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CHEMICALS WITH SPECIAL HAZARDS :
OCCUPATIONAL RISKS AND PREVENTION

PARIS
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ENDOCRINE DISRUPTORS AND SENSITISING SUBSTANCES

Endocrine Disruptors and Occupational Exposure: An Overview

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Outline

- Definition of Endocrine Disruptors (EDs)
- Which Substances Are Endocrine Disrupting Chemicals (EDCs)?
- Difficulties in Handling EDC
- What Have We Learned from Experimentation?
- Epidemiology Limitations
- Implication for Risk Assessment
- Summary

Definition of EDs

- "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations."

World Health Organization and the International Programme on Chemical Safety. 2002. Global Assessment of the State-of-the-Science of Endocrine Disruptors. Available at http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en

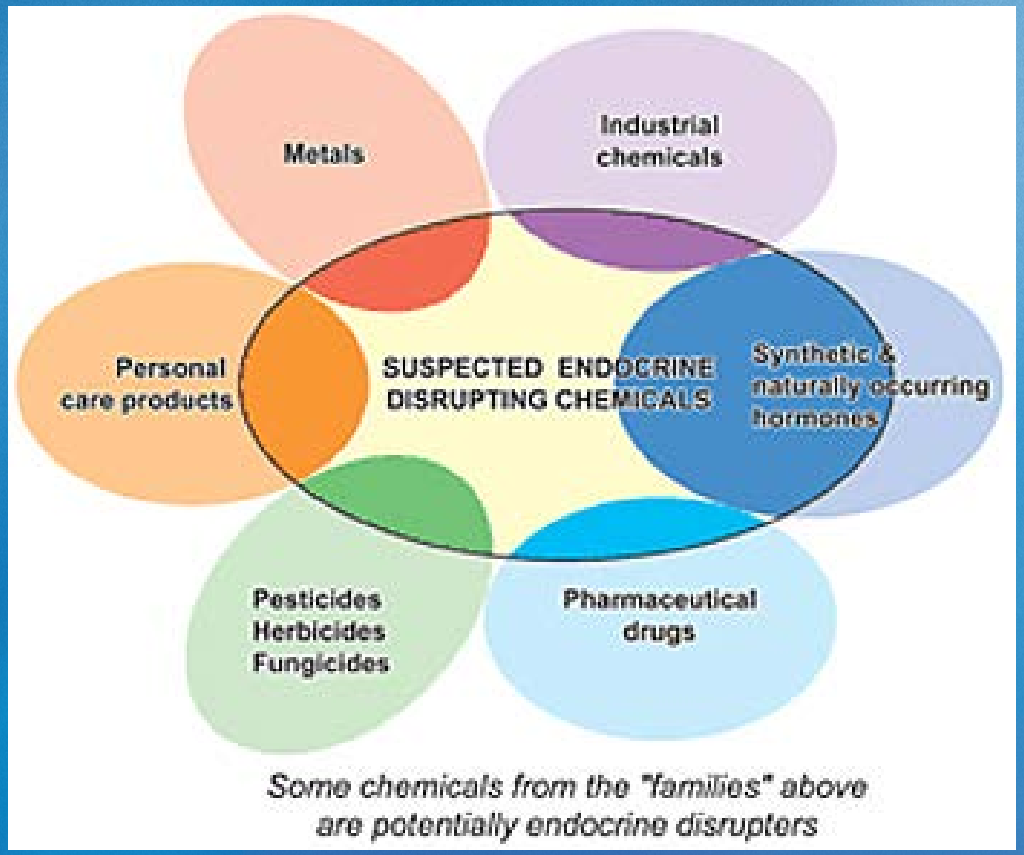
Which Substances Are EDCs?

Toxic Substances Control Act (TSCA)

- The initial reporting period by manufacturers, processors, and importers was January to May 1978 for chemical substances that had been in commerce since January 1975. The TSCA Inventory was initially published in 1979, and a second version, containing approximately 62,000 chemical substances, was published in 1982. The TSCA Inventory has continued to grow since then, and now lists approximately 85,000 chemicals.

U.S. EPA (Environmental Protection Agency). 2015. About the TSCA Chemical Substance Inventory: Available at https://www.epa.gov/tsca-inventory/about-tsca-chemical-substance-inventory#bonafide

Categories of Suspected Substances



Bradley, G., and C. Swanson. 2005. Endocrine Disruption: Endocrine Disrupting Chemicals. Available at http://www.public.iastate.edu/~bsbowen/ZOOL-EEOB507/pages/endocrinedisrupt.htm

Substances That Are Suspected EDs

Substance category	Name	Source / Uses	Reported properties
Dioxins and dibenzofurans	2,3,7,8-TCDD 2,3,7,8-p-TCDD 2,3,7,8-PCDF 2,3,4,7,8-PeCDF 1,2,3,7,8 (9)-PeCDF	Arise as unwanted by-products from certain incineration and industrial chemical process	Anti-estrogenic
Industrial Chemicals and Related substances	Phthalates (DEHP, BBP, DBP, DPP, DPrP)	Used as plasticisers in the production of flexible plastics	Estrogenic
	Alkylphenols (penta- to nonylphenols)	Degradation products of alkylphenol polyethoxylates	Estrogenic
	Alkylphenols polyethoxylates	Non-ionic surfactants used extensively	Estrogenic
	Bi-phenolic compounds (bisphenol A, Bisphenol F)	Used in the production of PVC, rubber, epoxy and polycarbonate resins, and plastics	Estrogenic
	PCB	No longer used manufactured or used, but some equipment (electrical) containing PCBs remains in use	Anti-estrogenic
Pesticides	DDT, DDD, DDE, alachlor, aldicarb, amitrole, atrazine, Beta-HCH, dieldrin, endosulfn, lindane, heptachlor, kepone, toxaphene, ziram and so on	Many pesticides used throughout the world today and present in aquatic environment in significant concentration. Organochlorins are highly lipophilc and bioaccumulate.	Influence the endocrine system in more than one way
Synthetic estrogens	Diethylstilbestrol (DES)	Prescribed to women to prevent miscarriages (banned in present)	Estrogenic
	Ethinylestradiol	Oral contraceptive pill	Estrogenic
Phyto-estrogens	Isoflavones, Coumestol, Lignans and stilbens	Synthesized in plants	Estrogenic
Myco-estrogens	beta-Zearalenol, Zearalenone	Found in fungi	Estrogenic

Lee, C.W., K.H. Choi, S.W. Jeong, H.L. Kim, and Y.R. Seo. 2009. An overview and future perspective on endocrine disruptors. *Journal of the Korean Endocrine Society 24*(1):7–14.

Endocrine Disrupting Substances in Food Contact Materials

Compound name	Role in FCMs	Mode of action toxicological endpoint
Benzophenone	Additive - photo initiator UV to printing inks used for printing cardboard food packaging	Weak estrogen, binds to estrogen receptor
Bis(2-ethylhexyl) phthalate (DEHP)	Additive - plasticiser in plastic foils, resins, PVC hoses, tubing, foams and plastic kitchenware	Affects reproduction and fertility in 2-gene-ration studies
Dibutyl phthalate (DBP)	Additive – plasticiser	Estrogen
Bisphenol A (4,4'-dihydroxy-2,2--diphenylpropane)	Monomer, starting compound in epoxy resins, lacquer coatings of internal surfaces of cans, polycarbonate plastic materials, thermal papers	Estrogen, binds to estrogen receptor
Butylated hydroxyanisole (BHA)	Additive - antioxidant	Estrogen in α and β cell lines of human osteoblasts
Cadmium	FCM contaminant	Activates estrogen receptor
Dimethyltin bis(isooctyl mercapto-acetate)	Plasticiser	Affects 17β-estradiol biosynthesis
Lead	FCM contaminant	Affects reproductive system
Perfluorooctanoic acid (PFOA)	Surface coatings, food containers surfaces	Alteration of thyroid hormone levels
Propyl gallate	Additive- antioxidant	Estrogen in α and β cell lines of human osteoblasts
Semicarbazide	Twist-off type closure internal coatings	Endocrine disrupting potential not confir-med
Thiram	Rubber vulcanisation accelerator, wood prese-rvative	Thyroid hormone disruption

Ćwiek-Ludwicka, K. and J.K. Ludwicki. 2014. Endocrine disruptors in food contact materials: Is there a health threat? *Roczniki Państwowego Zakładu Higieny 65*(3):169–177.

Environmental Chemicals Associated with Obesogens Properties

Chemical	Commercial use	Potential mechanism
Cigarette smoke	First-hand and second-hand smoke	Prenatal nicotine exposure alters neurological development and exposures ↑ rates of preterm and low-weight births[41,46,47]
Air pollution Polycyclic aromatic hydrocarbons	Incomplete combustion of fossil fuels	↑ Accumulation of visceral fat[55] Inflammation[56]
Tributyltin	Fungicide in paints and components of polyvinyl chlorides	Activation of peroxisome proliferator-activated receptor γ[37,58,59] and increased fat cell differentiation[60–63]
Bisphenol A	Plastics and epoxy resins	Estrogenic[82,83] Inhibition of proliferation of neural progenitor cells[86]
Flame retardants	Chemicals applied to furniture and electronics	↑ Rate of adipogenesis[105] ↑ Glucose intolerance[106]
Polychlorinated biphenyls	Coolants, plasticizers and flame retardants	Altered thyroid function[96,101] Altered metabolism[112] Bioaccumulation in fat cells[109]
Phthalates	Plasticizers, adhesives and personal care products	↑ Rate of adipocyte differentiation[117,120–122]
Perfluorooctanoic acid Perfluorooctanoate sulphonate	Components of lubricants, nonstick coatings and stain-resistant compounds	↑ Serum levels of insulin[126] ↑ Serum levels of leptin[126]

Heindel, J.J., R. Newbold, and T.T. Schug. 2015. Endocrine disruptors and obesity. *Nature Reviews, Endocrinology 11*(11):653–661.

Note: Obesogens are exogenous chemicals that directly or indirectly increase obesity through disruption of metabolic, hormonal, or developmental processes (La Merrill, M., C. Emond, M.J. Kim, J-P. Antignac, B. le Bizec, K. Clement, L.S. Birnbaum, and R. Barouki. 2013. Toxicological function of adipose tissue: Focus on persistent organic pollutants. *Environ Health Perspect 121*(2):162–169.

The reality is …

- These chemicals are now part of our daily lives because they are found in many products. Some examples include cosmetics, cleaners, toys, food storage containers, furniture and carpets, telephones, and appliances. These chemicals are also used in plastics and resins in vehicles, planes, and trains; in sporting goods and outdoor equipment; and in medical equipment dental sealants, and pharmaceuticals.

What Have We Learned from Experimentation?

Synthetic EDCs Can Disrupt a Variety of Endocrine Functions in the Body

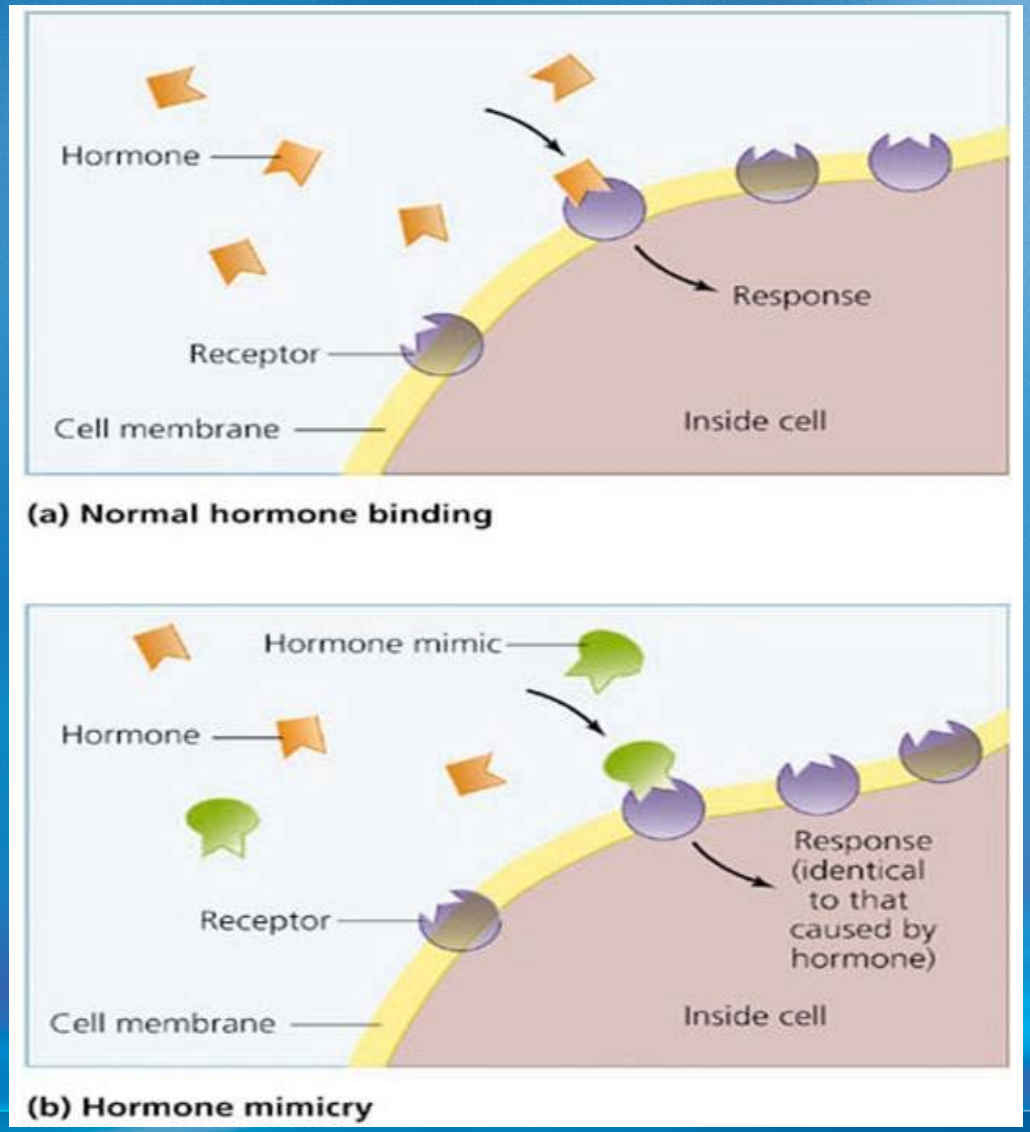
- They can mimic hormones and act as though they were the “keys” to the receptor “locks,” subsequently tricking the cells into thinking that they are hormones.
- They can interfere by binding to the protein carriers of hormones or other proteins that have signaling roles in the cell and between cells.

Synthetic EDCs Can Disrupt a Variety of Endocrine Functions in the Body (cont.)

- They can inhibit or induce enzymes, interfering with uptake and export from cells, and can modify the ways in which genes are read.

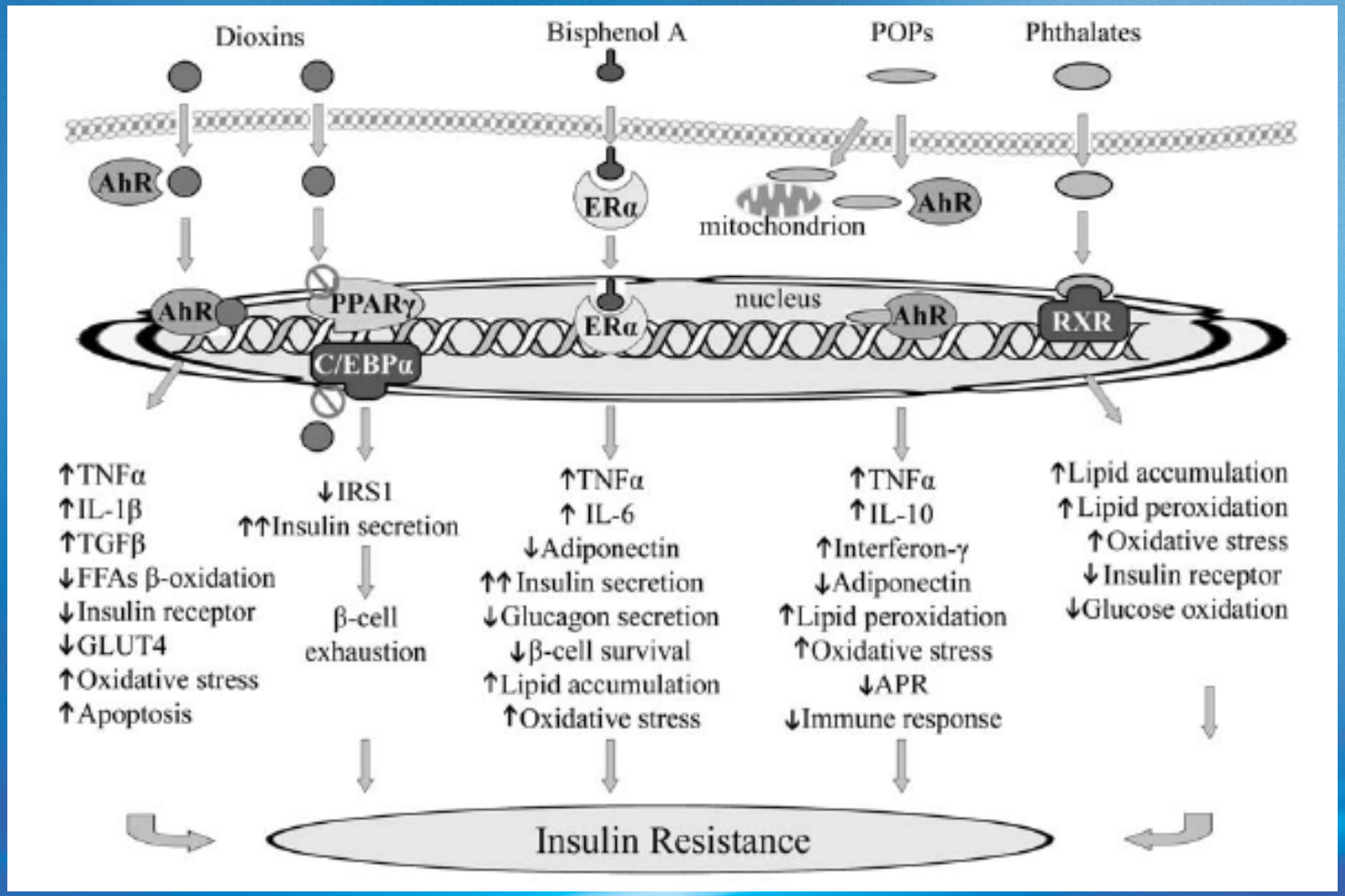
Exposures to chemicals that are EDs can result in effects on a variety of tissues and organs, particularly in developing infants and children.

Classical Mechanisms



http://web.bryant.edu/~dlm1/sc372/readings/toxicology/toxicology.htm

Proposed Mechanism of Action Linking EDCs with Insulin Resistance



Polyzos, S.A., J. Kountouras, G. Deretzi, C. Zavos, and C.S. Mantzoros. 2012. The emerging role of endocrine disruptors in pathogenesis of insulin resistance: A concept implicating nonalcoholic fatty liver disease. *Current Molecular Medicine 12*(1):68–82.

Factors Influencing the Observed Effects

- Diet
  - Phytoestrogen, Mycotoxin, Pesticides
- Bedding
- Water
- Water bottles
- Cages
- Time and Duration of the Exposure
  - Prenatal
  - Postnatal
  - Weanling
  - Adult
- Route of exposure
  - Oral gavage
  - Cutaneous
  - Subcutaneous
  - Inhalation
- Animal Factors
  - Species
  - Strain
  - Sex
  - Age

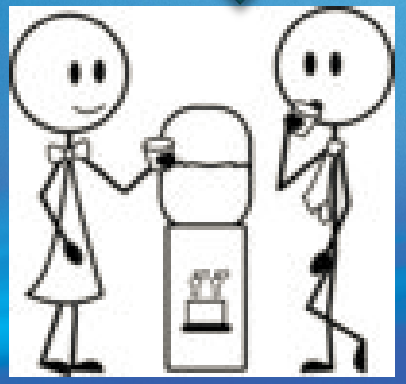
Thigpen, J.E., K.D. Setchell, H.E. Saunders, J.K. Haseman, M.G. Grant, and D.B. Forsythe. 2004. Selecting the appropriate rodent diet for endocrine disruptor research and testing studies. *ILAR Journal 45*(4):401–416.

Exposure interaction

Food production
Food processing
Food packaging

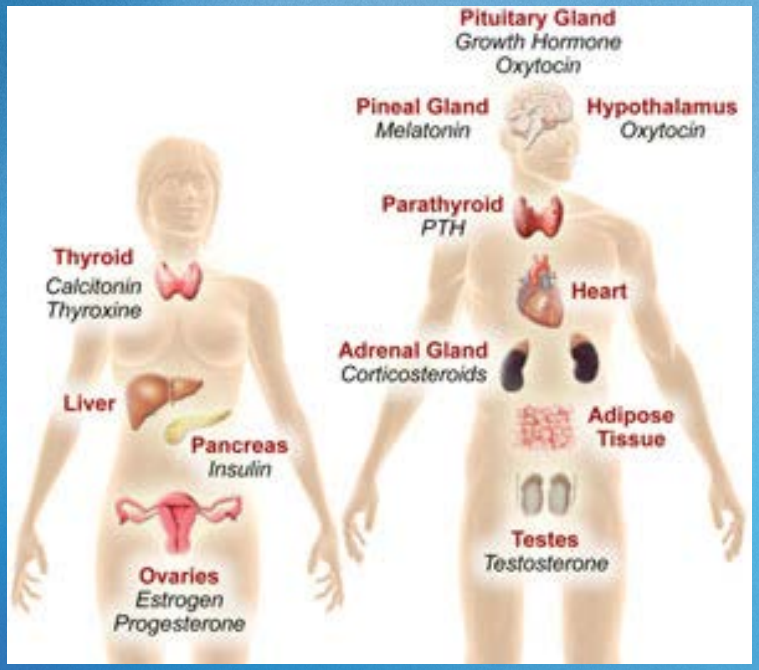
Mixture,
Cumulative,
Interaction

Mixture,
Cumulative,
Interaction



Glands or Tissues?

- Female reproductive system
- Male reproductive system
- Ratio of males to females
- Thyroid disorders
- Neurodevelopmental disorders in children in general
- Hormone-dependent cancers
- Metabolic diseases (e.g., diabetes, obesogenic effects)
- Adrenal gland disorders in humans
- Immune function diseases
- Bone pathology



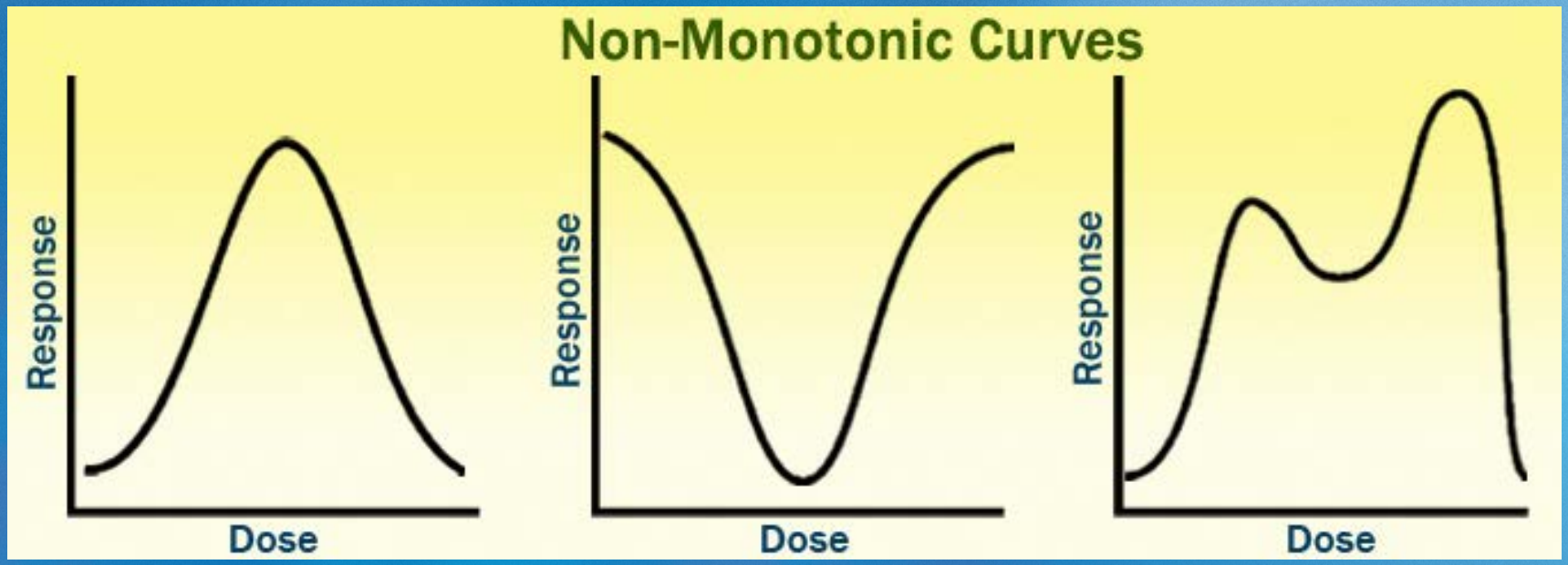
U.S. EPA (Environmental Protection Agency). 2016. Endocrine Disruption. Available at http://www.epa.gov/endo/pubs/edspoverview/whatare.htm

Difficulties in Handling ED

Exposure-Related Issues

- Low-dose exposure
- Route of exposure
- Mixtures
- Toxicity related to the route of exposure
- Risk assessment performed for 1 chemical at a time
- Internal dose
- Windows of sensitivity
- Non-monotonic dose response (NMDR)

NMDR



U.S. EPA (Environmental Protection Agency). 2016. Endocrine Disruption Research: Testing for Potential Low-Dose Effects. Available at https://www.epa.gov/chemical-research/endocrine-disruption-research-testing-potential-low-dose-effects

Di(2-ethylhexyl) phthalate (DEHP) Exposure Aromatase Activity in Newborn (PND 1) Male (A) and Female (B) Rats

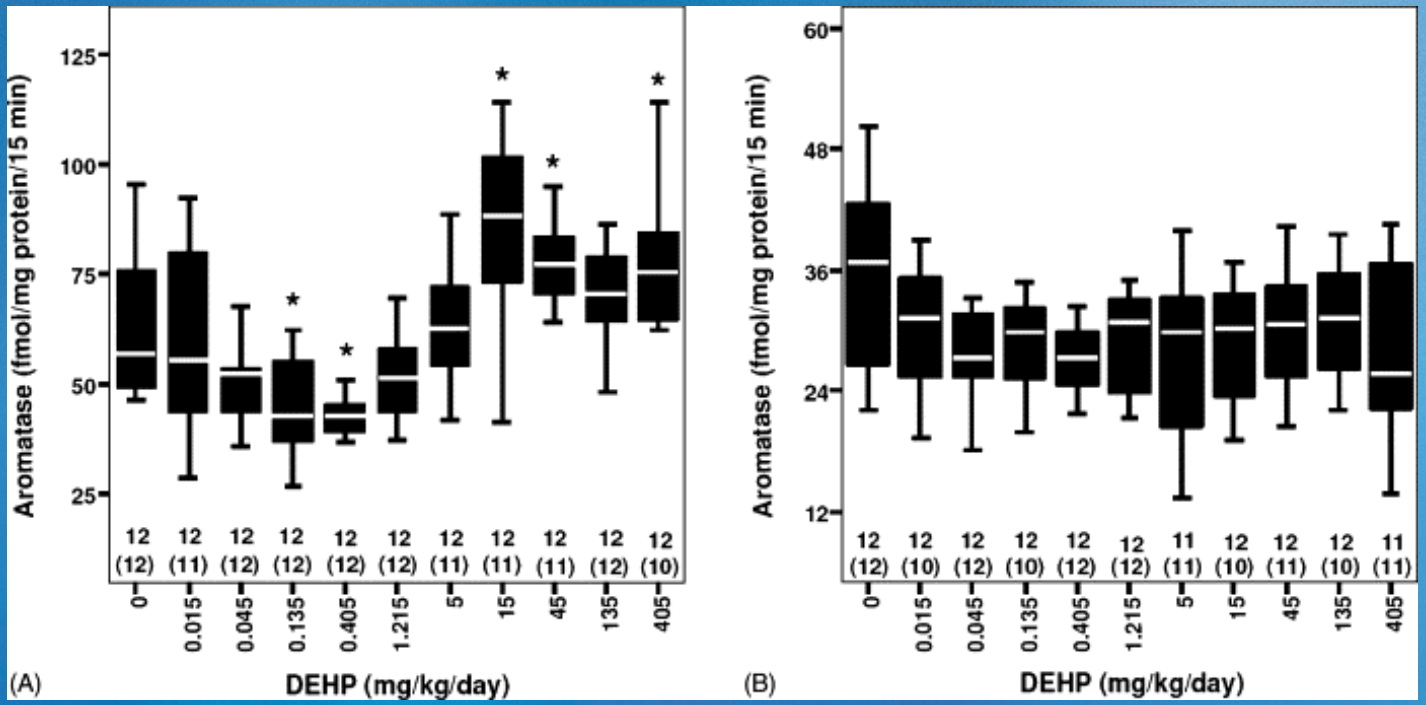


Fig. 3. Effects of developmental DEHP exposure on hypothalamic/preoptic area (HPOA) aromatase activity in newborn (PND 1) male (A) and female (B) rats. *Significantly different from control group. The number of pups is indicated below each box plot and the number of litters is in parenthesis. Box plots indicate medians (horizontal lines), 25 and 75% quartiles and maximum and minimum values.

Martino-Andrade, A.J., S.W. Grande, C.E. Talsness, K. Grote, and I. Chahoud. 2006. A dose–response study following in utero and lactational exposure to di-(2-ethylhexyl)-phthalate (DEHP): Non-monotonic dose–response and low dose effects on rat brain aromatase activity. *Toxicology 227*(3):185–192.

Decision Tree

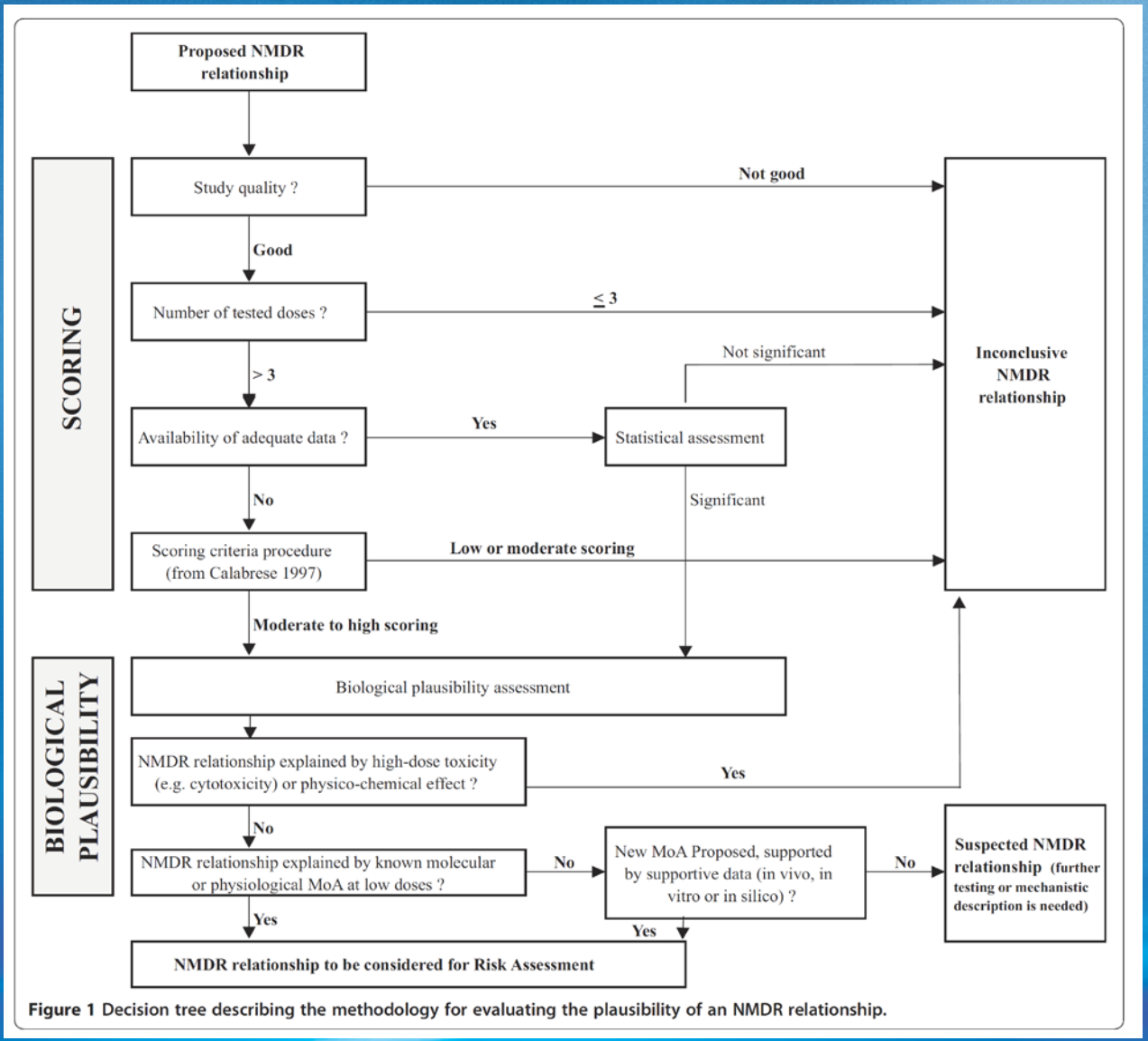


Figure 1 Decision tree describing the methodology for evaluating the plausibility of an NMDR relationship.

Lagarde , F., C. Beausoleil, S.M. Belcher, L.P. Belzunces, C. Emond, M. Guerbet, and C. Rousselle. 2015. Non-monotonic dose-response relationships and endocrine disruptors: A qualitative method of assessment. *Environmental Health 14*:13.

NMDR (Decision Tree)

Table 2 Summary of total score for plausibility of an NMDR relationship

Total score[a]	Plausibility of an NMDR relationship
1–2	No–low
>2–8	Low
>8–12	Low–moderate
>12–16	Moderate
>16–20	Moderate–high
>20	High

[a]These scores were extracted from Calabrese and Blain (2011) [14].

Lagarde , F., C. Beausoleil, S.M. Belcher, L.P. Belzunces, C. Emond, M. Guerbet, and C. Rousselle. 2015. Non-monotonic dose-response relationships and endocrine disruptors: A qualitative method of assessment. *Environmental Health 14*:13.

Epidemiology Limitations

Brophy et al., 2012

Brophy *et al. Environmental Health* 2012, **11**:87
http://www.ehjournal.net/content/11/1/87

ENVIRONMENTAL HEALTH

RESEARCH **Open Access**

Breast cancer risk in relation to occupations with exposure to carcinogens and endocrine disruptors: a Canadian case–control study

James T Brophy[1,2*], Margaret M Keith[1,2], Andrew Watterson[1], Robert Park[3], Michael Gilbertson[1], Eleanor Maticka-Tyndale[2], Matthias Beck[4], Hakam Abu-Zahra[5], Kenneth Schneider[5], Abraham Reinhartz[6], Robert DeMatteo[6] and Isaac Luginaah[7]

Brophy, J.T., M.M. Keith, A. Watterson, R. Park, M. Gilbertson, E. Maticka-Tyndale, M. Beck, H. Abu-Zahra, K. Schneider, A. Reinhartz, R. Dematteo, and I. Luginaah. 2012. Breast cancer risk in relation to occupations with exposure to carcinogens and endocrine disruptors: A Canadian case-control study. *Environmental Health 11*:87.

Brophy et al., 2012

Major and minor sectors, and counts of controls and cases by minor sector of longest duration

Major sector		Minor sector	Controls	Cases
			1146	1006
1	Farming	Agriculture/plants	23	37
		Agriculture/animals	3	5
		Textile manufacturing	3	5
		Footwear manufacturing	0	0
		Wood manufacturing	2	2
		Printing	8	6
		Electrical and electronics mfr	1	1
		Jewelry, furniture manufacturing	5	1
2	Non-plastics light manufacturing	Glass, ceramic manufacturing	2	1
3	Petroleum/Petrochemical	Petroleum, petrochemical, chemical manufacturing	8	6
4	Plastics	Plastics manufacturing (nonauto)	3	0
		Plastics manufacturing (auto)	9	26
5	Metal-related	Metallurgical, metalworking, metal fabrication	64	75
6	Transportation	Transportation	37	26
7	Cleaning/beauty care	Beauty salon/hair care	25	14
		Dry cleaning, laundry	2	8
8	Bars/gambling	Bars/gambling	11	16
	Not categorized as "major"	Mining	1	0
		Power Generation/distribution	4	5
		Construction	6	6
		Food manufacturing	10	30
		Liquor/beer/wine	12	6
		Tobacco manufacturing	1	1
		Media, culture	30	15
		Adm. non education or healthcare	242	229
		Education	176	149
		Healthcare	195	154
		Entertainment	13	5
		Hotels and motels	7	5
		Retail	193	124
		Restaurants, food services	46	36

Brophy, J.T., M.M. Keith, A. Watterson, R. Park, M. Gilbertson, E. Maticka-Tyndale, M. Beck, H. Abu-Zahra, K. Schneider, A. Reinhartz, R. Dematteo, and I. Luginaah. 2012. Breast cancer risk in relation to occupations with exposure to carcinogens and endocrine disruptors: A Canadian case-control study. *Environmental Health 11*:87.

Brophy et al., 2012 (Conclusions)

- These observations support hypotheses linking breast cancer risk and exposures likely to include carcinogens and EDCs.
- These observations also demonstrate the value of detailed work histories in environmental and occupational epidemiology.

Brophy, J.T., M.M. Keith, A. Watterson, R. Park, M. Gilbertson, E. Maticka-Tyndale, M. Beck, H. Abu-Zahra, K. Schneider, A. Reinhartz, R. Dematteo, and I. Luginaah. 2012. Breast cancer risk in relation to occupations with exposure to carcinogens and endocrine disruptors: A Canadian case-control study. *Environmental Health 11*:87.

Costa et al., 2015

BJC

British Journal of Cancer (2015) 112, 1251–1256 | doi: 10.1038/bjc.2015.83

Keywords: endocrine disruptors; chemicals; lymphoma; leukaemia; solvents; pesticides; alkylphenols

Occupational exposure to endocrine disruptors and lymphoma risk in a multi-centric European study

L Costas[*,1,2,3], C Infante-Rivard[4], J-P Zock[3,5,6,7], M Van Tongeren[8], P Boffetta[9], A Cusson[10], C Robles[1], D Casabonne[1,3], Y Benavente[1,3], N Becker[11], P Brennan[12], L Foretova[13], M Maynadié[14], A Staines[15], A Nieters[16], P Cocco[17] and S de Sanjosé[1,2,3]

Costas, L., C. Infante-Rivard, J-P. Zock, M. Van Tongeren, P. Boffetta, A. Cusson, C. Robles, D. Casabonne, Y. Benavente, N. Becker, P. Brennan, L. Foretova, M. Maynadie, A. Staines, A. Nieters, P. Cocco, and S. de Sanjose. 2015. Occupational exposure to endocrine disruptors and lymphoma risk in a multi-centric European study. *British Journal of Cancer 112*(7):1251–1256.

Costa et al., 2015

	Overall		
Total years of exposure to	Controls	Cases	OR[a] (95% CI)
Unexposed[a]	901	588	Ref
Pesticides			
Organochlorines	442	347	1.10 (1.00,1.20)*
Carbamates/pyrethroids	507	391	1.11 (1.02,1.21)*
Organophosphates	467	366	1.10 (1.01,1.20)*
Organic Solvents			
Ethylene glycol ethers	943	719	1.06 (1.00,1.12)*
Styrene	38	33	0.96 (0.67,1.39)
Toluene/xylene	735	565	1.05 (0.99,1.11)
Trichloroethylene	320	222	1.00 (0.90,1.11)
Perchloroethylene	315	223	1.00 (0.90,1.12)
Alkylphenolic compounds			
Alkylphenolic ethoxylates	736	578	1.07 (1.00,1.15)*
Alkylphenols	466	379	1.06 (0.98,1.16)
Metals			
Cadmium	108	77	0.90 (0.69,1.19)
Arsenic	78	80	1.06 (0.87,1.30)
Copper	824	617	1.07 (1.00,1.14)*
Lead	508	383	1.03 (0.95,1.12)
Mercury	14	6	1.27 (0.84,1.93)

Costas, L., C. Infante-Rivard, J-P. Zock, M. Van Tongeren, P. Boffetta, A. Cusson, C. Robles, D. Casabonne, Y. Benavente, N. Becker, P. Brennan, L. Foretova, M. Maynadie, A. Staines, A. Nieters, P. Cocco, and S. de Sanjose. 2015. Occupational exposure to endocrine disruptors and lymphoma risk in a multi-centric European study. *British Journal of Cancer 112*(7):1251–1256.

Costa et al., 2015 (Conclusions)

- According to the authors, this is the first comprehensive study that assessed the occupational exposure to EDCs and lymphoma risk.
- The authors used a large sample size to assess the exposure to chemicals with potential endocrine disrupting properties.
- The authors noted an association with some lymphoma subtypes for recent and prolonged exposures to several EDCs.

Costas, L., C. Infante-Rivard, J-P. Zock, M. Van Tongeren, P. Boffetta, A. Cusson, C. Robles, D. Casabonne, Y. Benavente, N. Becker, P. Brennan, L. Foretova, M. Maynadie, A. Staines, A. Nieters, P. Cocco, and S. de Sanjose. 2015. Occupational exposure to endocrine disruptors and lymphoma risk in a multi-centric European study. *British Journal of Cancer 112*(7):1251–1256.

Villeneuve et al., 2010

Original article

Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case–control study in Europe

Sara Villeneuve,[1,2] Diane Cyr,[1,2] Elsebeth Lynge,[3] Laurent Orsi,[1,2] Svend Sabroe,[4] Franco Merletti,[5] Giuseppe Gorini,[6] Maria Morales-Suarez-Varela,[7,8,9] Wolfgang Ahrens,[10] Cornelia Baumgardt-Elms,[11] Linda Kaerlev,[12] Mikael Eriksson,[13] Lennart Hardell,[14] Joëlle Févotte,[15,16] Pascal Guénel[1,2,16]

Villeneuve, S., D. Cyr, E. Lynge, L. Orsi, s. Sabroe, F. Merletti, G. Gorini, M. Morales-Suarez-Varela, W. Ahrens, C. Baumgardt-Elms, L. Kaerlev, M. Eriksson, L. Hardell, J. Fevotte, and P. Guenel. 2015. Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: A case-control study in Europe. *Occupational and Environmental Medicine 67*(12):837–844.

Villeneuve et al., 2010

Odds ratios* by occupation (ISCO codes†)– European study on male breast cancer

Ever employed as	ISCO	Cases N=104	Controls N=1901	OR	95% CI
Architects, engineers	0-2/0-3	7	153	0.9	[0.4;2.1]
Administrators and managers	2-0/2-1	7	161	0.9	[0.4;1.9]
Clerical and related workers NEC‡	3-9	9	174	0.8	[0.4;1.6]
Salesmen, shop assistants	4-5	7	186	0.6	[0.3;1.4]
Cooks, waiters, bartenders	5-3	7	77	1.5	[0.7;3.3]
Protective service workers	5-8	6	63	1.7	[0.7;4.0]
Farmers	6-0/6-1	7	118	0.7	[0.3;1.5]
Agricultural and animal husbandry w.	6-2	17	278	0.8	[0.5;1.4]
Metal processers	7-2	6	91	1.1	[0.4;2.5]
Wood preparation workers, paper makers	7-3	5	26	2.4	[0.9;6.5]
Food and beverage processers	7-7	6	96	1.0	[0.4;2.3]
Cabinet makers	8-1	5	75	1.1	[0.4;2.7]
Blacksmiths, toolmakers, machine-tool op.	8-3	14	218	1.1	[0.6;1.9]
Machinery fitters, machine assemblers	8-41	5	73	1.2	[0.5;3.1]
Motor vehicle mechanics	8-43	9	74	2.1	[1.0;4.4]
Machinery fitters, machine assemblers NEC	8-49	6	139	0.7	[0.3;1.7]
Electricians	8-5	8	178	0.9	[0.4;1.9]
Plumbers and pipe fitters	8-71	6	55	2.0	[0.8;4.8]
Welders and flame cutters	8-72	6	65	1.4	[0.6;3.4]
Painters	9-3	7	54	2.3	[1.0;5.2]
Bricklayers, carpenters, construction workers	9-5	8	177	0.8	[0.4;1.4]
Material handling op., dockers	9-7	16	193	1.4	[0.8;2.3]
Transport equipment operators	9-8	15	288	0.9	[0.5;1.6]
Laborers NEC	9-9	11	143	1.1	[0.6;2.1]

Villeneuve, S., D. Cyr, E. Lynge, L. Orsi, s. Sabroe, F. Merletti, G. Gorini, M. Morales-Suarez-Varela, W. Ahrens, C. Baumgardt-Elms, L. Kaerlev, M. Eriksson, L. Hardell, J. Fevotte, and P. Guenel. 2015. Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: A case-control study in Europe. *Occupational and Environmental Medicine 67*(12):837–844.

Villeneuve et al., 2010 (Conclusions)

- Incidence of male breast cancer was increased in the following:
  - Wood preparation workers
  - Paper makers
  - Motor vehicle mechanics
  - Painters
  - Workers in the forestry industry, such as logging
  - Furniture manufacturing
- Incidence of male breast cancer was more particularly associated with alkylphenolic compounds.

Villeneuve, S., D. Cyr, E. Lynge, L. Orsi, s. Sabroe, F. Merletti, G. Gorini, M. Morales-Suarez-Varela, W. Ahrens, C. Baumgardt-Elms, L. Kaerlev, M. Eriksson, L. Hardell, J. Fevotte, and P. Guenel. 2015. Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: A case-control study in Europe. *Occupational and Environmental Medicine 67*(12):837–844.

Villeneuve et al., 2010 (Conclusions, cont.)

- The elevated risk of male breast cancer in specific occupations provided some clues about possible environmental mammary carcinogens.

- The elevated risk of male breast cancer among motor vehicle mechanics which points to a role of PAHs and gasoline or petroleum solvents in breast carcinogenesis.

- For the first time in male breast cancer, we have shown that EDCs could affect male breast cancer risk.

Villeneuve, S., D. Cyr, E. Lynge, L. Orsi, s. Sabroe, F. Merletti, G. Gorini, M. Morales-Suarez-Varela, W. Ahrens, C. Baumgardt-Elms, L. Kaerlev, M. Eriksson, L. Hardell, J. Fevotte, and P. Guenel. 2015. Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: A case-control study in Europe. *Occupational and Environmental Medicine 67*(12):837–844.

How we perform Risk Assessment in the real life in 2016.

- Single compound at the time
- Literature review (Hazard identification)
  - Experimental studies
  - Report (confidential or published)
  - Epidemiology studies
- Identification of health effect.
- Species, Exp. design and Temporal Adjustment (or PBPK)
- Characterization of the Exposure (Probalistic approach).
- Characterization of Risk Based on Hazard and Exposure.
- Toxicological Reference Value determination.

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Workgroup at Anses

Human Risk Assessment for BPA

Summary

- Maybe the question is ‘‘The difficulty with EDs is that these compounds are considered to be EDC rather than substances that are part of any other chemicals family’’. Or maybe not!
- Because of the number of mechanisms of action, it can become difficult to classify EDC. Mode of Action should at least identify to classify and substance EDC.
- Without the label EDC, maybe the Risk Assessment would simply based on the most sensitive effect for a lower exposure dose.
- The challenges of Low Dose, NMDR, Windows of Sensitivity increase the complexity for the RA.
- For now the majority of the ‘‘Toxicological Reference Value are based on the individual chemical from experimental exposure.
- Exposure management from Food and at Workplace can always be better but it is controlled, but what we do at home during our free time!

In the end, it is possible to know whether a substance has an ED potential, but it is very difficult to know whether a potential ED is not a ED.

Acknowledgments

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Thank you!

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