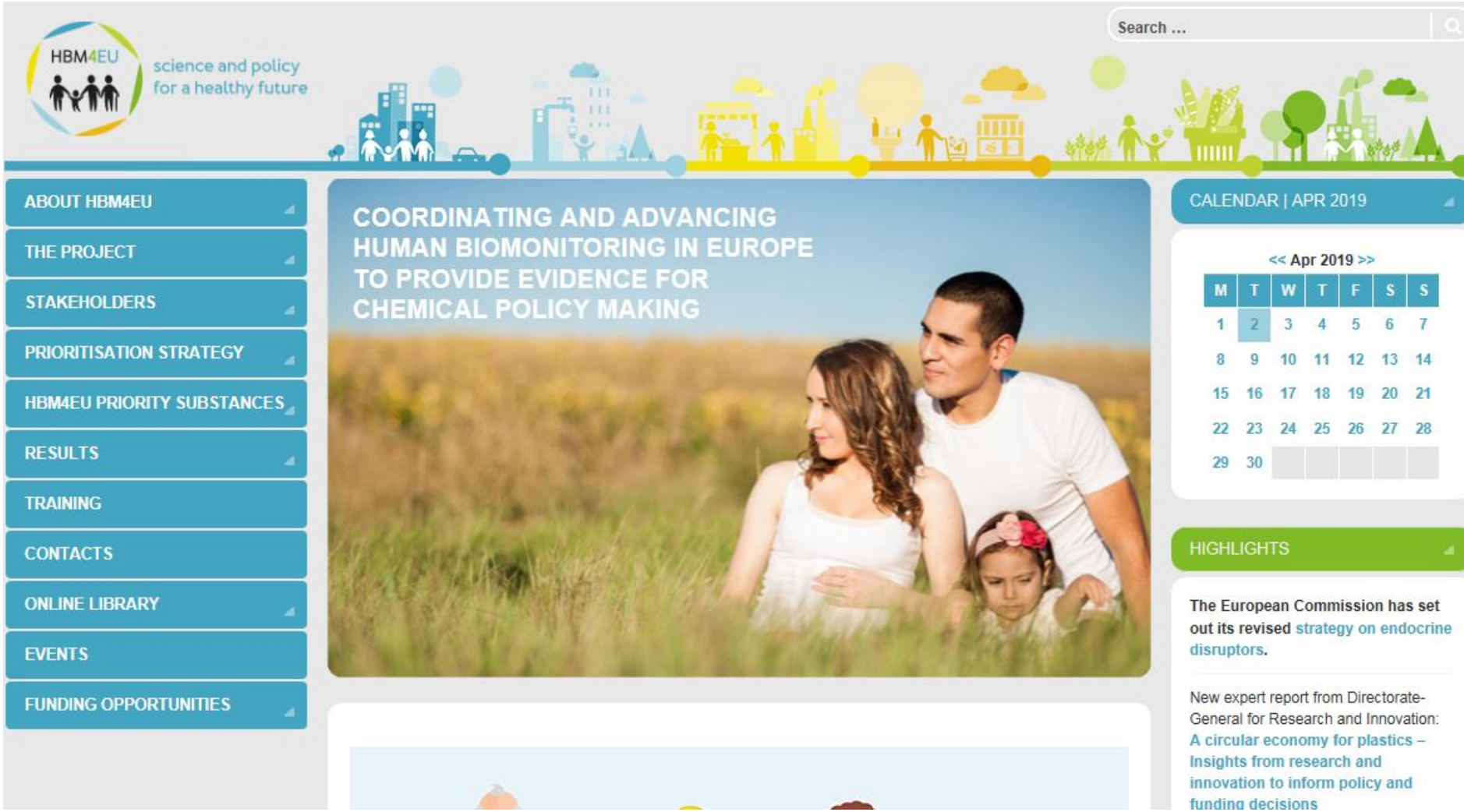
Bisphenols time trend analysis

Study name	German Environmental Specimen Bank (ESB)	Health Related Environmental Monitoring (HÄMI)	Male Reproductive Health Study
Data Owner			
Country	Germany	Sweden	Denmark
Study population	Young students 20-29 years	Children 4-18 years	Young men 18-25 years
Period covered	1985* - 2017	1996*- 2017	2007**-2017
Frequency sampled	annually	2-4 years intervals	Annually
Number of samples	?	1400	~2000 (~300 pr year)
Regional/national	Regional (4 different locations)	Regional/national (?)	Regional (greater Copenhagen area)
Samples available	Yes	-	Yes
Sample type	24 h sample	Spot urine (random and first morning)	Spot urine (random)
Bisphenol data available	No?#	No?#	BPA data available for samples collected September 2008 through June 2009 33 men with spot, morning and 24 h samples BPA data
Access to bisphenol data	Individual data - yes	Individual data - yes	Individual data- depending on use and collaboration - yes Aggregated data - yes

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)?

https://www.hbm4eu.eu/



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

HBM4EU science and policy for a healthy future

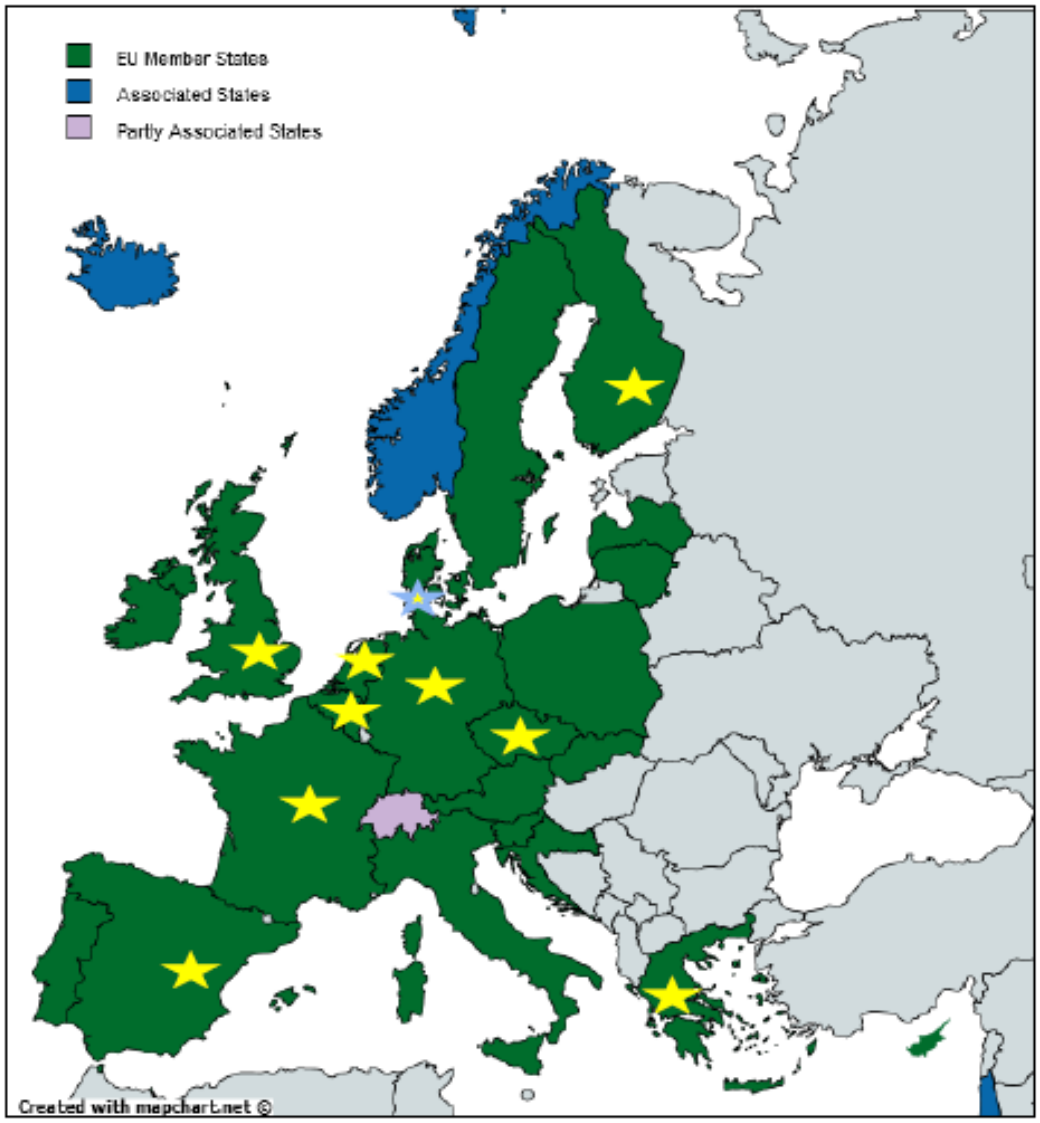
22 EU Member States
3 Associated States
1 Partly Associated State

(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.

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